Cerebellum (2015) 14:570–577
DOI 10.1007/s12311-015-0649-9

REVIEW

The Emotional Cerebellum

Piergiorgio Strata

Published online: 28 January 2015

Abstract Great attention has been given so far to cerebellar control of posture and of skilled movements despite the well-demonstrated interconnections between the cerebellum and the autonomic nervous system. Here is a review of the link between these two structures and a report on the recently acquired evidence for its involvement in the world of emotions. In rodents, the reversible inactivation of the vermis during the consolidation or the reconsolidation period hampers the retention of the fear memory trace. In this region, there is a long-term potentiation of both the excitatory synapses between the parallel fibres and the Purkinje cells and of the feed-forward inhibition mediated by molecular layer interneurons. This concomitant potentiation ensures the temporal fidelity of the system. Additional contacts between mossy fibre terminals and Golgi cells provide morphological evidence of the potentiation of another feed-forward inhibition in the granular layer. Imaging experiments show that also in humans the cerebellum is activated during mental recall of emotional personal episodes and during learning of a conditioned or unconditioned association involving emotions. The vermis participates in fear learning and memory mechanisms related to the expression of autonomic and motor responses of emotions. In humans, the cerebellar hemispheres are also involved at a higher emotional level. The importance of these findings is evident when considering the cerebellar malfunctioning in psychiatric diseases like autism and schizophrenia which are characterized behaviourally by emotion processing impairments.

Keywords Cerebellar vermis · Fear learning and memory · Purkinje cells · LTP/LTD · Feed-forward inhibition · Emotions

P. Strata (✉)
Department of Neuroscience, University of Turin and National Institute of Neuroscience, 10125 Turin, Italy
e-mail: piergiorgio.strata@unito.it

Background

Historically, for a long period of time, the possible function of the cerebellum was outlined without experimental evidence [1]. The first interesting and noteworthy observation with a formulation of a hypothesis was made by Vincenzo Malacarne [2] who published the first work entirely devoted to the cerebellum. In order to understand cerebellar function, he attempted to establish a correlation between cerebellar size and various pathologies. At his time, because of the lack of iodine in the drinking water, people living in the Po Valley in Italy were often affected by cretinism. In two patients affected by this disease, Malacarne observed that there was a reduction of the cerebellar size and a decrease in the number of folia. In his book, he reported a wide variation in the number of folia from 500 to 780 while in an idiot the number was 340. In a series of letters exchanged with the Swiss anatomist Carlo Bonnet [3], there was a discussion on whether such variability is innate or acquired by experience. Malacarne proposed bringing up twins of different species of mammals and birds in poor and enriched environments and then verifying the number of folia. It is not known whether the experiment was ever done. The most interesting aspect of his finding remains the hypothesis that the number of folia is influenced by the environment, thus providing the first nature-nurture hypothesis made on the basis of observations, and the concept of neuroplasticity in the scientific literature.

The true history of cerebellar functions came much later with Rolando [4]. Following ablation experiments in different species of mammals and birds, he showed that cerebellar deficiency concerned motor activity as differentiated from sensory function, thus providing a foundation stone in cerebellar physiology. It was Flourens [5] who established that the cerebellum was involved in movement coordination. For a long time, these concepts dominated the literature, and to date, attention has mainly been focussed along these lines with

the attempt to describe the mechanisms of motor control and the role of the cerebellum in motor learning [6]. Even at present, in most textbooks, the function of the cerebellum is confined solely to its role in motor functions. This term commonly implies skeletal motor functions like body posture and skilled movements.

Indeed, a series of experiments shows that the cerebellum receives afferents from the autonomic nervous system, it is connected with the limbic system and it exerts control on several vegetative functions [7]. The vegetative nervous system, also known as the autonomic nervous system, is most directly involved in the maintenance of life by regulating all vital functions, and it is made up of the sympathetic and the parasympathetic divisions. It is not under voluntary control but is heavily influenced by 'state of the mind' and particularly by the world of emotions, the main topic of this review.

The proposal that the phylogenetically newest structures of the cerebellum may contribute to mental skills [8] was followed by a flurry of papers along this line. As noted by Sultan [9], there is a parallel growth of both cerebral and cerebellar cortices, suggesting a functional dependence of the one upon the other. There is now solid evidence that the output of the cerebellum targets not only cortical motor areas but also several non-motor regions in the prefrontal and parietal lobes which are typically involved in higher brain function and that they are essential to achieve a state of consciousness and more generally in cognition [10]. Additional evidence for the cerebellar involvement in cognition was revealed by using brain imaging experiments in humans during word processing. When an individual was performing a test to associate a verb to the presentation of a noun, the right lateral cerebellum became active [11]. However, the role of the cerebellum in cognition is still a debated issue [12].

Here, there is a report of a series of pioneering experiments made in the 1930s by Giuseppe Moruzzi (see [7]) aimed at showing the involvement of the cerebellum in the control of the autonomic nervous system. At the beginning of the nineteenth century, several papers showed contradicting results on this issue mainly due to the lack of control on the localization of lesion and of stimulation. With a series of carefully controlled paradigms, Moruzzi showed that this structure was unequivocally involved in blood circulation and respiration.

In studying the circulation, he showed that a stimulus applied to the vermis of the anterior lobe did not affect the systemic blood pressure. However, when blood pressure increased spontaneously or by stimulating the central stump of the laryngeal nerve, vermal stimulation clearly hampered the increase. In addition, when the blood pressure was decreased by a vasodilator response elicited by the stimulation of the central stump of the vagus nerve, the stimulation limited the evoked hypotension. In an additional series of experiments, he investigated the effect of vermal stimulation on the vasomotor carotid sinus reflexes. In decerebrated cats, he confirmed that only minor vasopressor effects could be elicited against a background of normal systemic blood pressure. However, the depressor response was clear-cut when the vermal stimulation was applied against a background of released vasomotor tonus elicited by clamping both common carotid arteries. More recently, Smith and Nathan [13] have shown that nerve fibres from rostral brainstem areas, which produce pressor responses and tachycardia, terminate in the inferior olive whose electrical stimulation produces no cardiovascular response but inhibits the depressor component of the carotid sinus reflex. Additional experiments by Moruzzi were made on the 'sham rage' which occurs spontaneously in acute thalamic cats. Sham rage is characterized by an outburst of mass activity resembling an infuriated animal. When lobuli V, VI and VII were stimulated, the autonomic components consisting of an increase in blood pressure, mydriasis and retraction of the lid were clearly inhibited. Since these generalized autonomic responses were abolished in decerebrated animals lacking the hypothalamus, Moruzzi suggested that the observed effects were due to cerebellar efferent fibres projecting to the hypothalamic centres.

Concerning the respiratory system, he demonstrated that normal breathing patterns were slightly inhibited by the vermal stimulation in the decerebrated cat. However, the inhibitory effect was much greater when the stimulation occurred against a background of hyperpnea obtained by clamping both carotid arteries or by intracarotid injection of potassium cyanide. Similar respiratory responses were present in sham rage.

In summary, Moruzzi provided evidence that the vermis of the cerebellum, and not the hemispheres, acts by preventing oscillations of the basic parameters of the circulatory and respiratory systems as a kind of homeostatic control on the vegetative functions. He suggested that the cerebellum acts on an ensemble of behavioural responses that belong to a complex autonomic reaction.

The first supporting evidence for this hypothesis came from Snider [14] with the demonstration of anatomical projections from the fastigial nucleus to the hypothalamus. Following these discoveries, many papers provided evidence of interconnections between the vermis, the hypothalamus and the limbic system [15–19].

Another series of experiments has more recently addressed the investigation of visceral afferent projections to the cerebellum. Splanchnic and vagus nerve stimulation elicited evoked responses in the vermis [20–22]. Splanchnic afferents project to the vermis as climbing fibre responses [23] and to the inferior olive, the source of climbing fibres [24]. Very recently, the involvement of the interpositus nucleus in the modulation of autonomic and emotional functions has achieved a wide consensus [25].

Taken together, the above-described experiments demonstrate the close relationship between the cerebellar vermis and

vegetative functions. Since these functions are strictly related to the emotions, the experiments strongly suggest cerebellar control at least in the emotion expressions.

Cerebellum and Emotional Life; the Fear Paradigm

Emotions play a major role in human behaviour. The cognitive aspects of an emotional event, either being pleasure or displeasure, have a strong motivational component in memorizing the event in order to instruct the brain how to change its behavioural strategy in similar future situations. Fear-related processes are essential for survival and they have a very strong emotional impact [26]. Therefore, they provide a privileged model to study emotions.

A fear innate response based on an evolutionary memory may be elicited by dangerous environmental stimuli or by previous innocuous stimuli when repeatedly associated with harmful ones. In an often-used paradigm, a neutral stimulus, usually a sound, acts as a conditioning stimulus and is repeatedly paired with a noxious unconditioned stimulus, usually an electric foot shock in laboratory animals. In humans, the unconditioned stimulus may be an electric shock applied to the hand or a loud noise. Following pairing, the conditioned stimulus elicits defensive behavioural responses.

Several papers have been devoted to supporting the hypothesis that the cerebellum participates in non-motor functions and that they are involved in emotional processes [27, 28, 10]. Following vermal lesion in animal experiments, there is a decrease in the reactivity of animals to fear stimuli like when a rodent is facing a cat or in an open field [29–31]. In addition, the lesion to the anterior cerebellar vermis severely attenuated the acquisition of conditioned bradycardia [32]. Schmahmann and Sherman [33] showed that, in human subjects, the cognitive affective syndrome associated with vermis and fastigial nucleus deficit, involves a dysregulation of affects. In patients with medial cerebellar lesions, conditioned bradycardia is impaired [34]. On the whole, these results support the hypothesis formulated a long time ago of a limbic cerebellum located in the vermis and fastigial nucleus [29].

Memory Trace Location in the Cerebellum in Animal Models

Sacchetti et al. [35] provided the first strong evidence for the involvement of the cerebellum in fear conditioning and more precisely for its role in fear memory consolidation. Fear conditioning provides a form of learning that transforms an innocuous stimulus into a stimulus predicting an aversive situation. Rats were submitted to acoustic conditioning stimuli and context fear training. Reversible brief inactivation was applied to the cerebellar vermis by injecting tetrodotoxin at different time intervals from the training. The authors showed that the inactivation applied during the days following the training led to the reduction of the contextual and of the cued freezing response while injections made at longer time intervals from the training were ineffective.

A similar technique to examine memory consolidation has been used in a different experimental situation. Consolidated memories may be retrieved by a memory recall, and this is followed by a reconsolidation process. During these events, a memory trace may be manipulated and therefore the original trace may be changed. When a reversible block of activity is applied to the vermis immediately after the memory recall, the fear responses became attenuated, thus showing the weakening of the fear memory trace [36]. In the same paper, it was shown that when stronger fear memories are installed as a consequence of the application of a higher strength of conditioning paradigms, they are unaffected by the inactivation of the vermis, but they are affected by the combined blockade of the amygdala and of the cerebellum. These findings suggest that in some conditions, the cerebellum may act independently from the amygdala. In strong memories, these two structures appear to be complementary.

The acoustic startle response in rats shows both a short-term habituation, which recovers in seconds or minutes, and a long-term habituation, which is effectively permanent. Leaton and Supple [37] showed that lesions of the cerebellar vermis significantly attenuated the long-term habituation without affecting the short-term process or altering the initial response levels. They conclude that in this response system, the cerebellar vermis is part of an essential circuit for long-term habituation. Lopiano et al. [38] confirmed these results, but in addition, they showed that if the cerebellar vermis lesion was made after training for long-term habituation, the learned behaviour was retained. These results indicate that the cerebellar vermis is essential for the acquisition, but not for the retention, of long-term habituation of the startle response.

Fear Memory Location in the Human Cerebellum

Neuroimaging studies have been used to address the issue of fear memory in the human cerebellum. The most common technology used to map brain responses is positron emission tomography (PET) and now predominantly functional magnetic resonance (fMR), both of which measure local changes which occur in brain circulation and metabolism. The limitation of these techniques, relative to those described in animal experiments, is due to the difficulty in distinguishing between excitatory and inhibitory processes since metabolic activity may increase as a consequence of an enhancement of the inhibitory GABAergic synapses which abound in the cerebellum ([39], see [40]). Another limitation met in imaging studies is the difficulty in defining the precise spatial localization.

Often, a change of activity is referred to the anterior or to the posterior cerebellum, rather than distinguishing vermal versus hemispheric localization or in the anteroposterior direction to identify which lobuli are involved.

As in animal models, pain stimuli have been applied to human subjects while observing the region of the cerebellum showing changes in metabolic activity. Ploghaus et al. [41] applied painful heat stimuli to human subjects and found changes of metabolic activity in the 'anterior cerebellum'. However, when a visual stimulus was used to anticipate an incoming painful one, it was the 'posterior cerebellum' that showed an increased metabolism. Damasio et al. [42] used PET imaging to study the localization of signals during mental recall of personal emotionally charged episodes. They found that both sides of the midline cerebellum were significantly activated for sadness, anger and fear while the left midline cerebellum was activated for happiness. Anger and fear activated also the right lateral cerebellum.

Singer et al. [43] showed that in healthy human subjects receiving a painful stimulus, the anterior cerebellum was activated while the posterior cerebellum was activated in the same subjects when they were observing pain induced in other subjects. In both conditions, there was a concomitant activation of the lateral cerebellum. The conclusion drawn by the authors is that the cerebellum is involved in empathic experience. In addition, the fact of having two different regions in this representation is important for our ability to 'mentalize or to understand the thoughts, beliefs, and intentions of others'.

Cellular Mechanisms of Fear Memory Trace in the Cerebellar Cortex; the Excitatory Synapses

According to Supple et al. [44], following acoustic fear conditioning in rabbits, the administration of an acoustic stimulus elicited an increased firing of Purkinje cells in vermal lobuli III–V. Along this line of investigation, a series of experiments has been performed to better understand the cellular mechanism of fear memory in the cerebellar cortex.

The nature of a memory trace in the brain is assumed to consist of a persisting change in synaptic strength under the form of long-term potentiation (LTP) or long-term depression (LTD) of excitatory or inhibitory synapses.

A large number of sites have been identified in the mammalian brain to subserve learning and memory. In the cerebellum, following an original proposal by Marr [45] and Albus [46], a series of investigations provided support to the hypothesis that LTD is induced in the parallel fibre to Purkinje cell synapses when a simultaneous activation of climbing fibres occurs [6, 47]. However, in vitro experiments have shown that a LTP may be induced in the Purkinje cells by a repetitive stimulation of only the parallel fibres [48, 49]. Several experiments showing LTP or LTD in the cerebellar cortex were obtained by electrical stimulation, and from these experiments, it is clear that the results depend on stimulus parameters. To work in more physiological conditions, it is necessary to adopt a protocol of a behaviourally induced synaptic plasticity like the LTP described in the amygdala following fear associative conditioning [50].

Here is a report of investigations performed in our laboratory to identify the mechanisms leading to the fear memory trace in the cerebellar cortex. To this aim, rats were first submitted to an acoustic or a context fear conditioning. At 10 min or at 24 h following the conditioning, in cerebellar slices collected in vitro, there was a LTP of the parallel fibre to Purkinje synapses in lobuli V and VI, but not in lobulus IX, while the synapses made by the climbing fibres showed no change in synaptic strength. The potentiation occurred at postsynaptic level and it was mediated by AMPA receptors [51].

Hotfoot mice are characterized by a primary deficiency of the parallel fibre to Purkinje cell synapses due to the lack of the selective delta-2 receptors. They provided an interesting model to assess whether such a deficiency was affecting fear learning. In these mice, fear conditioning obtained by means of the acoustic stimulus was affected while the context conditioning was not.

From these experiments, it has been concluded that parallel fibres to Purkinje cell synapses are important for the process of fear memory in the cerebellar cortex and that the LTP induced in these synapses is to be considered the memory substrate. This is the first evidence that this type of LTP is present when learning and memory in the cerebellar cortex is obtained by means of a behaviourally induced protocol without the use of artificial electrical stimulation. Recently, evidence that LTP is a mechanism of cerebellar learning and memory has been provided in other animal models [52–54]. Sacchetti et al. [51] suggested that the LTP obtained in their experimental conditions might be the results of a conjunctive action of two separate parallel fibre channels activated by the conditioned and the unconditioned stimuli (Fig. 1a).

In another experiment, it has been shown that an electrically induced LTP by stimulation of parallel fibres is reduced in size in rats previously submitted to fear conditioning. This occlusion demonstrates that the in vivo potentiation induced by associative learning shares common mechanisms with the electrically induced one [55].

A further step addressed the issue whether the LTP obtained by the fear conditioning is due only to the modulation of synaptic receptors. It is known that the intrinsic excitability of a neuron may be involved in memory processes and that changes in intrinsic membrane excitability may contribute to synaptic plasticity. It has been shown that in lobulus VI, conditioning of the nictitating membrane response leads to a change of simple spike firing of the Purkinje cells [56–58] and that an increase of the intrinsic excitability of the Purkinje cell dendrites contributes to the change [59, 60]. In our

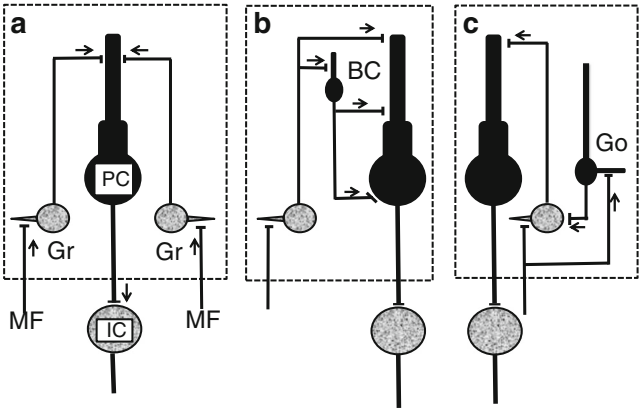

Fig. 1 Outline of the proposed cellular mechanisms of fear memory trace formation in the cerebellar cortex. **a** Two beams of parallel fibres activated by a conditioned and an unconditioned stimulus converge on the same Purkinje cell. Their concomitant action would be responsible for the LTP. **b** Feed-forward inhibition exerted by a beam of parallel fibres on Purkinje cells through the action of basket (and stellate, not shown) cells. **c** An additional feed-forward inhibition is exerted on the granule cells by the mossy fibres through the Golgi cells. *MF* mossy fibre; *Gr* granule cell; *PC* Purkinje cell; *BC* basket cell; *Go* Golgi cell; *IC* intracerebellar nuclei

experimental model of fear conditioning, the main parameters that characterize intrinsic excitability were unchanged following associative fear learning [61].

The Cerebellar Cortex Inhibitory Synapses

Long-term changes in excitatory synapses have been widely investigated in relation to learning and memory while we know much less about the role of inhibitory synapses. LTP induced in excitatory synapses of the amygdala by fear conditioning is controlled by GABAergic inhibition [62, 63]. In addition, genetic deletion of the delta subunit of the GABA receptors reduces the synaptic inhibition in the hippocampus. Compared to controls, delta knockout mice exhibited an enhanced acquisition of tone and context fear [64]. In our experimental model, we asked whether in addition to the LTP found in the parallel fibres to Purkinje cell synapses, there was any long-term change in the inhibitory synapses.

Purkinje cells have abundant inhibitory synapses both in the dendrites and in the soma made by the basket and the stellate cells and by neighbouring Purkinje cells via their recurrent collaterals [65] (Fig. 1b). It should be noted that in the cerebellar cortex, inhibition is also exerted on granule cells by the mossy fibres through the Golgi cells (Fig. 1c).

First, miniature GABAergic events were recorded in Purkinje cells in lobuli V and VI of the vermis, with the technique of whole-cell patch-clamp. Up to 24 h after the usual fear conditioning session, spontaneous miniature potential showed significantly larger amplitude while their frequency was unchanged [66]. This means that following fear conditioning, there was a presynaptic and not a postsynaptic change in the inhibitory afferents; in other words, we are in front of a presynaptic form of inhibitory LTP.

In order to understand the possible significance of the presence of LTP in both excitatory and inhibitory inputs to the Purkinje cells, it is necessary to address the issue of the timing of these two convergent actions. In the central nervous system, it is very common to have a single excitatory neuron that in addition to exerting a direct excitatory action, induces a disynaptic inhibition mediated by an interneuron. Such a feed-forward inhibition reduces the spike generation by asynchronous inputs. It has been demonstrated that the temporal resolution of the neuronal integration depends on the time window within which excitatory inputs summate to reach the threshold for spike generation and that the time period of the window is controlled by the disynaptic inhibition. In rat hippocampal pyramidal cells, this window is very narrow and less than 2 ms and this is due to the short delay with which disynaptic feed-forward inhibition follows the monosynaptic excitation [67]. A narrow window improves the precision of the performance.

Lamsa et al. [68] showed that when the LTP occurs only in the excitatory synapses of hippocampal pyramidal neurons, the temporal fidelity of the synaptic integration and the action potential generation is compromised. However, when the LTP occurs also at synapses on feed-forward interneurons, the temporal fidelity is preserved. In the cerebellar cortex, an excitatory-inhibitory wiring occurs in the parallel fibres acting directly on the Purkinje cells and disynaptically through the cerebellar interneurons located in the molecular layer (Fig. 1b). Mittmann et al. [69] showed that this cerebellar feed-forward inhibition, activated within 1 ms, sharply curtails the excitation and increases the precision of the resulting action potentials. The time window for summation of the excitatory drive is reduced to 1–2 ms in the presence of the feed-forward inhibition.

Experiments have been performed to evaluate the time period of the window in the physiological conditions of our protocol of fear learning. It has been found that in lobuli V and VI of the vermis, the probability of summation of the excitatory inputs and of reaching the threshold for spike generation in the Purkinje cells increases following fear learning. This means that the summation of close events is facilitated. On the other hand, the concomitant presence of a LTP in the inhibitory synapses allows the time window to be maintained unaltered. In conclusion, the excitatory LTP provides an effective signal detection while the inhibitory LTP maintains the coincidence detection unchanged, thus ensuring the temporal fidelity of the system [66].

Morphological Changes

A morphological study performed in both the hippocampus and the cerebellar cortex provided additional information on the mechanism of the fear memory consolidation processes by analysing the morphology of the synapses made in the granular layer by the mossy fibre terminals with the dendrites of the Golgi cells (Fig. 1c) [70]. As regards the cerebellum, two experimental paradigms were used. In the first, cued fear conditioning was obtained in a single session according to the protocol described above where the conditioning stimulus was a sound. In the second paradigm, the experiment consisted of training mice in an accelerating rotarod apparatus where the motor learning was incremental for 4–6 days. In both cerebellar protocols, learning was accompanied by a robust long-lasting, but reversible, increase in the number and total length of filopodia emerging from the mossy fibres. These new terminals were making contact with dendrites of the Golgi cells in the granular layer. In the case of one learning session of fear conditioning, growth was observed in lobulus V, but not in lobulus IX. This growth lasted a few days and excess filopodia were lost within 8–10 days. In the 4–6 days of rotarod learning, the morphological changes were present in lobulus IX, but not in lobulus V, and the number and total length of filopodia increased in parallel with the duration of the learning period. In conclusion, in both paradigms, learning is specifically associated with the growth of feed-forward inhibition connectivity, thus suggesting in both paradigms a relationship with the processes of memory consolidation.

The potentiation of this feed-forward inhibition in the granular layer described at morphological level [70] complements a similar potentiation of the feed-forward inhibition described in the molecular layer at physiological level [66], and it is likely that both mechanisms collaborate to improve memory efficiency. In addition, the morphological findings at the input side of the cerebellar cortex, in addition to providing interesting data about general mechanisms on the way to select and store information [see 71], add evidence to the concept of the involvement of the cerebellum in emotion.

Concluding Remarks

From this overview, it is evident that the cerebellum is closely connected with the autonomic nervous system and with the world of emotions. In animal models, the principal region involved in these functions has been identified in lobuli III to VII of the vermis. In humans, there is an additional involvement of the hemispheres at higher emotional levels.

At least in some models, the vermis is important for the consolidation mechanisms of fear learning and memory, but this does not imply that the cerebellum is the site of a permanent emotional memory trace.

The debate on the participation of the cerebellum in higher cognitive functions is interesting, but it is beyond the scope of our review. We focussed on the participation of the cerebellum to the world of emotions which does not necessarily involve cognition. It is possible that the cerebellum is simply involved in the control of the expression of emotions. An illustration of the cerebellar participation in the circuit of the emotional memory may be found in LaBar and Cabeza [72]. The importance of this aspect of cerebellar research is quite evident considering the hypothesized cerebellar malfunctioning in psychiatric diseases [73] and particularly in schizophrenia [74–76] and autism [77–81] which are characterized behaviourally by clear emotion processing impairments.

Conflict of Interest The author declares that he has no conflict of interest.

References

1. Glickstein M, Strata P, Voogd J. Cerebellum: history. Neuroscience. 2009;162:549–59.
2. Malacarne V. Nuova esposizione della vera struttura del cervelletto umano. Torino: Briolo; 1776.
3. Malacarne V, Bonnet C. Sulla nevro-encefalotomia. Lettere anatomico-fisiologiche di Vincenzo Malacarne e di Carlo Bonnet. Pavia: s.i.t.; 1791.
4. Rolando L. Saggio sopra le vera struttura del cervello dell'uomo e degli animali e sopra le funzioni del sistema nervoso. Sassari: Stamperia da S.S.R.M; 1809.
5. Flourens P. Recherches expérimentales sur les propriétés et les fonctions du système nerveux dans les animaux vertébrés. Paris: Crevot; 1824.
6. Ito M. The cerebellum and neural control. New York: Raven Press;1984.
7. Dow RS, Moruzzi G. The physiology and pathology of the cerebellum. Minneapolis: The University of Minnesota Press; 1958.
8. Leiner HC, Leiner AL, Dow RS. Does the cerebellum contribute to mental skills? Behav Neurosci. 1986;100:443–54.
9. Sultan F. Analysis of mammalian brain architecture. Nature. 2002;415:133–4.
10. Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. Annu Rev Neurosci. 2009;32:413–34.
11. Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the processing of single words. J Cogn Neurosci. 1989;1:153–70.
12. Doron KW, Funk CM, Glickstein M. Fronto-cerebellar circuits and eye movement control: a diffusion imaging tractography study of human cortico-pontine projections. Brain Res. 2010;1307:63–71.
13. Smith Jr OA, Nathan MA. Inhibition of the carotid sinus reflex by stimulation of the inferior olive. Science. 1966;154:674–5.
14. Snider RS. Recent contribution to the anatomy and physiology of the cerebellum. Arch Neurol Psychiatry. 1950;64:196–219.
15. Aas JE, Brodal P. Demonstration of topographically organized projections from the hypothalamus to the pontine nuclei: an experimental anatomical study in the cat. J Comp Neurol. 1988;268:313–28.
16. Anand BK, Malhotra CL, Singh B, Dua S. Cerebellar projections to limbic system. J Neurophysiol. 1959;22:451–7.

17. Dietrichs E, Haines DE. Observations on the cerebello-hypothalamic projection, with comments on non-somatic cerebellar circuits. Arch Ital Biol. 1985;123:33–9.
18. Haines DE, Dietrichs E, Sowa TE. Hypothalamo-cerebellar and cerebello-hypothalamic pathways: a review and hypothesis concerning cerebellar circuits which may influence autonomic centers affective behavior. Brain Behav Evol. 1984;24:198–220.
19. Supple Jr WF. Hypothalamic modulation of Purkinje cell activity in the anterior cerebellar vermis. Neuroreport. 1993;4:979–82.
20. Newman PP, Paul DH. The representation of some visceral afferents in the anterior lobe of the cerebellum. J Physiol. 1969;182:195–208
21. Newman PP, Paul DH. The projection of splanchnic afferents on the cerebellum of the cat. J Physiol. 1969;202:223–7.
22. Rubia FJ. The projection of visceral afferents to the cerebellar cortex of the cat. Pflugers Arch. 1970;320:97–110.
23. Langhof H, Höppener U, Rubia FJ. Climbing fiber responses to splanchnic nerve stimulation. Brain Res. 1973;53:232–6.
24. Perrin J, Crousillat J. Responses of single units in the inferior olive nucleus to stimulation of the splanchnic afferents in the cat. J Auton Nerv Syst. 1980;2:15–22.
25. Perciavalle V, Apps R, Bracha V, Delgado-García JM, Gibson AR, Leggio M, et al. Consensus paper: current views on the role of cerebellar interpositus nucleus in movement control and emotion. Cerebellum. 2013;12:738–57.
26. Ledoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155–84.
27. Sacchetti B, Scelfo B, Strata P. Cerebellum and emotional behavior. Neuroscience. 2009;162:756–62.
28. Schmahmann JD. From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. Hum Brain Mapp. 1996;4:174–98.
29. Berntson GG, Torello MW. The paleocerebellum and the integration of behavioural function. Physiol Psychol. 1982;10:2–12.
30. Snider RS, Maiti A. Cerebellar contributions to the Papez circuit. J Neurosci Res. 1976;2:133–46.
31. Supple WFJR, Leaton RN, Fanselow MS. Effects of cerebellar vermal lesions on species-specific fear responses, neophobia, and taste-aversion learning in rats. Physiol Behav. 1987;39:579–86.
32. Supple Jr WF, Kapp BS. The anterior cerebellar vermis: essential involvement in classically conditioned bradycardia in the rabbit. J Neurosci. 1993;13:3705–11.
33. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998;121:561–79.
34. Maschke M, Schugens M, Kindsvater K, Drepper J, Kolb FP, Diener HC, et al. Fear conditioned changes of heart rate in patients with medial cerebellar lesions. J Neurol Neurosurg Psychiatry. 2002;72:116–8.
35. Sacchetti B, Baldi E, Lorenzini CA, Bucherelli C. Cerebellar role in fear-conditioning consolidation. Proc Natl Acad Sci U S A. 2002;99:8406– 11.
36. Sacchetti B, Sacco T, Strata P. Reversible inactivation of amygdala and cerebellum but not perirhinal cortex impairs reactivated fear memories. Eur J Neurosci. 2007;25:2875–84.
37. Leaton RN, Supple Jr WF. Cerebellar vermis: essential for long-term habituation of the acoustic startle response. Science. 1986;232:513–5.
38. Lopiano L, de'Sperati C, Montarolo PG. Long-term habituation of the acoustic startle response: role of the cerebellar vermis. Neuroscience. 1990;35:79–84.
39. Batini C, Benedetti F, Buisseret-Delmas C, Montarolo PG, Strata P. Metabolic activity of intracerebellar nuclei in the rat: effect of inferior olive inactivation. Exp Brain Res. 1984;54:259–65.
40. Raichle ME, Mintun MA. Brain work and brain imaging. Annu Rev Neurosci. 2006;29:449–76.
41. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, et al. Dissociating pain from its anticipation in the human brain. Science. 1999;284:1979–81.
42. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, et al. Subcortical and cortical brain activity during the feeling of selfgenerated emotions. Nat Neurosci. 2000;3:1049–56.
43. Singer T, Seymour B, O'doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. Science. 2004;303:1157–62.
44. Supple Jr WF, Sebastiani L, Kapp BS. Purkinje cell responses in the anterior cerebellar vermis during Pavlovian fear conditioning in the rabbit. Neuroreport. 1993;4:975–8.
45. Marr D. A theory of cerebellar function. J Physiol. 1969;202:437–70.
46. Albus JS. A theory of cerebellar function. Math Biosci. 1971;10:25–61.
47. Ito M, Kano M. Long-lasting depression of parallel fiber-Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. Neurosci Lett. 1982;33:253–8.
48. Lev-Ram V,Wong ST, Storm DR, Tsien RY. A new form of cerebellar long-term potentiation is postsynaptic and depends on nitric oxide but not cAMP. Proc Natl Acad Sci U S A. 2002;99:8389–93.
49. Lev-Ram V, Mehta SB, Kleinfeld D, Tsien RY. Reversing cerebellar long-term depression. Proc Natl Acad Sci U S A. 2003;100:15989–93.
50. Rogan MT, Stäubli UV, LeDoux JE. AMPA receptor facilitation accelerates fear learning without altering the level of conditioned fear acquired. J Neurosci. 1997;17:5928–35.
51. Sacchetti B, Scelfo B, Tempia F, Strata P. Long-term synaptic changes induced in the cerebellar cortex by fear conditioning. Neuron. 2004;42:973–82.
52. Gao Z, van Beugen BJ, De Zeeuw CI. Distributed synergistic lasticity and cerebellar learning. Nat Rev Neurosci. 2012;13:619–35.
53. Ly R, Bouvier G, Schonewille M, Arabo A, Rondi-Reig L, Léna C, et al. T-type channel blockade impairs long-term potentiation at the parallel fiber-Purkinje cell synapse and cerebellar learning. Proc Natl Acad Sci U S A. 2013;110:20302–7.
54. Rahmati N, Owens CB, Bosman LW, Spanke JK, Lindeman S, Gong W, et al. Cerebellar potentiation and learning a whisker-based object localization task with a time response window. J Neurosci. 2014;34:1949–62.
55. Zhu L, Scelfo B, Hartell NA, Strata P, Sacchetti B. The effects of fear conditioning on cerebellar LTP and LTD. Eur J Neurosci. 2007;26:219–27.
56. Berthier NE, Moore JW. Cerebellar Purkinje cell activity related to the classically conditioned nictitating membrane response. Exp Brain Res. 1986;63:341–50.
57. Gould TJ, Steinmetz JE. Changes in rabbit cerebellar cortical and interpositus nucleus activity during acquisition, extinction, and backward classical eyelid conditioning. Neurobiol Learn Mem. 1996;65:17–34.
58. Thompson RF. Neural mechanisms of classical conditioning in mammals. Philos Trans R Soc Lond B Biol Sci. 1990;2:331–7.
59. Schreurs BG, Tomsic D, Gusev PA, Alkon DL. Dendritic excitability microzones and occluded long-term depression after classical conditioning of the rabbit's nictitating membrane response. J Neurophysiol. 1997;77:86–92.
60. Schreurs BG, Gusev PA, Tomsic D, Alkon DL, Shi T. Intracellular correlates of acquisition and long-term memory of classical conditioning in Purkinje cell dendrites in slices of rabbit cerebellar lobule HVI. J Neurosci. 1998;18:5498–507.
61. Zhu L, Scelfo B, Tempia F, Sacchetti B, Strata P. Membrane excitability and fear conditioning in cerebellar Purkinje cell. Neuroscience. 2006;140:801–10.
62. Lang EJ, Paré D. Similar inhibitory processes dominate the responses of cat lateral amygdaloid projection neurons to their various afferents. J Neurophysiol. 1997;77:341–52.
63. Li XF, Armony JL, Ledoux JE. GABAA and GABAB receptors differentially regulate synaptic transmission in the auditory

thalamo-amygdala pathway: an in vivo microiontophoretic study and a model. Synapse. 1996;24:115–24.
64. Wiltgen BJ, Sanders MJ, Ferguson C, Homanics GE, Fanselow MS. Trace fear conditioning is enhanced in mice lacking the delta subunit of the GABAA receptor. Learn Mem. 2005;12:327–33.
65. Eccles JC, Ito M, Szentàgothai J. The cerebellum as a neuronal machine. Berlin: Springer; 1967.
66. Scelfo B, Sacchetti B, Strata P. Learning-related long-term potentiation of inhibitory synapses in the cerebellar cortex. Proc Natl Acad Sci U S A. 2008;105:769–74.
67. Pouille F, Scanziani M. Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. Science. 2001;293:1159–63.
68. Lamsa K, Heeroma JH, Kullmann DM. Hebbian. LTP in feed-forward inhibitory interneurons and the temporal fidelity of input discrimination. Nat Neurosci. 2005;916-24.
69. Mittmann W, Koch U, Hausser M. Feed-forward inhibition shapes the spike output of cerebellar Purkinje cells. J Physiol. 2005;563:369–78.
70. Ruediger S, Vittori C, Bednarek E, Genoud C, Strata P, Sacchetti B, et al. Learning-related feedforward inhibitory connectivity growth required for memory precision. Nature. 2011;473:514–8.
71. Caroni P, Chowdhury A, Lahr M. Synapse rearrangements upon learning: from divergent-sparse connectivity to dedicated sub-circuits. Trends Neurosci. 2014;37:604–14.
72. LaBar KS, Cabeza R. Cognitive neuroscience of emotional memory. Nat Rev Neurosci. 2006;7:54–64.
73. Heath RG, Franklin DE, Shraberg D. Gross pathology of the cerebellum in patients diagnosed and treated as functional psychiatric disorders. J Nerv Ment Dis. 1979;167:585–92.
74. Lungu O, Barakat M, Laventure S, Debas K, Proulx S, Luck D, et al. The incidence and nature of cerebellar findings in schizophrenia: a quantitative review of fMRI literature. Schizophr Bull. 2012;39:797–806.
75. Picard H, Amado I, Mouchet-Mages S, Olié JP, Krebs MO. The role of the cerebellum in schizophrenia: an update of clinical, cognitive, and functional evidences. Schizophr Bull. 2008;34:155–72.
76. Shakiba A. The role of the cerebellum in neurobiology of psychiatric disorders. Neurol Clin. 2014;32:1105–15.
77. Brielmaier J, Matteson PG, Silverman JL, Senerth JM, Kelly S, Genestine M, et al. Autism-relevant social abnormalities and cognitive deficits in engrailed-2 knockout mice. PLoS One. 2012;7(7): e40914.
78. Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, Blatt GJ, et al. Consensus paper: pathological role of the cerebellum in autism. Cerebellum. 2012;11:777–807.
79. Piochon C, Kloth AD, Grasselli G, Titley HK, Nakayama H, Hashimoto K, et al. Cerebellar plasticity and motor learning deficits in a copy-number variation mouse model of autism. Nat Commun. 2014;5:5586.
80. Reith RM, McKenna J, Wu H, Hashmi SS, Cho SH, Dash PK, et al. Loss of Tsc2 in Purkinje cells is associated with autistic-like behavior in a mouse model of tuberous sclerosis complex. Neurobiol Dis. 2013;51:93–103.
81. Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM, et al. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. Nature. 2012;488:647–51.