



## Research paper

## Cerebellar vermis contributes to the extinction of conditioned fear



A. Utz<sup>a</sup>, M. Thürling<sup>a</sup>, T.M. Ernst<sup>a</sup>, A. Hermann<sup>b</sup>, R. Stark<sup>b</sup>, O.T. Wolf<sup>c</sup>, D. Timmann<sup>a,\*</sup>, C.J. Merz<sup>c,d</sup>

<sup>a</sup> Department of Neurology, University Clinic Essen, University of Duisburg-Essen, Hufelandstrasse 55, 45147 Essen, Germany

<sup>b</sup> Department of Psychotherapy and Systems Neuroscience and Bender Institute of Neuroimaging, Justus Liebig University Giessen, Otto-Behaghel-Str. 10H, 35394 Giessen, Germany

<sup>c</sup> Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum, Universitätsstr. 150, 44780 Bochum, Germany

<sup>d</sup> Department of Biological and Clinical Psychology, University of Trier, Johanniterufer 15, 54290 Trier, Germany

## HIGHLIGHTS

- Re-analysis of a human fMRI study on fear extinction focusing on the cerebellum.
- The anterior vermis plays a role in the extinction of conditioned fear.
- The cerebellum is likely part of the neural circuitry underlying extinction of conditioned fear.

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## ABSTRACT

The cerebellum is known to contribute to the acquisition and retention of conditioned motor and emotional responses. Eyeblink conditioning and fear conditioning have been studied in greatest detail. Whereas a considerable number of studies have shown that the cerebellum is also involved in extinction of conditioned eyeblink responses, the likely contribution of the cerebellum to extinction of conditioned fear responses has largely been ignored. In the present study, we analyzed functional brain imaging data (fMRI) of previous work investigating extinction of conditioned fear in 32 young and healthy men, in which event-related fMRI analysis did not include the cerebellum. This dataset was analyzed using a spatial normalization method optimized for the cerebellum. During fear acquisition, an unpleasant electric shock (unconditioned stimulus; US) was paired with one of two pictures of geometrical figures (conditioned stimulus; CS+), while the other picture (CS−) was never paired with the US. During extinction, CS+ and CS− were presented without the US. During the acquisition phase, the fMRI signal related to the CS+ was significantly higher in hemispheric lobule VI in early compared to late acquisition ( $p < .05$ , permutation corrected). During the extinction phase, the fMRI signal related to the contrast CS+ > CS− was significantly higher within the anterior vermis in early compared to late extinction ( $p < .05$ , permutation corrected). The present data show that the cerebellum is not only associated with the acquisition but also with the extinction of conditioned fear.

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**Abbreviations:** BOLD, blood oxygenation level dependent; CR, conditioned response; CS, conditioned stimulus; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; FWHM, full width at half maximum; LTP, long-term potentiation; MPRAGE, magnetization prepared rapid acquisition gradient echo; PET, positron emission tomography; SCR, skin conductance response; SPM, statistical parametric mapping; SUIT, spatially unbiased infratentorial (and cerebellar) template; SVC, small volume correction; US, unconditioned stimulus.

\* Corresponding author.

E-mail address: [dagmar.timmann-braun@uni-due.de](mailto:dagmar.timmann-braun@uni-due.de) (D. Timmann).

## 1. Introduction

In cued fear conditioning, the association of an initially neutral conditioned stimulus (CS, for example a sound) with an unpleasant unconditioned stimulus (US, often an electric shock) is learned. After successful acquisition, the presentation of the CS already provokes the fear response, which is the conditioned response (CR, e.g. freezing, change of heart rate). During extinction learning the CS is presented alone leading to a decrease of fear responses [1].

In classical eyeblink conditioning an involvement of the cerebellum during acquisition is well known [2,3]. There is also animal and human data showing that the cerebellum is equally involved

in extinction of conditioned eyeblinks [4]. The cerebellum is also known to play a role in acquisition of conditioned fear, although this has been studied in less detail. Whereas the intermediate cerebellum appears to be most important in acquisition of conditioned eyeblinks, the vermis plays a role in fear conditioning [5]. For example, Supple and Leaton [6] showed that lesions of the vermis severely attenuated the acquisition and retention of conditioned fear responses in rats, with no weakening of the fear response to the US. Sacchetti et al. [7] found that the vermis is important in consolidation of learned fear. Likewise, impaired acquisition of fear conditioning has been shown in humans with vermal lesions [8].

Because the cerebellum is known to contribute both to the acquisition and extinction of conditioned eyeblink responses, and there is evidence that the cerebellum contributes to acquisition of conditioned fear, it is reasonable to assume that the cerebellum is part of the neural circuitry underlying extinction of conditioned fear as well. The contribution of the cerebellum to extinction of learned fear, however, has only rarely been assessed. For example, there are no animal lesion or recording studies examining the possible contribution of the cerebellum to fear extinction. Likewise, no studies in humans with cerebellar lesions have been performed. As yet, brain imaging studies focused on the contributions of the amygdala and other fear-related cerebral areas on extinction of conditioned fear. The cerebellum has largely been ignored. Earlier brain imaging studies did not include the cerebellum in their field of view, in later studies the cerebellum was scanned but usually not considered a region of interest [9–11]. Linnman et al. [12] report fear extinction related activation in the cerebellum in supplementary materials, but do not discuss their observation. As yet, only Kattoor et al. [13] focused on cerebellar activation related to acquisition and extinction. Different to most other fear conditioning studies, however, they used rectal extensions as US.

In the present study a previously published data set of classical fear conditioning in young and healthy subjects was analyzed using optimized normalization methods of the cerebellum [11]. In the study of Merz et al. [11] cerebral areas, known to be involved in fear conditioning, that is the amygdala, anterior cingulate gyrus, hippocampus, medial frontal cortex, nucleus accumbens and orbitofrontal cortex, were analyzed. The cerebellum, however, was not considered a region of interest. In the present study, we hypothesized that the activation of the cerebellum is also associated with the extinction of learned fear.

## 2. Materials and methods

Previously published data by Merz et al. [11] were analyzed. The experimental procedure is presented in short. The normalization procedure of the cerebellum, which has additionally been performed in the present study, will be described in more detail.

Thirty-two healthy men (mean age 24.6 years, standard deviation 3.9 years, range 18–35 years) participated in this fMRI experiment. In the original study, half of all participants were given cortisol after acquisition, the other half placebo, to measure its effect on extinction learning. Since no significant between group differences (cortisol vs. placebo) during extinction were observed in the cerebellum, data analyses were based on all 32 subjects.

One of two pictures (a gray rhomb or square displayed on a black background) was used as CS+ and was paired with an unpleasant but not painful electrical stimulation (US) applied to the left shin. The CS– consisted of the other picture and was not paired with the US. In extinction trials, neither the CS– nor the CS+ was paired with the US. 16 CS+ and 16 CS– were presented for 8 s for acquisition as well as for extinction. 7.9 s after CS+ onset the US was presented for 100 ms during acquisition. The intertrial interval was randomly jittered and lasted between 9.5 and 12 s. Each phase lasted about

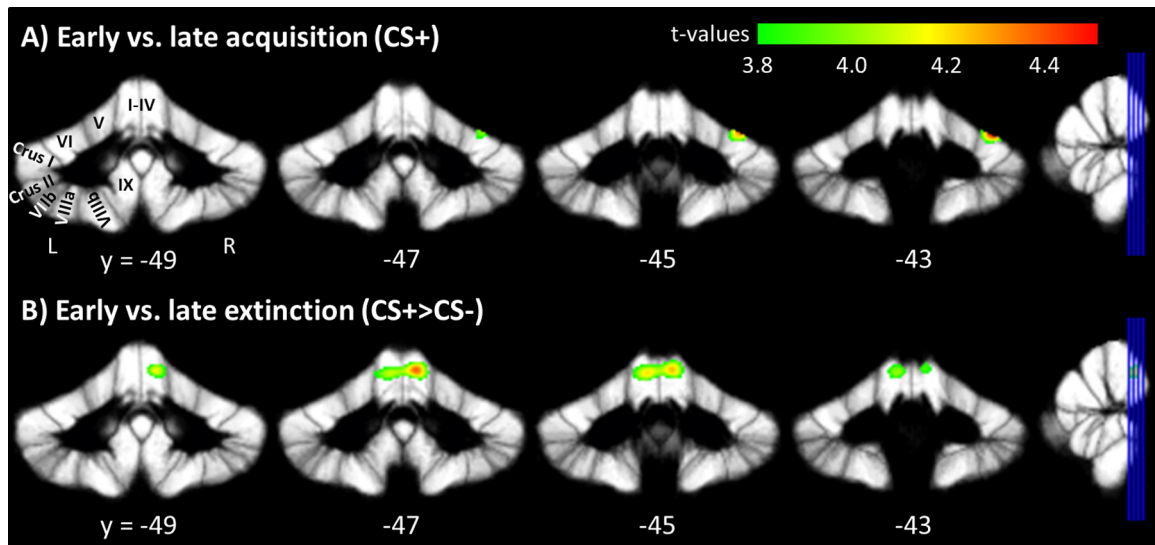
10 min in total. To slow down acquisition and extinction and to make learning non-trivial a partial reinforcement schedule was used. Only in 10 out of 16 trials the CS+ was linked with the US. The first half of acquisition was defined as early acquisition and the second half as late acquisition. The same was done for extinction. After the acquisition phase participants had to decide whether the CS+ or CS– preceded electrical stimulation to confirm contingency awareness (for details see [11]). Skin conductance responses (SCRs) were obtained as a behavioral measure of fear responses (for details see [11]).

During acquisition and extinction fMRI data was obtained using a 1.5 T whole body tomograph (Siemens Symphony with a quantum gradient system) with a standard head coil. Structural imaging included 160 T1-weighted sagittal images (MPRAGE; 1 mm slice thickness). Functional imaging encompassed 245 volumes for fear acquisition and 245 volumes for fear extinction. They were registered using a T2\*-weighted gradient echo planar imaging sequence with 25 slices covering the whole brain (slice thickness = 5 mm; 1 mm gap; descending slice order; TA = 100 ms; TE = 55 ms; TR = 2.5 s; flip angle = 90°; field of view = 192 mm × 192 mm; matrix size = 64 pixel × 64 pixel). The axial slices were oriented parallel to the orbitofrontal cortex-bone transition and a gradient echo field map sequence was measured before both functional runs to get information for unwarping  $B_0$  distortions [11].

Due to an incomplete steady state of magnetization the first three volumes of each session were discarded. Realigned EPI images were co-registered to the T1 volume but otherwise unsmoothed. First level single subject analysis was calculated using an event related design. Individual normalizations were calculated using the SUI toolbox (version 2.7) in SPM8 (<http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm>; [14]). For the T1-weighted images a brain extraction was performed, and the resulting images were segmented using the isolate function provided by the SUI toolbox. Segmented images were used to calculate the normalization to the spatially unbiased atlas template (SUIT) of the human cerebellum [14]. For each subject the normalization was applied to the first level contrast images, and images were subsequently smoothed by a three-dimensional convolution with an isotropic Gaussian kernel of 12 mm full width at half maximum (FWHM). Relevant first level contrast images included CS+ and CS+ > CS– in early and late acquisition, and CS+ and CS+ > CS– in early and late extinction (for details on the complete statistical model see [11]). CS+ alone was included in accordance with eyeblink conditioning studies, in which a CS– is usually not presented [4,5]. Normalized contrast images were used for second-level random-effects analysis. Time-dependent changes in fMRI signal between early and late acquisition as well as extinction were compared using the flexible factorial design with group (cortisol vs. placebo) as between subjects factor, stimulus (CS+ vs. CS– or CS+ alone) and phase (early vs. late) as within subjects factor. The “explicit masking” option was used in SPM. Small volume correction (SVC), based on the probabilistic atlas of the cerebellar cortex (Cerebellum\_SUIT.nii), was performed. A height threshold of  $p < .05$  (permutation corrected, 1000 permutations) was used. To depict the localization of cerebellar activation the maximum probability atlas of the cerebellum cortex was used (Cerebellum\_SUIT\_maxprob.nii) [15].

## 3. Results

SCRs were significantly higher for the CS+ than for the CS– during acquisition. Likewise, SCRs were higher for the CS+ than for the CS– during early extinction, although the difference was less compared to the acquisition phase. SCRs and the difference between CS+ and CS– showed a significant decline both during late



**Fig. 1.** Cerebellar cortical activations during (A) fear acquisition and (B) fear extinction. (A) Shows activation related to the contrast early minus late acquisition for CS+. (B) Shows activation related to early minus late extinction for CS+ > CS-. Threshold levels of  $p < .05$  (permutation corrected). Activation of the cerebellar lobules is mapped onto coronal slices of the SUI maximum probability template (Cerebellum-SUIT-maxprob.nii). Positions of slices are indicated in the sagittal view (from  $y = -49$  mm to  $y = -43$ ). L = left; R = right;  $y$  = SUI coordinates (mm); Roman numerals indicate cerebellar lobules according to Schmahmann et al. [29].

acquisition and late extinction compared to the early phases (for details concerning SCR results see [11]).

The activation of the right hemispheric lobule VI was higher during early acquisition compared to late acquisition concerning the CS+ ( $p < .05$ , permutation corrected;  $T > 3.8$ ; Fig. 1a; Table 1). Increased activation was observed in the lateral parts of lobule VI. No significant differences were found when comparing the contrast CS+ vs. CS- in early and late acquisition.

Activation related to the contrast CS+ vs. CS- was significantly higher in the anterior parts of the vermis bilaterally (lobules I–IV) in early fear extinction compared to late fear extinction ( $p < .05$ , permutation corrected;  $T > 3.8$ ; Fig. 1b, Table 1). Increased activation was highest on the right side and extended to the left side of the vermis. No significant activation difference was found when comparing the contrast CS+ in early and late extinction. None of the group effects (cortisol vs. placebo) were significant.

#### 4. Discussion

The present fMRI study provides evidence that the cerebellum is involved not only in the acquisition but also in the extinction of conditioned fear. During fear acquisition activation was observed in the right lateral cerebellar hemisphere within lobule VI (CS+, early > late acquisition), whereas activation was found in the anterior vermis during extinction (CS+ vs. CS-, early > late extinction). The acquisition and extinction of conditioned fear responses during fMRI was confirmed by changes in skin conductance responses (SCRs).

Activation of lobule VI related to acquisition of conditioned fear has also been reported by others [16]. Whereas in the present study activation was found in right lobule VI, activation was observed in the left cerebellar hemisphere by Frings et al. [16]. Differences

may be explained by differences in study design (classical fear conditioning vs. fear-conditioned potentiation of the acoustic startle response) and brain imaging methods [fMRI vs. positron emission tomography (PET) study]. Lobule VI is known to contribute both to sensorimotor and cognitive functions [17]. In their review of neuroimaging and human cerebellar lesion data, Stoodley and Schmahmann [17] report that lobule VI is involved in emotional processing, for example when viewing emotional compared to neutral faces [18], or when observing another person's pain [19]. The present and previous findings suggest that lobule VI is equally involved in conditioning of the emotion fear. Because the lateral cerebellum is thought to support cognitive processes, lobule VI may be involved in the cognitive components of learned fear as opposed to the vermis which is involved in learning of fear-related autonomic and skeletal responses (see below). Activation of lobule VI has also been found in response to nociceptive stimuli and unpleasant pictures [20]. Thus, activation of lobule VI may reflect the expression of fear because SCRs were higher in early compared to late acquisition in the present study, comparable to the activation pattern in lobule VI. Responses to aversive stimuli in the study by Moulton et al. [20], however, were found more medially than in the present study and may involve the sensorimotor parts of lobule VI.

Based on previous animal and human lesion data, activation related to acquisition of conditioned fear would have been expected in the cerebellar vermis. The cerebellar vermis likely supports conditioning of fear-related changes in autonomic function, like respiration, heart rate and blood pressure, and defensive motor behavior [21], even in the absence of contingency awareness [22]. Anatomical connections of the vermis with the brainstem and hypothalamus explain an influence of the vermis over automatic functions [23]. Learned fear-related changes in autonomic function

**Table 1**

Cerebellar cortex activation related to fear acquisition and fear extinction. Threshold levels of  $p < .05$  (permutation corrected, 1000 permutations). L = left; R = right; x, y, z = SUI coordinates (mm); Roman numerals indicate cerebellar lobules according to Schmahmann et al. [29].

	Localization	x	y	z	t-Value	Voxel
Early acquisition > late acquisition CS+	R lobule VI	35	-44	-24	4.37	144
Early extinction > late extinction CS+ > CS-	L + R vermis (I-IV)	7	-47	-11	4.36	735

may have been too weak to lead to significant changes of the fMRI signal in the vermis in the present study.

The CS+ was related to a significantly higher blood oxygenation level dependent (BOLD) signal in early compared to late acquisition in lobule VI. The BOLD signal in the cerebellar cortex has been shown to be increased by synaptic input of climbing and mossy fibers, as well as inhibitory interneurons, but to be relatively independent of the spiking rate of the Purkinje cells [24]. Sacchetti et al. [7,25,26] found evidence that long-term potentiation (LTP) at the parallel fiber/Purkinje cells synapse is the neural correlate of fear conditioning. The increased BOLD signal during early acquisition is consistent with LTP; that is increased synaptic input of the parallel fibers at the Purkinje cells, underlying fear conditioning. Although learning likely occurred within the very first trials, this cannot explain why fMRI signal dropped in the later acquisition phase. LTP is thought to persist once acquisition is achieved [7]. In a previous fMRI study, however, a similar time course of the BOLD signal was found during acquisition of conditioned eyeblinks with an increase in early acquisition and a subsequent decrease of BOLD signal as soon as the maximum number of CRs was achieved. Decreased mossy fiber input or local inhibitory processes might explain this unexpected finding [3].

Extinction related activation was found in the anterior vermis. Animal studies have shown that the anterior vermis (vermal lobules III–V), but also vermal lobule VI are involved in acquisition and retention of conditioned fear [7,25–27]. As stated in the introduction, until now, no animal studies have been performed to investigate cerebellar contributions to extinction of learned fear. There is evidence from the eyeblink conditioning literature that learning within the cerebellar cortex is bidirectional, i.e., that plastic changes underlying acquisition are reversed during extinction (see [28] for details). Analogous to extinction of conditioned eyeblinks, one may assume that plastic changes related to acquisition are reversed during extinction learning [28]. As a consequence, acquisition and extinction would take place, at least in part, in the same vermal areas. Furthermore, LTP and therefore parallel fiber synaptic input would decline during extinction. Reduced BOLD signal related to the contrast CS+ minus CS– in late compared to early extinction is consistent with this view. However, compared to acquisition, a different time course of extinction learning needs to be assumed.

In the present study, increased vermal activation during early extinction learning was observed for the differential contrast CS+ > CS–, but not for the CS+ alone. However, a significant larger vermal response has been reported related to the CS+ in early compared to late fear extinction in a PET study [12]. Kattoor et al. [13] reported larger vermal activation in early compared to late extinction related for the differential contrast CS+ > CS in visceral aversive extinction learning, the contrast CS+ was not considered. In that fMRI study, cerebellar activation related to extinction was more widespread and observed also in the lateral cerebellum including lobule VI. Of note, however, based on imaging studies alone it cannot be excluded that the observed change in vermal activation is related to a decrease in motor and autonomic fear responses during extinction learning.

No extinction-related activation was observed in the posterolateral hemisphere. As stated above, the contribution of the vermis and posterolateral hemispheres to fear conditioning are likely different. Different processes may underlie extinction of autonomic/skeletal and cognitive fear responses. On the other hand, similar to lack of vermal activation during acquisition, extinction-related changes in the posterolateral hemisphere may not have been sufficient to cause significant changes of the fMRI signal.

In conclusion, the present study confirmed previous findings that the cerebellum contributes to acquisition of conditioned fear. Furthermore, and more importantly, the present study showed that

the cerebellar vermis is likely involved in fear extinction learning. Future human lesion and imaging studies as well as animal inactivation and recording studies are warranted to provide further evidence that the cerebellum is part of the neural circuitry underlying extinction of conditioned fear.

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