The Cerebellum (2019) 18:166–177
https://doi.org/10.1007/s12311-018-0973-y

ORIGINAL PAPER

Extinction and Renewal of Conditioned Eyeblink Responses in Focal Cerebellar Disease

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Published online: 28 August 2018

Abstract

Extinction of conditioned aversive responses (CR) has been shown to be context-dependent. The hippocampus and prefrontal cortex are of particular importance. The cerebellum may contribute to context-related processes because of its known connections with the hippocampus and prefrontal cortex. Context dependency of extinction can be demonstrated by the renewal effect. When CR acquisition takes place in context A and is extinguished in context B, renewal refers to the recovery of the CR in context A (A-B-A paradigm). In the present study acquisition, extinction and renewal of classically conditioned eyeblink responses were tested in 18 patients with subacute focal cerebellar lesions and 18 age- and sex-matched healthy controls. Standard delay eyeblink conditioning was performed using an A-B-A paradigm. All cerebellar patients underwent a high-resolution T1-weighted brain MRI scan to perform lesion-symptom mapping. CR acquisition was not significantly different between cerebellar and control participants allowing to draw conclusions on extinction. CR extinction was significantly less in cerebellar patients. Reduction of CR extinction tended to be more likely in patients with lesions in the lateral parts of lobule VI and Crus I. A significant renewal effect was present in controls only. The present data provide further evidence that the cerebellum contributes to extinction of conditioned eyeblink responses. Because acquisition was preserved and extinction took place in another context than acquisition, more lateral parts of the cerebellar hemisphere may contribute to context-related processes. Furthermore, lack of renewal in cerebellar patients suggest a contribution of the cerebellum to context-related processes.

Keywords Cerebellum · Eyeblink conditioning · Extinction · Renewal · Lesion-symptom mapping

Introduction

Eyeblink and fear conditioning have been extensively studied to unravel the neural correlates of associative learning in humans and various animal models [1–7]. The simplest form of eyeblink conditioning, i.e., short delay conditioning, is considered as a model for motor learning [8, 9]. Fear conditioning is considered as a model for emotional learning [10, 11]. The acquisition of conditioned eyeblink responses is critically dependent on the cerebellum, particularly on intermediate lobule VI of the cerebellar cortex and the interposed nuclei [8, 12–14]. The amygdala is of major importance in learning of conditioned fear responses [11, 15]. In recent years, the neural mechanisms underlying extinction of conditioned fear responses have been studied in great detail [15], whereas studies of extinction of conditioned eyeblink responses remain comparatively sparse. A deeper understanding of extinction-related processes is of general interest because of their likely importance both in the pathophysiology and treatment of anxiety and chronic pain disorders [16, 17]. Exposure therapy has been a mainstay of treatment in phobias and other anxiety disorders for many years and is increasingly applied in the treatment of pain-related fear in chronic pain conditions [16, 18]. Exposure therapy, however, is often only partly effective. Context dependency of extinction learning likely plays a role.

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Extinction of learned fear responses has been found to be context-dependent and to involve more extended brain areas than acquisition [19, 20]. Context dependency of fear extinction is most commonly demonstrated by the renewal effect [19, 21]. Here, acquisition takes place in context A and extinction in a different context B. If subjects return to context A and continue to receive extinction trials, conditioned fear responses reappear despite successful extinction in context B (A-B-A renewal paradigm). There is good experimental evidence that the amygdala is under the inhibitory control of the ventromedial prefrontal cortex (vmPFC) which leads to retrieval of extinction memory in a context, which is the same as the extinction context (see "extinction recall network" in Fig. 1 [23, 24 for reviews]). In case the context is different from the extinction context, i.e., the renewal situation, the amygdala is under the excitatory control of the anterior cingulate cortex (ACC), and the initial fear memory is retrieved (see "CR recall network" in Fig. 1). The vmPFC and ACC likely receive contextual information from the hippocampus [23, 25]. In addition to this context-dependent, newly learned inhibition, there is also experimental evidence that part of the original learned fear memory is erased during extinction [26].

Similarly to the proposed parallels in the acquisition process [27], there is initial evidence that extinction of conditioned eyeblink responses works according to the same principles as extinction of conditioned fear responses. Firstly, animal recording and inactivation studies suggest that acquisition-related plasticity within the cerebellar cortex is at least partly reversed during extinction of conditioned eyeblink responses (see "intrinsic cerebellar circuitry" in Fig. 1; [28–30]). Recent fMRI data in healthy human subjects are in accordance with the hypothesis that part of the original cerebellar memory is erased during extinction of conditioned eyeblink responses [31]. Secondly, it has long been proposed that a new inhibitory learning process plays an additional role in extinction of conditioned eyeblinks ([32], [33], for reviews). Hu et al. [33] proposed that the same hippocampus-vmPFC-amygdala extinction neural network may be at work, which is known to suppress the expression of conditioned fear responses (see "extinction recall network" in Fig. 1). Inhibition of the amygdala may decrease the reactivity of the pontine nuclei (and therewith the cerebellum) to the conditioned stimulus (CS). Reduced salience of the CS may result in extinction. There is evidence from lesion [34, 35] and local field recording studies in rodents [36] and positron emission brain tomography studies in humans (e.g., [37], [38]) that prefrontal areas contribute to extinction. There is also evidence from early animal studies that the hippocampus is involved in extinction of conditioned eyeblinks. Lesions and dysfunction of the hippocampus impair extinction of conditioned eyeblinks (e.g., [39]).

There are reasons to believe, however, that the role of the cerebellum in extinction goes beyond the intrinsic unlearning and/or external inhibition of learned associations within the intermediate cerebellum. The posterolateral cerebellar hemispheres have structural connections with the anterior cingulate cortex (ACC) and the hippocampus [40–42]. There are no known anatomical connections between the cerebellum and ventromedial prefrontal cortex, at least in the monkey

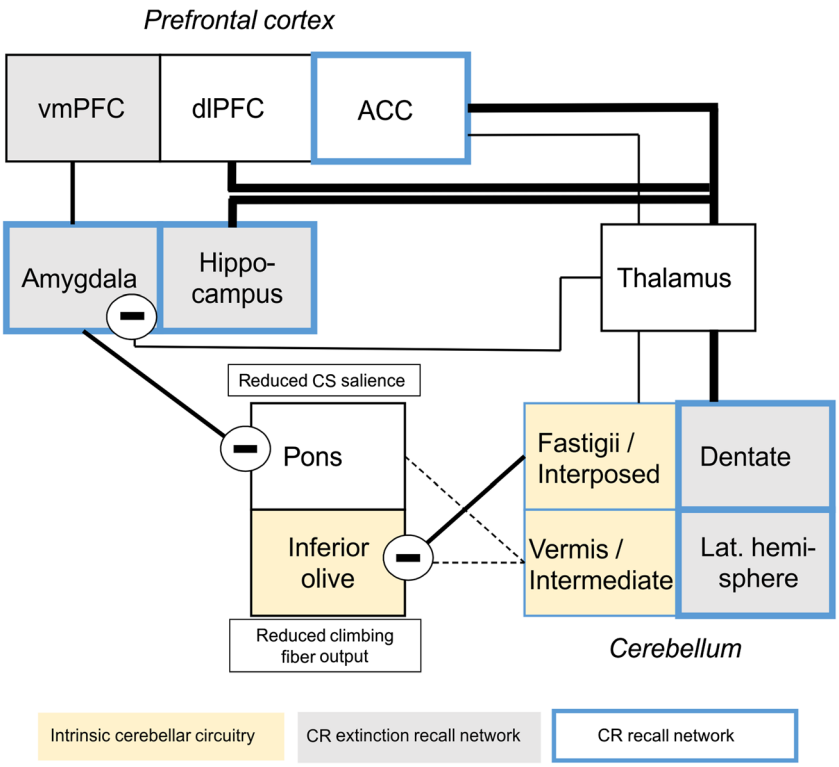

Fig. 1 The hypothesized role of the cerebellum in the brain network underlying extinction of conditioned responses. The cerebellum may support context-related effects in extinction via its connections to the hippocampus. In addition, the posterolateral cerebellar hemispheres and dentate nuclei have known connections to the dlPFC. The dlPFC may play a role in extinction by shifting attention to the context [22]. For further details, see introduction. ACC = anterior cingulate cortex, CS = conditioned stimulus, CR = conditioned response, dlPFC = dorsolateral prefrontal cortex, vmPFC = ventromedial prefrontal cortex

(vmPFC; [43]). Resting-state fMRI, however, shows functional connectivity between vmPFC and the cerebellar hemispheres in humans [44]. As stated above, the ACC is involved in the return of fear memory during renewal, whereas the vmPFC is most important in recall of fear extinction memory in the extinction context [23]. One may therefore postulate that the posterolateral cerebellum interacts with the prefrontal cortex during extinction recall primarily in the renewal situation. In fact, using a cognitive predictive learning task, Kinner et al. [45] found that connectivity of the vmPFC with the ACC and the cerebellar hemisphere was increased in the renewal situation. There is also initial evidence that the cerebellum is involved in dysfunction of the fear extinction cerebral network in anxiety disorders. Milad et al. [46] reported that patients with posttraumatic stress disorder (PTSD) had increased activation of ACC and the cerebellum during (abnormally reduced) extinction recall in the extinction context, whereas activation of vmPFC and hippocampus was reduced compared to controls. A fuller understanding of the role of the cerebellum in extinction may open new treatment options. For example, non-invasive cerebellar stimulation or cerebellar-dependent motor learning tasks may be able to improve malfunctioning of the neural network underlying extinction in anxiety and chronic pain disorders [47].

Renewal effects have been reported in short delay eyeblink conditioning in healthy humans subjects in an A-B-A renewal paradigm [21]. The aim of the present study was to test the hypothesis that the cerebellum contributes to the modulation of context-related processes involved in extinction of conditioned eyeblink responses. We predicted that the renewal effect was reduced in patients with lesions of the posterolateral cerebellum compared to healthy controls.

Materials and Methods

Participants

Eighteen participants with subacute focal cerebellar lesions (11 male, 7 female, mean age 53.2 years, range 24 to 79 years) and 18 age- and sex-matched healthy controls (11 male, 7 female, mean age 53.5 years, range 22 to 85 years) took part in the present study. Fourteen patients presented with ischemic cerebellar stroke, two patients with cerebellar hemorrhage, and two had undergone resection of a cerebellar hemangioblastoma.

Neurological examination was performed by an experienced neurologist. In order to quantify cerebellar deficits, the International Cooperative Ataxia Rating Scale (ICARS [48]) and the Scale for the Assessment and Rating of Ataxia (SARA [49]) were applied. The Inventory of Non-Ataxia Symptoms (INAS [50]) was used to quantify extracerebellar involvement. None of the control subjects had a history of neurological disease, and clinical examination revealed no neurological deficits. Neither patients nor controls were taking centrally acting medication except for antidepressants in two patients. All patients' characteristics are summarized in Table 1. Oral and written informed consent was obtained from all subjects. The study was approved by the ethics committee of the Medical Faculty of the University of Duisburg-Essen.

Eyeblink Conditioning

Standard short delay eyeblink conditioning was performed using an experimental paradigm which has been described in detail in Gerwig et al. [51] and Ernst et al. [52]. An in-house written software was used to control application of conditioned (CS) and unconditioned (US) stimuli. The software was programmed in DIAdem (National Instruments Corp., Austin, TX) and installed on a standard PC equipped with a multifunction I/O device (NI PCI-6221, National Instruments Corp., Austin, RX). A tone-CS was applied via headphones (70 decibels (dB), duration 550 ms) superimposed on a white background noise (60 dB) generated by an audiometer (AD229, Interacoustics, Middelfart, Denmark). An air puff-US was applied to the outer corner of one eye (strength of 4 bar at source, duration 100 ms) and coterminated with the US. CS und US were applied to the ipsilesional side in cerebellar patients and the right side in controls. The lesion was unilateral in all but three cerebellar patients. Two of the patients with bilateral lesions (Cer-6, Cer-16 in Table 1) received the US and CS on the right, and one patient on the left (Cer-9). Conditioned (CR) and unconditioned (UR) responses were recorded using surface electromyography (EMG). EMG electrodes (gold cup electrode, diameter 10 mm; GVB-geliMED KG, Bad Segeberg, Germany) were fixed on the orbicularis oculi muscles (below the lower eyelid) and on the nasal bridge.

At the beginning of the experiment five CS only and five US only trials were presented in a pseudorandom order (Fig. 2). This was followed by 80 paired CS-US trials (acquisition phase) in context A, 30 CS only extinction trials in context B (extinction phase), and 30 CS only extinction trials in context A (renewal phase). The inter-phase interval was 5 min, and this gave the participants enough time to change between rooms. The inter-trial interval (ITI) varied between 16, 18, and 20 s in a pseudorandom order (which was the same in all participants). To maintain vigilance subjects watched a silent movie during the experiment.

Contexts A and B were two different rooms. Room A was a small office room and room B a larger laboratory room. Room A was brightly lit, whereas room B was darkened. Two different in-house built eyeblink conditioning set-ups were used. Two different movies genres were shown to further enhance the difference between contexts A and B (context A: "The Artist" by Michel Hazanavicius, context B: "Spiderman" by Sam Raimi).

Table 1 Cerebellar subjects' clinical characteristics

ID	Age/sex/ handedness	Diagnosis	Time since onset of pathology	ICARS total [0–100]	ICARS posture and gait [0–34]	ICARS kinetic function [0–52]	ICARS speech [0–8]	ICARS oculomotor [0–6]	SARA [0–40]
Cer-1	60y/m/r	PICA stroke right	1 m	7	4	3	0	0	1.5
Cer-2	48y/f/r	PICA stroke right	2 m	6	5	1	0	0	1
Cer-3	59y/f/r	SCA stroke left	2 m	10	4	5	0	1	4
Cer-4	45y/m/r	PICA stroke left	2 m	5	2	3	0	0	2.5
Cer-5	24y/f/r	Hemangioblastoma right	2 m	0	0	0	0	0	0
Cer-6	44y/f/r	PICA/SCA strokes left and right	2 m	30	28	2	0	0	12.5
Cer-7	79y/m/r	Hemangioblastoma left	1 m	12	1	10	0	1	4
Cer-8	42y/m/r	PICA stroke right	3 m	8	3	5	0	0	3
Cer-9	63y/m/r	SCA stroke left and PICA stroke right	1 m	4	2	2	0	0	2.5
Cer-10	47y/m/r	Cerebellar hemorrhage left	1 m	8	8	0	0	0	4
Cer-11	54y/m/b	PICA stroke left	1 m	6	3	3	0	0	2
Cer-12	62y/m/b	PICA stroke left	2 m	6	2	2	0	2	3
Cer-13	56y/m/r	PICA stroke right	1 m	0	0	0	0	0	0
Cer-14	56y/f/r	Cerebellar hemorrhage left	2 m	5	4	1	0	0	3
Cer-15	62y/f/r	PICA stroke right	1 m	7	5	2	0	0	3.5
Cer-16	46y/f/r	PICA stroke left and right	2 m	1	1	0	0	0	1
Cer-17	58y/m/l	PICA stroke left	2 m	3	1	0	0	2	1
Cer-18	61y/m/r	PICA stroke right	1 m	9	6	0	0	3	3.5

Maximal possible ranges of ataxia (sub-)scores are given in brackets (0 = no ataxia)

Y years, *f* female, *m* male, *r* right, *l* left, *b* both, *PICA* posterior inferior cerebellar artery, *SCA* superior cerebellar artery, *m* months, *ICARS* International Cooperative Ataxia Rating Scale [48], *SARA* Scale for the Assessment and Rating of Ataxia [49]

Rectified EMG recordings were semi-automatically analyzed using in-house written software [53]. EMG responses which began after 150 ms of CS onset and prior to US onset were considered CRs. Responses within the first 150 ms after CS onset were considered as alpha responses [54]. CRs were not counted in trials which showed a spontaneous blink in the 300 ms prior CS onset [55]. CR area was quantified in the time interval between CR onset and US onset.

Statistical Analysis

Trials were divided into blocks of 10 trials each (acquisition phase: blocks 1–8, extinction phase: blocks 9–11, renewal phase: blocks 12–14). CR incidences were calculated as percentage of trials that showed a CR in each block. CR incidence was used as dependent measure. Analysis of variance (ANOVA) with repeated measures was performed to investigate potential group differences across blocks. Firstly, we analyzed potential group differences in the acquisition phase. CR incidences were compared between groups (cerebellar patients vs. controls) and across acquisition blocks (blocks 1–8). Secondly, group differences in extinction were analyzed. CR incidence in the last acquisition block was set as 100%. CR incidences were expressed in the extinction blocks as percentage of the last acquisition block. CR incidences were compared between groups (cerebellar patients vs. controls) and across the last acquisition and the three extinction blocks (blocks 8–11). Finally, renewal effects were compared between groups. CR incidences were compared between groups (cerebellar patients vs. controls) and the last extinction and first renewal block (blocks 11 and 12). Statistical tests were performed using the SPSS software (version 20, IBM Company, New York, USA). Differences were considered to be significant at $p < 0.05$. For all effects, the degrees of freedom were adjusted, if appropriate, according to Greenhouse and Geisser [56].

Magnetic Resonance Imaging and Lesion-Symptom Mapping

All cerebellar patients underwent a 1.5-T structural MRI scan (Magnetom Avanto, Siemens, Erlangen, Germany, 1.5 T). Images were acquired using an MPRAGE sequence (magnetization-prepared rapid acquisition gradient echo; 160 sagittal slices, TR = 2400 ms, TE = 3.53 ms, TI = 1200 ms, acquisition matrix 256 × 256, TA = 10:16 min, slice thickness 1 mm; non-interpolated isotropic voxel size 1 mm^3, flip angle = 8°) and a FLAIR sequence (fluid-attenuated inversion recovery;

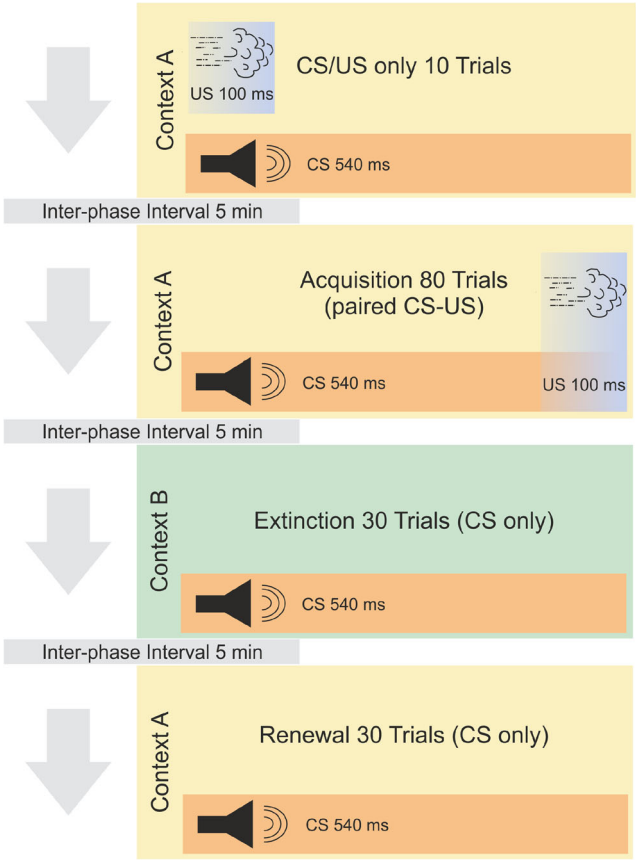

Fig. 2 Eyeblink conditioning paradigm (delay eyeblink conditioning). CS = conditioned stimulus, US = unconditioned stimulus. At the beginning, 5 CS only and 5 US only trials were presented. Acquisition phase: 80 paired trials. Extinction phase: 30 CS only trials. Renewal phase: 30 CS only trials. Inter-phase interval: 5 min. CS-US only trials, acquisition phase and renewal phase took part in context A, the extinction phase took part in context B

176 sagittal slices, TR = 6000 ms, TE = 356 ms, TI = 2200 ms, acquisition matrix 256 × 256, pMRI GRAPPA R = 2, TA = 7:00 min, slice thickness 1 mm; non-interpolated isotropic voxel size 1 mm^3). MRI scans were evaluated by an experienced neuroradiologist (SLG). None of the patients revealed extracerebellar pathology on MRI scans except mild to moderate cerebral small vessel disease in Cer-11.

Cerebellar lesions were manually drawn on axial, sagittal, and coronal slices of the anatomical MPRAGE images and saved as volumes of interest (VOI) using the MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron). Left-sided lesions were flipped onto the right cerebellar hemisphere. Normalization of the VOIs and MRI scans was performed by means of the SUIT atlas template of the cerebellum [57] and the SPM 12 software (Wellcome Department of Cognitive Neurology London, UK) based on MATLAB (Version R2014a, The MathWorks Inc., Natick, MA). Post-processing methods are described in more detail in Ernst et al. [52].

Subtraction analysis was performed using the MRIcron software. Voxels were considered which were at least 25% more likely to be lesioned in patients with abnormal behavior. Because subtraction analysis is descriptive, Liebermeister tests were performed for statistical confirmation using the non-parametric mapping (NPM) software as part of MRIcron [58–60]. Results are reported at a permutation-corrected threshold of $p < 0.05$.

Results

CR Acquisition

Both control subjects and cerebellar patients were able to acquire conditioned responses. Examples of eyeblink recordings in individual subjects are shown in Fig. 3. Group data is shown in Fig. 4. Both patients and controls showed a significant increase of CR incidences across the acquisition blocks (block effect: $F(3.875, 131.748) = 11.193$, $p < 0.001$, ANOVA with repeated measures). This increase was not significantly different between cerebellar patients and controls (block by group interaction: $F(7, 131.7) = 0.126$, $p = 0.97$). Although group mean CR incidence was numerically lower in cerebellar patients (27.3%, standard deviation (SD) 14.4) compared to controls (32.3%, SD 18.0), the group effect was not significant [$F(1, 34) = 0.874$, $p = 0.356$]. Lack of difference between groups is further illustrated in Fig. 5a. None of the patients (red circles) showed a total CR incidence that was below the worst performing control participant (black circles). Only two control participant performed better than the best performing patient.

Because acquisition was not significantly different between groups, lesion-symptom mapping was not performed. Overlap of all cerebellar lesions and individual cerebellar lesions are shown in Fig. 6a, b. Maximum lesion overlap was observed in Crus II ($n = 7$; $x = 98–109$ mm, $y = 20–32$ mm, $z = 34–41$ mm, SUIT coordinates; [57]). Note that maximum lesion overlap was only two in lobule VI. The interposed nuclei were spared in most cerebellar subjects except for small lesions in Cer-5, Cer-9, and Cer-10.

CR Extinction

In the extinction phase, both cerebellar patients and controls showed a decrease of CR incidences across blocks (Figs. 3 and 4). In the control group, CR incidence showed a sharp decline already in the first extinction block. Already in the first extinction block, CR incidences were lower than in the first acquisition block. The decrease was slower in cerebellar patients. CR incidence remained higher in the last extinction block compared to the first acquisition block.

For statistical analysis, CR incidences in extinction blocks were expressed as percentage of the last acquisition block which was set as 100% (Fig. 7). One control and one cerebellar patient (Cer-14, Con-15) showed no conditioned responses

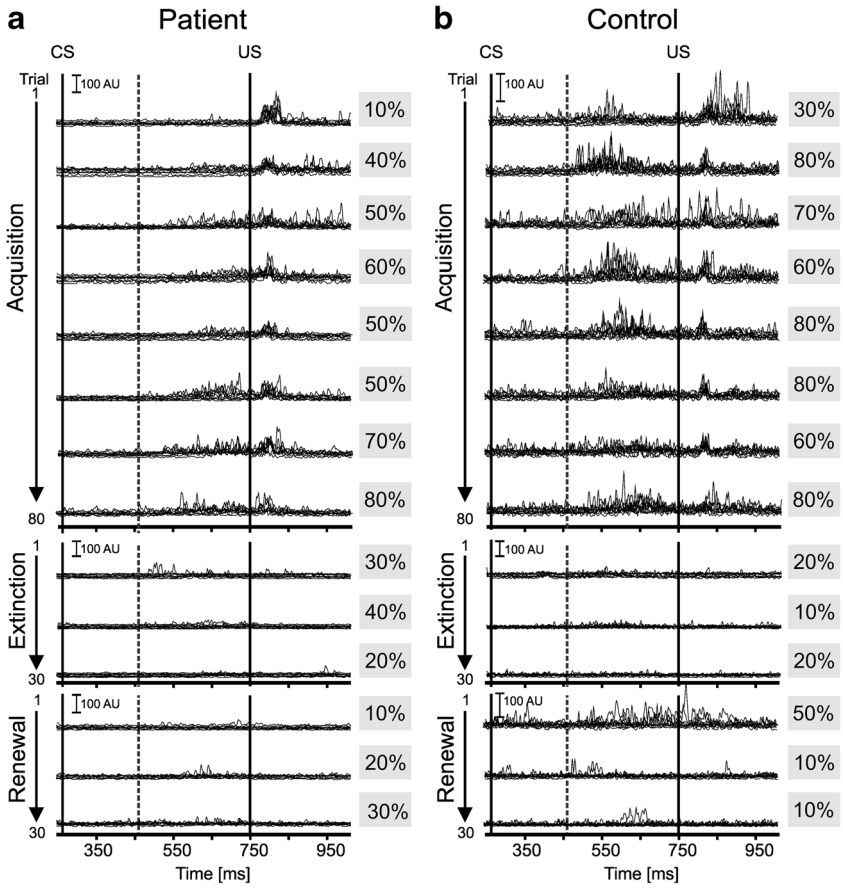

Fig. 3 Eyeblink recordings in a 44-year-old female cerebellar patient (Cer-6) and a 59-year-old male control subject (Con-17). Rectified and filtered (100 Hz) EMG data of the orbicularis oculi muscles of 80 paired CS-US acquisition trials (first ten trials on the top, last ten trial on the bottom), 30 CS only—extinction trials and 30 CS only—renewal trials are shown for the eye tested. Recordings are shown in blocks of ten superimposed trials. The first (solid) vertical line indicates the beginning of the tone (CS), the second (solid) vertical line the beginning of the air puff (US). Responses occurring within the 150-ms interval after CS onset (dotted vertical line) were considered alpha responses

in the last acquisition block and were excluded from statistical analysis. One control participant (Con-18) showed an increase of CR incidence of 30% in extinction. The subject was considered an outlier and also excluded.

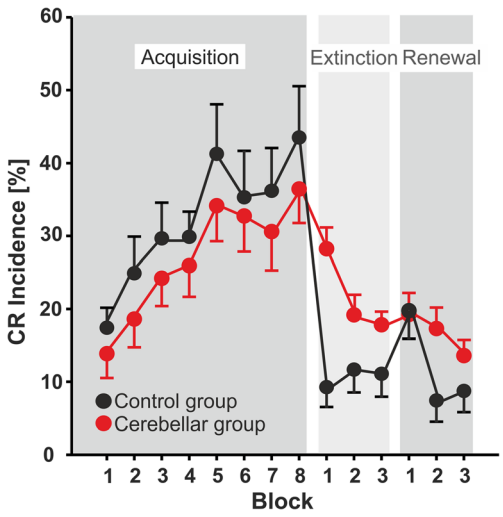

Fig. 4 **a**, **b** Mean CR incidences and standard errors (SE) in the cerebellar group (red) and the control group (black) during acquisition (8 blocks, 10 CS-US trials per block), extinction (3 blocks, 10 CS only trials per block), and renewal phases (3 blocks, 10 CS only trials per block)

ANOVA with repeated measures showed a significant difference between cerebellar patients and controls (group effect: $F(1,31) = 25.916$, $p < 0.001$), a significant block by group interaction ($F(3,93) = 7.55$, $p < 0.001$) and block effect (across the last acquisition and the three extinction blocks; $F(3,93) = 38.595$, $p < 0.001$).

To perform lesion-symptom mapping, the amount of extinction was calculated in each participant. The difference between the CR incidence in the last acquisition block and in the last extinction block was calculated and expressed as percentage of the CR incidence in the last acquisition block. Cerebellar patients were considered as impaired who showed less extinction than the worst performing control subject (< 57%; $n = 12$; see Fig. 5b). Cerebellar patients who showed extinction within the range of the controls were considered as unimpaired ($n = 5$; Fig. 5b).

Subtraction analysis revealed that extinction was 25% more likely to be impaired in patients with lesions affecting lateral parts of lobule VI and adjacent parts of Crus I (Fig. 8). Liebermeister test showed no significant difference between groups at a permutation-corrected threshold of $p < 0.05$ ($Z = 2.12$). There was no significant correlation between lesion size and extinction performance ($R = 0.043$; $p = 0.87$; Pearson's correlation coefficient).

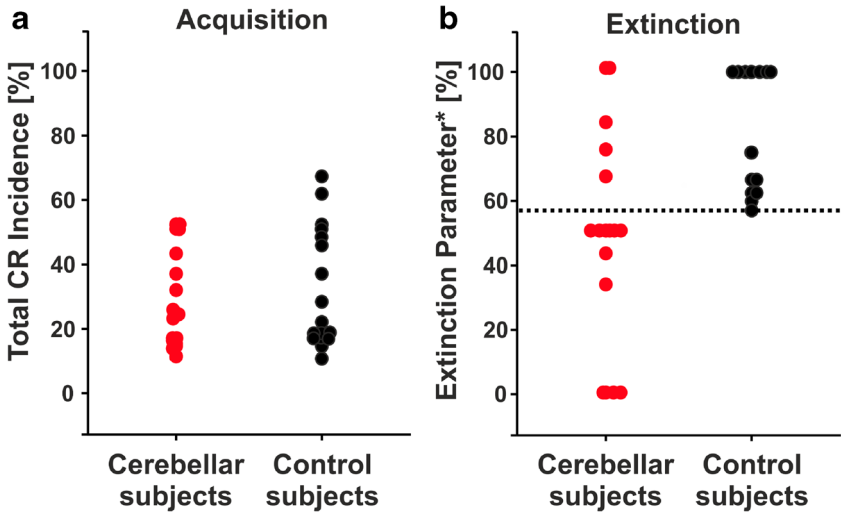

Fig. 5 Mean CR incidences in each individual cerebellar subject (red) and control subject (black) in **a** the acquisition phase (total CR incidence) and **b** the extinction phase. The extinction parameter* was calculated as follows: ((CR incidence in acquisition block 8 minus CR incidence in extinction block 3) / CR incidence in acquisition block 8) × 100. The dotted line indicates extinction in the worst performing control (57% reduction of CR incidence)

CR Renewal

The same three participants (Cer-14, Con-15, Con-18) were excluded from CR renewal analysis who have been excluded from CR extinction analysis for reasons given above. Controls showed an increase of CR incidences in the first block of the renewal phase compared to the last extinction block (Figs. 3 and 4). This was followed by a renewed decline in the second and third renewal block. In cerebellar patients, there was no difference between the last extinction and the first renewal block. CR incidences continued to decline in the subsequent renewal blocks.

ANOVA with repeated measures revealed no significant difference between cerebellar participants and controls comparing the last extinction block and the first renewal block (group effect: $F(1,34) = 0.726$, $p = 0.49$) and no significant

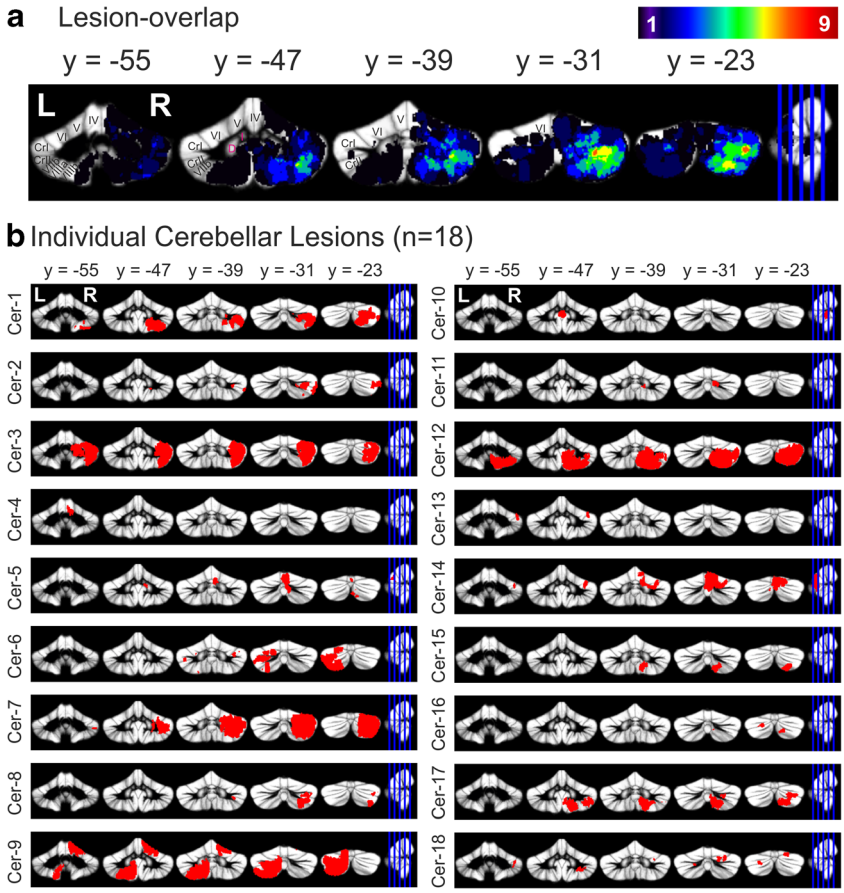

Fig. 6 Overlap of all cerebellar lesions (**a**) and individual cerebellar lesions (**b**). Left-sided lesions are flipped to the right side. Lesions are superimposed on the maximum probability SUIT template of the cerebellum [57]. Color code in **a** refers to the number of lesions which overlap in a given voxel (1 = purple, 9 = red). Positions of the coronal slices are indicated in a sagittal view of the SUIT template, y = SUIT coordinate. Nomenclature of cerebellar lobules (I–X) according to Schmahmann et al. [61], D = dentate nucleus, I = interposed nucleus L = left, R = right

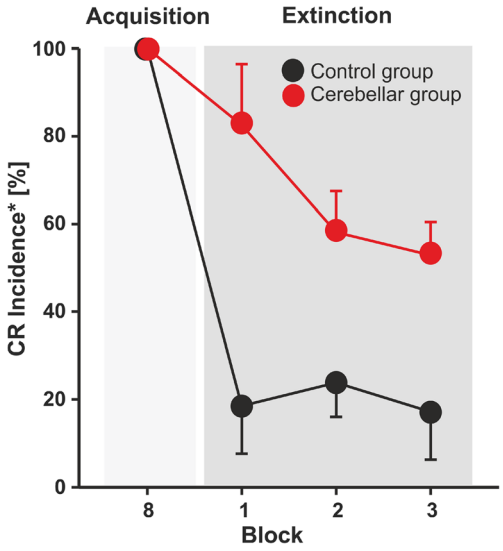

Fig. 7 Mean CR incidence and SE in the last acquisition block and the three extinction blocks in the cerebellar group (red) and control group (black). CR incidences* are expressed as percentage of the last acquisition block (block 8) which was set as 100%. Subjects Cer-14, Con-15, and Con-18 were excluded (see the main text for details)

block by group interaction ($F(1,34) = 2.408$, $p = 0.13$). The block effect was significant ($F(1,34) = 5.144$, $p = 0.03$). Considering each group separately, controls showed a significant difference between the last extinction and first renewal block (i.e., renewal effect; $F(1,15) = 7.5$; $p = 0.015$) that was not observed in cerebellar patients ($F(1,16) = 0.261$; $p = 0.616$). Because extinction was impaired in 12 cerebellar patients in the first place, analysis was repeated considering only the five patients with preserved extinction. Numerically, CR incidence was higher in the first renewal block (mean 14% SD 5.5) compared to the last extinction block (mean 8%, SD 8.4%). The difference was not significant (block effect: $F(1,4) = 1$; $p = 0.374$). Lesion-symptom mapping was not performed. Cerebellar patients would have to be excluded who showed lack of extinction. The remaining number of patients ($n = 5$) was too small to perform meaningful lesion-symptom mapping.

CR Area

Surface EMG recordings did not allow comparing absolute EMG amplitudes between groups (because of differences in skin thickness, etc.). To compare CR amplitudes in the extinction and renewal phases between groups, individual CR areas were expressed as percentage of mean CR area in all acquisition trials in each individual subject. As expected (because of the normalization procedure), in the acquisition phase, there was no significant difference between patients and controls ($t(31) = -0.029$, $p = 0.97$; unpaired t test) (Fig. 9). In the extinction phase, normalized CR area was significantly smaller in control subjects compared to patients ($t(26) = 2.458$, $p = 0.021$). Findings further support our observation that extinction effects were diminished in cerebellar patients. In the renewal phase, normalized CR area increased compared to the extinction phase. The increase was more prominent in controls. Statistical comparison showed no significant difference between the extinction and the renewal phase, neither in controls ($t(26) = -1.872$, $p = 0.073$) nor in cerebellar patients ($t(23{,}387) = -0.713$, $p = 0.48$).

Alpha Responses

Alpha responses were less in extinction and renewal phases compared to acquisition phase in both control subjects and cerebellar patients (phase effect: $F(2,34) = 21.16$, $p < 0.001$). There was no significant group difference ($F(1,34) = 2.89$, $p = 0.09$) and no significant group by phase interaction

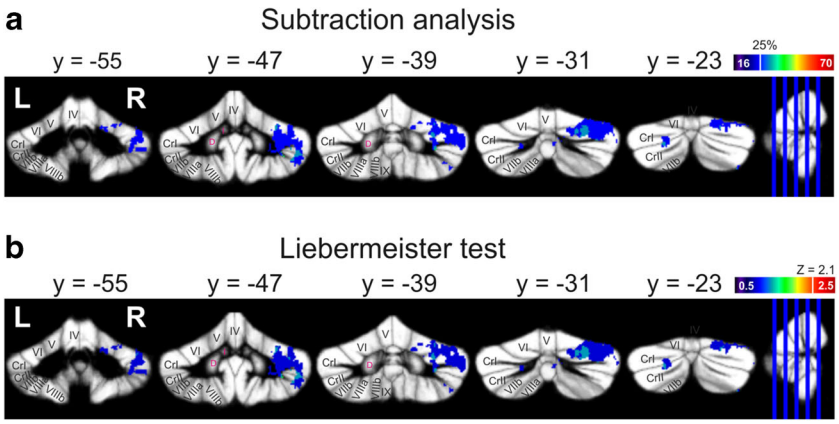

Fig. 8 Lesion-symptom mapping considering extinction. Results of **a** subtraction analysis and **B** Liebermeister tests superimposed on the maximum probability SUIT template of the cerebellum [57]. Color code in subtraction analysis: percentage of consistency (threshold of 25% indicated by white line). Color code in Liebermeister test: Z values (permutation-corrected threshold of $p < 0.05$, $Z = 2.12$ indicated by a white line). Note that results of the Liebermeister test are shown at a trend level and did not reach significance. Positions of the coronal slices are indicated in a sagittal view of the SUIT template, y = SUIT coordinate. Nomenclature of cerebellar lobules (I–X) according to Schmahmann et al. [61], D = dentate nucleus, I = interposed nucleus, L = left, R = right

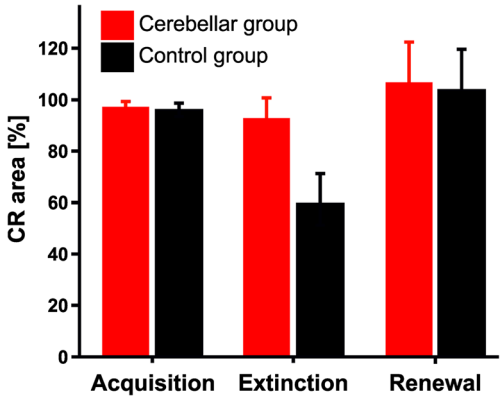

Fig. 9 Mean normalized CR area and standard error (SE) in the cerebellar group (red) and the control group (black) in the acquisition, extinction, and renewal phases. CR area is expressed as percentage of mean CR area in the acquisition phase. Subjects Cer-14, Con-15, and Con-18 were excluded (see the main text for details)

($F(2,34) = 0.12$, $p = 0.82$). Mean absolute number of alpha responses ± SD in each phase and group were as follows: acquisition phase: patients 4.72 ± 3.1, controls 3.83 ± 3.51; extinction phase: patients 1.89 ± 1.64, controls 1.27 ± 1.6; renewal phase: patients 2.06 ± 1.56, controls 1 ± 0.84.

Discussion

The main finding of the present study is that extinction of conditioned eyeblink responses was significantly reduced in a group of patients with focal cerebellar lesions who showed preserved acquisition. Because extinction took place in another context than acquisition, which led to fast extinction in controls, one possible interpretation of the present results is that the cerebellum contributes to context-related processes in extinction. This is further supported by a lack of renewal effect in cerebellar participants.

CR Acquisition

Acquisition of conditioned responses was intact in the present patient population. At first sight, this finding appears to be at variance with findings in the literature [3, 5, 54]. Analysis of lesion localization, however, showed that the cerebellar areas known to be critically involved in acquisition of conditioned eyeblink responses were largely intact, i.e., intermediate parts of lobule VI and interposed nuclei [14, 62, 63]. Most cerebellar patients suffered from strokes in the territory of the posterior inferior cerebellar artery (PICA). In PICA strokes, acquisition is commonly intact [51]. Likewise, Ernst et al. [52] showed that eyeblink conditioning was intact in participants with surgical lesions which spared the intermediate parts of lobule VI and lobule Crus I. In the present patient population, the majority of lesions were in the lateral parts of Crus II. Different to the study by Ernst et al. [52], we were unable to subdivide cerebellar patients in learners and non-learners (compare Fig. 5a in the present study and Fig. 3 in Ernst et al. [52]). None of the present patients performed below the worst performing control. In the present study, most cerebellar participants suffered from stroke. As a consequence mean age (53.2 SD 11.7 years) was significantly higher compared to the participants included in Ernst et al. [52]. Here, cerebellar patients suffered from surgery of benign cerebellar tumors which typically occur in childhood or youth (mean age 25.6, SD 6.2 years). Aging is known to significantly reduce eyeblink conditioning [64] and likely contributed to low conditioning rates in a subset of controls.

Of note, the lack of significant reduction of CR acquisition in cerebellar participants compared to controls allowed for comparison of extinction. In most previous human cerebellar lesions studies, the interpretation of findings in extinction was hampered because cerebellar patients did not acquire conditioned responses in the first place [53, 65], see also [52] for the discussion.

CR Extinction

In cerebellar patients, the rate and the amount of extinction of conditioned eyeblinks was significantly less compared to controls. Because acquisition was not significantly different between groups, and extinction took place in a different context than acquisition, this finding is consistent with a contribution of the cerebellum to context-related processes in extinction. In the following, the present findings will be discussed in more detail. As outlined in the introduction, different processes likely contribute to extinction. First, there is evidence from animal inactivation, recording and modeling studies that learning is reversed in the cerebellar cortex during extinction [28–30]. Bidirectional learning has to take place in the same cerebellar areas. Because areas involved in acquisition were spared, bidirectional learning was likely preserved in the present patient population. In addition to bidirectional learning and therefore erasure of part of the original memory, there is initial evidence that a newly learned inhibition also contributes to extinction of conditioned eyeblink responses [33]. Forebrain areas likely play an important rule which were intact in the present patient population. The newly learned inhibition is known to be context-dependent in extinction of learned fear [19, 20]. In the present study, controls showed a sharp decline of conditioned responses already in the first extinction block. This finding is in accordance with a previous study of our group investigating extinction of the visual threat eyeblink response (VTER). The VTER is assumed to be a naturally learned conditioned eyeblink response [55]. Claassen et al. [66] found that healthy subjects showed faster extinction in a context, which was different from the acquisition context, compared to a context which was the same. Likewise, it has been shown that the time course of extinction of learned fear responses was changed in a context that is different from the acquisition context [67].

The present findings suggest that cerebellar areas which are different from acquisition/intrinsic extinction-related areas, contribute to context-related processes in extinction. In fact, most lesions were localized in the posterolateral areas of the cerebellar hemispheres which have known connections with forebrain areas including the prefrontal cortex and hippocampus [68–71]. Results of lesion-symptom mapping further support this interpretation. Subtraction analysis showed that cerebellar subjects with lesions of lateral parts of lobule VI extending into Crus I were more likely to show impaired extinction. These areas are more lateral than the areas commonly assumed to be involved in CR acquisition [51, 14]. Findings are in accordance with a previous fMRI study of extinction learning in a cognitive associative learning paradigm [22]. Chang et al. found context-related cerebellar activation in the posterolateral cerebellum mostly in Crus II and adjacent parts of Crus I in healthy subjects [22]. The present lesion-symptom mapping findings, however, were present only at a trend level and need to be confirmed in future studies using a larger and preferably younger cerebellar population. As stated above, age effects likely prevented the classification of subjects into learners and non-learners. It cannot be excluded that acquisition was at least partially impaired in part of the subjects confounding lesion-symptom mapping of context-related effects. Likewise, although no significant group difference in CR acquisition was found, CR incidence was numerically lower in cerebellar patients than in controls. Furthermore, although no obvious difference was observed, performance of the observed conditioned responses may be different in patients than in controls. Therefore, it cannot be excluded that dysfunction in CR acquisition reduced the extinction process at least in part. Furthermore, no cognitive tests were performed. Thus, we cannot exclude that group differences in attention and working memory played a role. Another limitation of the study is that no control condition was included where the context was the same in acquisition and extinction. Patients with circumscribed cerebellar lesions are rare. The available patient population did not allow to form a second group to test the control condition. In previous studies of our group, however, extinction of conditioned eyeblink responses was performed in the same context as acquisition. Here, the degree of extinction was less in healthy subjects compared to findings in the present study supporting context-related effects of extinction (compare Fig. 2 of the present paper with Fig. 3 in Gerwig et al. [51] and Fig. 1 in Gerwig et al. [72]). A comparison with previous data in cerebellar patients is limited because here acquisition rate was significantly reduced.

CR Renewal

Control subjects showed a significant renewal effect. Thus, conditioned responses returned in extinction trials in the acquisition context after successful extinction had occurred in a context which was different from the acquisition context (A-B-A paradigm). These findings agree with the previous study from Grillon et al. [21] who also found significant renewal effects in a short delay eyeblink conditioning paradigm in healthy subjects. In their study, an A-B-A/B paradigm was used, i.e., subjects received extinction trials in the third phase both within the extinction and the acquisition context. Following successful extinction in context B, CR incidence was significantly higher in the acquisition context compared to the extinction context in the renewal phase. The only other study which examined renewal effects in eyeblink conditioning examined the VTER [66]. Here, CR incidence was close to 50% at the end of the extinction phase, and no renewal effects were found. The highly overlearned character of the VTER likely prevented the observation of the renewal effect.

In contrast to the control subjects, no renewal effect was present in the cerebellar participants. This finding further supports the hypothesis that the cerebellum modulates context-related processes in extinction. We used an A-B-A design. Based on the literature of extinction of learned fear, in this situation, context information is mediated via the hippocampus to the ACC [25, 73]. In analogy to the inhibitory effect of the vmPFC on the amygdala during recall of extinction proposed by Hu et al. [33], the ACC may have an excitatory effect on the amygdala which may increase the reactivity of the pontine nuclei (and therewith the cerebellum) to the conditioned stimulus (CS). Increased salience of the CS may result in recall of the eyeblink CR. Cerebellar lesions may reduce this context-dependent renewal effects via its known connections to the ACC and/or hippocampus. Alternatively, the cerebellar connection to the dorsolateral prefrontal cortex (dlPFC) may play a role ([74]; see also Fig. 1). The role of the dlPFC in extinction is thought to be the initial shift of attention to the next context [75]. It has to be noted, however, that extinction was significantly impaired in many of the cerebellar subjects. Just as an impaired acquisition limits validity of extinction analyses, an impaired extinction allows only limited conclusions on renewal.

The present findings further widen the possible spectrum of cerebellar functions. In recent years, evidence has been accumulating that the role of the cerebellum goes beyond motor control and extends to the cognitive, emotional, and behavioral domains [76, 77]. The present findings suggest that the cerebellum may contribute to context-related extinction processes. Because extinction-related processes are of particular importance in emotional control, it would be of interest to evaluate whether the cerebellum contributes to the extinction of learned fear in the future. Extinction of learned fear has been found to be altered in anxiety and chronic pain disorders [46, 78]. Impaired extinction of initially meaningful aversive emotional reactions is thought to contribute to the development of these diseases. Thus, anxiety or chronic pain disorders may be more

likely (or less likely) to occur in cerebellar patients. This, however, has never been assessed systematically in cerebellar populations.

Conclusions

The present data suggest that the contribution of the cerebellum to extinction of conditioned eyeblink responses goes beyond the local unlearning of the original association. Posterolateral areas of the cerebellum appear to contribute to context-related processes of extinction. Findings need to be confirmed in future studies.

Funding Information This work was funded by German Research Foundation (DFG) grant SFB 1280 (A05) to DT.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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