The cerebellum is involved in processing of predictions and prediction errors in a fear conditioning paradigm

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**Figure 1.** Experimental paradigm and overview of individual events. CS = conditioned stimulus; US = unconditioned stimulus. For further details see text.

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Figure 2. Behavioral data. (a) Group mean valence and arousal ratings for CS+ and CS- during acquisition and extinction. (b) Example of bandpass filtered individual SCR in a paired CS+/US trial depicting response interval windows and displaying a distinct response in each interval. (c) Group mean SIR. (d) Group mean TIR. Please note the different scales of the y-axis used for illustration purposes. Error bars represent standard errors of the mean.

acq 1, acq 2 = early and late acquisition; CS = conditioned stimulus; ext 1, ext 2 = early and late extinction; FIR = first interval response; hab = habituation; SCR = skin conductance response; SIR = second interval response; TIR = third interval response; US = unconditioned stimulus.

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Figure 2—figure supplement 1. SCR related to CS presentation: FIR and SIR in comparison. Group mean (a) FIR and (c) SIR related to the CS presentation. In (b,d) mean differences of FIR and SIR to CS+ and CS- presentations are displayed (CS+ - CS-). Note, that (c) is identical to Figure 2c in the main document. Error bars represent standard errors of the mean. acq 1, acq 2 = early and late acquisition; CS = conditioned stimulus; ext 1, ext 2 = early and late extinction; FIR = first interval response; hab = habituation; SCR = skin conductance response; SIR = second interval responses.

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Figure 3. Differential activations during fear acquisition. (a–c) Differential cerebellar activations during fear acquisition in SUIT space projected on a cerebellar flatmap (Diedrichsen and Zotow, 2015). (d–f) Corresponding differential whole brain activations in MNI normalized space. All contrasts collapsed over early and late acquisition blocks and calculated using TFCE and familywise error correction (p<0.05). CS = conditioned stimulus; L = left; MNI = Montreal Neurological Institute standard brain; R = right; SUIT = spatially unbiased atlas template of the cerebellum; TFCE = threshold-free cluster-enhancement; US = unconditioned stimulus.

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Figure 3—figure supplement 1. Changes in differential cerebellar activation across acquisition and extinction blocks based on F-tests. (a) Related to the prediction of the US (contrast ‘CS+ > CS-’), and (b) related to the omission of the US (contrast ‘no-US CS+ > no US CS-’) [p<0.05 FWE corrected, using TFCE; http://dbm.neuro.uni-jena.de/tfce/]. Mean β values across blocks are shown in the inserts. Note that all no-US CS+ trials were considered as a single block which was compared first against the early and then against the late ‘no-US post CS-’ block. (c) Cerebellar activation during extinction trials considering the contrast ‘no-US CS+ > no US post CS-’ (p<0.05 FWE corrected, TFCE). CS = conditioned stimulus; FWE = familywise error; TFCE = threshold-free cluster-enhancement; US = unconditioned stimulus.

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**Figure 3—figure supplement 2.** Effect of physiological denoising and smoothing kernel. Differential cerebellar activations during fear acquisition (p<0.05 FWE corrected, TFCE) in SUIT space projected on a cerebellar flatmap (Diedrichsen and Zotow, 2015): following application of (a–c) a 4 mm smoothing kernel on the normalized functional images and without use of RETROICOR physiological denoising, (d–f) 4 mm smoothing kernel and physiological denoising, and (g–i) physiological denoising but without any smoothing. Note that data displayed in (d–f) are identical to data shown in Figure 3a–c of the main manuscript. For comparability, data overlays in (a–f) are scaled to the range of the overall minimal to maximal value. Cerebellar activation patterns were essentially unchanged. Physiological denoising and spatial smoothing, however, improved statistical power. CS = conditioned stimulus; FWE = familywise error; L = left, R = right; TFCE = threshold-free cluster-enhancement; US = unconditioned stimulus.

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Figure 4. Conjunction analyses. Conjunction analyses testing global null hypotheses (a,c) and analyses of differences (b,d) between the three contrasts ‘US post CS+ > no US post CS-‘, ‘CS+ > CS-‘ and ‘no-US post CS+ > no US post CS-‘ (shown in Figure 3) during fear acquisition. Data in (a,b) is shown in SUIT space and in (c,d) in MNI space. All contrasts displayed using FWE correction (p<0.05), (b,d) using TFCE. Bar graphs display group mean β values for each contrast considering the whole activation volume (error bars: standard error). VOI were defined based on conjunction analyses and are shown in the inserts: cerebellar VOI (a) and bilateral insula VOI (c). CS = conditioned stimulus; FWE = familywise error; TCFE = threshold-free cluster-enhancement; US = unconditioned stimulus; VOI = volumes of interest.

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Figure 4—figure supplement 1. Comparison of cerebellar areas related to the presentation, the prediction and the omission of the aversive stimulus. (a–c) Common areas of cerebellar activation considering any two of the three main acquisition contrasts as revealed by conjunction analyses testing global null hypothesis; (d–f) significant differences in activation considering any two of the three main acquisition contrasts as revealed by F-tests (using TFCE; inverse tests do not show any significant activation). All data presented at a significance level of p<0.05 FWE-corrected. CS = conditioned stimulus; FWE = familywise error; TCFE = threshold-free cluster-enhancement; US = unconditioned stimulus; VOI = volumes of interest.
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Figure 5. Group mean β values related to each event (presentation of US, CS+, CS-, omission of US) compared to rest. (a) Volume of interest (VOI) in the left cerebellar hemisphere; (b) VOI in the bilateral insula. Error bars represent standard errors. acq 1, acq 2 = early and late acquisition; CS = conditioned stimulus; ext 1, ext 2 = early and late extinction; hab = habituation; US = unconditioned stimulus. DOI: https://doi.org/10.7554/eLife.46831.014
Figure 6. PPI analysis based on a seed region in the left lateral cerebellar cerebellum (p<0.05 FWE corrected level after TFCE application). CS = conditioned stimulus; FWE = familywise error; L = left; PPI = psychophysiological interaction; R = right; TFCE = threshold-free cluster-enhancement; US = unconditioned stimulus; VOI = volumes of interest.

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Figure 6—figure supplement 1. Reanalysis of PPI data to exclude "bleed over" from visual cortex. To exclude this possibility, data were reanalyzed using the mean signal modulation in the occipital lobe as first level nuisance regressor in analogy to the method applied by Buckner et al. (2011) (b). For comparison, data of the original analysis are shown in (a), which is identical to Figure 6 in the main manuscript. Note that the main results did not change, that is functional connectivity of the cerebellum was increased with visual cortical areas when comparing CS+ with CS- trials. Data are shown at p<0.05 FWE corrected level after TFCE application. CS = conditioned stimulus; FWE = familywise error; L = left; PPI = psychophysiological interaction; R = right; TFCE = threshold-free cluster-enhancement; US = unconditioned stimulus; VOI = volumes of interest.

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