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Distinct cerebellar lobules process arousal, valence and their interaction in parallel following a temporal hierarchy

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ABSTRACT

The cerebellum participates in emotion-related neural circuits formed by different cortical and subcortical areas, which sub-serve arousal and valence. Recent neuroimaging studies have shown a functional specificity of cerebellar lobules in the processing of emotional stimuli. However, little is known about the temporal component of this process. The goal of the current study is to assess the spatiotemporal profile of neural responses within the cerebellum during the processing of arousal and valence. We hypothesized that the excitation and timing of distinct cerebellar lobules is influenced by the emotional content of the stimuli. By using magnetoencephalography, we recorded magnetic fields from twelve healthy human individuals while passively viewing affective pictures rated along arousal and valence. By using a beamformer, we localized gamma-band activity in the cerebellum across time and we related the foci of activity to the anatomical organization of the cerebellum. Successive cerebellar activations were observed within distinct lobules starting ~160 ms after the stimuli onset. Arousal was processed within both vermal (VI and VIIIa) and hemispheric (left Crus II) lobules. Valence (left VI) and its interaction (left V and left Crus I) with arousal were processed only within hemispheric lobules. Arousal processing was identified first at early latencies (160 ms) and was long-lived (until 980 ms). In contrast, the processing of valence and its interaction to arousal was short lived at later stages (420–530 ms and 570–640 ms respectively). Our findings provide for the first time evidence that distinct cerebellar lobules process arousal, valence, and their interaction in a parallel yet temporally hierarchical manner determined by the emotional content of the stimuli.

Introduction

Neurobiological and cognitive models conceptualize emotions respectively in terms of either discrete categories or underlying dimensions (Russell, 2009). Discrete-category theories propose the presence of distinct universal emotions that have discriminable signatures (Ekman and Cordaro, 2011; Ekman, 1992; Panksepp, 2005, 2007, 2011) in cortical and subcortical regions (Murphy et al., 2003; Phan et al., 2002) and specific temporal activity profiles (Esslen et al., 2004; Hot and Sequeira, 2013). Dimensional theories conceptualize emotions as a representation of at least two independent dimensions, (i.e., arousal and valence) that span the affective space as orthogonal entities (Russell, 1980). Arousal and valence are each processed by distinct neural circuits of cortical and subcortical regions regardless of the sensory modality (Anderson et al., 2003; Dolcos et al., 2004; Lewis et al., 2007; Royet et al., 2000). These distinct brain regions may become active in emotion-specific time sequences, which depend on both arousal and valence (Olofsson et al., 2008). Both emotional theories support an anatomical segregation and specialization of cortical and subcortical structures either for distinct emotions (e.g., Adolphs, 2002; Davidson and Irwin, 1999; Wicker et al., 2003) or different dimensions of emotions (Anders et al., 2004; Anderson et al., 2003; Dolcos et al., 2004).

The cerebellum is a recent addition to our view of the emotion-related distributed circuitry. Its anatomical integration with circuits associated with emotional processing was initially observed by convergent and multimodal data (Blatt et al., 2013). Though a clear anatomical substrate for cerebello-limbic connection is still absent in humans (Strick et al., 2009), animal studies have shown that vermis (anatomical substrate of the limbic cerebellum, Schmahmann, 2000) has reciprocal

Abbreviations: PFC, prefrontal cortex; MFT, magnetic field tomography; SAM, synthetic aperture magnetometry; IAPS, International Affective Picture System; PHA, pleasant with high arousal; PLA, pleasant with low arousal; UHA, unpleasant with high arousal; ULA, unpleasant with low arousal; AC, apparent contrast; ICA, independent component analysis; TFA, time–frequency analysis.

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connections with the amygdala and the hypothalamus (Schmahmann, 2000; Strick et al., 2009), which both integrate limbic-related activity (Armony, 2012; Beauregard et al., 2001). Anatomical connections from the cingulate cortex to the cerebellum (Schmahmann and Pandya, 1997; Vilensky and van Hoesen, 1981) also favor a cerebellar contribution to emotional processing. Viral tracing techniques in non-human primates have provided evidence that both cerebellar lobules Crus I and Crus II send and receive projections from the prefrontal cortex (PFC) (Kelly and Strick, 2003), which in turn is implicated in high-order processing, important for the integration of cognition and emotion (Gray et al., 2002). Clinical studies on patients with cerebellar lesions have complemented these lines of research. They proposed key roles for the vermis in the processing of primitive emotions and for the cerebellar hemispheric lobules (VI and VII) in the modulation of higher cognitive functions (Schmahmann and Sherman, 1998; Schmahmann, 1991). It was suggested that the higher cognitive functions may include experience of higher order emotions such as happiness (Turner et al., 2007).

These key insights from animal and clinical studies provided the neuroanatomical foundation for later neuroimaging findings of emotion-related activity in specific cerebellar lobules across a variety of experimental designs and stimuli (E et al., 2014; Stoodley and Schmahmann, 2009). Right VI was found to be related to positive emotions, while left VI, right IV/V and bilateral Crus I to negative emotions (E et al., 2014). Additionally, neural activity in the vermis has been associated with high arousal (Colibazzi et al., 2010) and to each of the five primary emotions (Baumann and Mattingley, 2012), while hemispheric VI activity with unpleasantness (Colibazzi et al., 2010) and aversive stimuli (Moulton et al., 2011). The findings by Moulton et al. (2011) suggested a degree of neural specialization within the cerebellum for aversive stimuli, while those by Baumann and Mattingley (2012) highlighted an anatomical segregation and specialization for different emotional categories within the cerebellum.

The recurring observation that different cerebellar lobules are active due to specific emotional content, i.e., for the processing of arousal (Colibazzi et al., 2010; Posner et al., 2009) and valence (Colibazzi et al., 2010) indicates a possible functional segregation and specialization within the cerebellum in the processing of emotional dimensions. This can be anatomically underpinned by the cerebellum's connections with the cortical and subcortical areas of the limbic system that play pivotal roles in the processing of arousal and valence. The amygdala's sub-divisions (i.e., laterobasal and centromedial) have been found to be functionally connected to vermal and hemispheric cerebellar lobules (Roy et al., 2009). These sub-divisions play specific roles in the processing of valence and its interaction to arousal (Ball et al., 2009; Styliadis et al., 2014). Crus I has been proposed to be functionally connected with the medial PFC (Krienen and Buckner, 2009), a region involved in higher-order regulation or evaluative aspects of emotions, such as valence (Etkin et al., 2011). Additionally, Crus II–ventromedial PFC coupling has been suggested to relate to cognitive function whereas vermal–posterior cingulate cortex coupling to emotional processing in geriatric depression (Alalade et al., 2011).

Despite the converging evidence favoring a possible functional segregation and specialization of cerebellar lobules in the processing of emotional dimensions, the temporal component of this process is still unknown. Neuroimaging studies that provided the functional specificity evidence have used functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET), techniques with limited temporal resolution ranging from a couple of seconds (for fMRI) to minutes (for PET). Studying the time course of emotions is important due to the different aspects of emotional responses that develop across time (Davidson, 1998). Responses to affective stimuli unfold differentially in time due to arousal and valence with a general agreement for a late arousal effect (200–1000 ms) and a rather varied and less consistent latency range for valence (usually 100–300 ms) (Codispoti et al., 2007; Olofsson et al., 2008). The significance of the temporal component of emotions can be amplified with respect to the cerebellum's plausible involvement in this process, since the cerebellum is an organ that provides exquisite timing as testified in studies dealing with fine control of movements (Keele and Ivry, 1990; Thach et al., 1992). The operations of the cerebellum are likely to involve timing control at the millisecond level to effectively coordinate neural circuits spread over wide brain areas in the cortex and subcortical areas. It will be thus insightful to disentangle the so far unknown temporal interplay of arousal and valence within the cerebellum by using neuroimaging techniques that offer high temporal resolution.

Although magnetoencephalography (MEG) could serve as an attractive neuroimaging tool for studying the spatiotemporal dynamics of cerebellar neural activity in a fine time scale, it has not been extensively used for this purpose. Traditionally, cerebellar activity was considered not to contribute sufficiently to the MEG signal so as to be properly measured. Undoubtedly, cerebellar activations have been previously reported in numerous MEG studies but these findings were frequently received with skepticism. The first studies to consider that MEG signals can be recorded from the cerebellum and that from such signals cerebellar activations can be reliably identified were from the low temperature laboratory in Helsinki (Jousmäki et al., 1996; Tesche and Karhu, 1997, 2000). The next major attempt was made by Hashimoto and colleagues (Hashimoto et al., 2003) who identified cerebellar responses after the electrical stimulation of the median nerve. A whole-head array with good coverage over the cerebellum was used to record a very large number of trials (~10,000) and the data were analyzed by a beamformer. Cerebellar activity has also been identified even in single trials by using magnetic field tomography (MFT) (Ioannides et al., 1990) in a variety of experimental settings ranging from eye movements, median nerve stimulation, to face affect recognition in control and schizophrenic individuals (Ioannides and Fenwick, 2005). All these studies have provided support to claims that cerebellum activity can be identified and localized with MEG (even when a relatively small number of trials are available) provided the protocol and analysis methods are appropriate. However, the accumulated evidence although mounting must still be viewed as indirect because there is as yet no confirmatory direct evidence with recordings from the cerebellum.

The aim of the present study is to reveal the spatiotemporal profile of cerebellar responses during the processing of emotional stimuli. We hypothesized that different levels of arousal and valence will excite distinct cerebellar lobules in a sequence determined by the emotional content of the stimuli (i.e., the arousal and valence content of the affective experience). By using MEG, we recorded magnetic fields elicited from healthy adult individuals passively viewing affective pictures rated along arousal and valence. We focused our analysis on the gamma-band activity since it is considered to be of particular importance for emotions (Keil et al., 2001; Luo et al., 2007, 2009, 2010; Müller et al., 1999; Oya et al., 2002). A beamformer technique called Synthetic Aperture Magnetometry (SAM) (Robinson and Vrba, 1998) was used to localize the gamma-band cerebellar responses to the emotional stimuli across time. The foci of activity were finally related to the anatomical organization of cerebellum by using the cerebellar probabilistic maps (Diedrichsen et al., 2009).

Materials and methods

Participants

Our subject pool comprised twelve healthy volunteers (7 males, mean age 30.8 ± 5.3, range 23 to 40 years, 5 females mean age 27.8 ± 5.3, range 21 to 35 years) of normal or corrected-to-normal visual acuity. Participants were informed of the stimuli type and modality and gave their written informed consent in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the host institution's ethics committee.

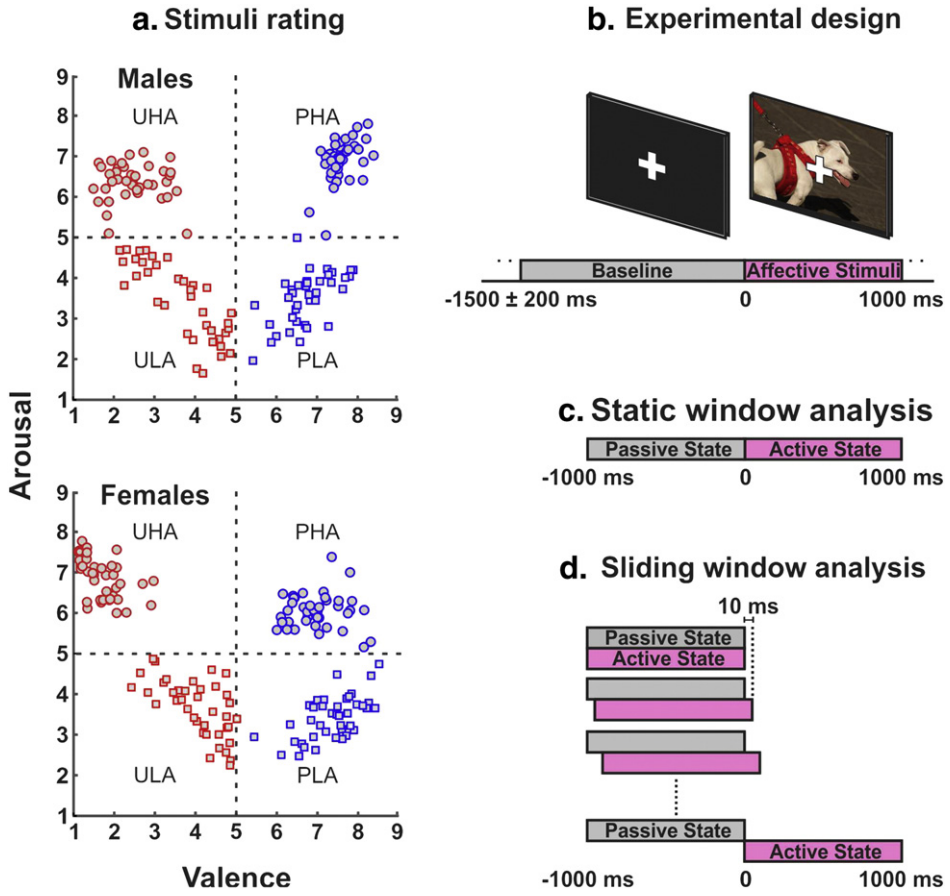

Fig. 1. Selection of the affective stimuli, experimental design, and data analysis: (a) Ratings of IAPS affective pictorial stimuli for arousal and valence (upper panel: males' ratings, lower panel: females' ratings) forming a 2D affective space. Normative valence and arousal on the x- and y-axis respectively. Red circles, UHA stimuli; red rectangles, ULA stimuli; blue circles, PHA stimuli; blue rectangles, PLA stimuli. (b) Experimental paradigm. Affective stimuli (from PHA, UHA, PLA, and ULA) were presented for 1000 ms (in a pseudo-random order) preceded by a black background with a superimposed fixation cross serving as baseline (1500 ± 200 ms). The picture depicted serves as an example of the original picture (not taken from the IAPS). (c) Static window analysis was performed for a 1000 ms window length (passive state: from −1000 to 0 ms, active state from 0 to 1000 ms). (d) Sliding window analysis was performed on the same window length with a step of 10 ms. [Double column (full width)].

We recruited only self-identified heterosexual participants to ensure the erotic stimuli effectiveness. Exclusion criteria included history of medical illness (i.e., psychiatric, neurological, and physical), any reported drug or alcohol abuse, regular medication consumption and the existence of metal implants in the volunteer's body. We requested that the participants abstain from alcohol and caffeine the day before and the day of the experiment. The participants were informed that they could terminate the experiment at any time without the need to provide any justification for their decision (no one did).

Affective stimuli

Participants passively viewed stimuli pooled from the International Affective Picture System (IAPS) collection (Lang et al., 2008) on a homogenous black background. IAPS has standard photographic stimuli calibrated for affective response. The IAPS stimuli are distributed in the two dimensional affective space, based on co-varying normative ratings of arousal and valence. Passive viewing of IAPS stimuli produces automatically a broad range of emotional responses (see Olofsson et al., 2008 for a review). We manipulated arousal and valence orthogonally so that arousal and valence effects were well separated (Fig. 1a) (Bradley and Lang, 1994; Lang et al., 1997). In addition, we considered the possible interaction of valence and arousal since previous studies have shown that arousal and valence interact (Cuthbert et al., 2000; Robinson et al., 2004).

The level of arousal within pleasant and unpleasant pictures (Cuthbert et al., 1996) was distributed in four categories[1]; (i) pleasant with high arousal (PHA), e.g., erotica, sports, (ii) pleasant with low

[1] PHA for males: 1720, 1811, 4001, 4006, 4141, 4142, 4150, 4180, 4210, 4220, 4225, 4232, 4240, 4250, 4255, 4290, 4300, 4310, 4311, 4320, 4607, 4608, 4651, 4652, 4658, 4659, 4660, 4664, 4664.1, 4670, 4681, 4683, 8080, 8185, 8186, 8190, 8340, 8400, 8499, 8501; PHA for females: 2150, 2216, 2303, 2345, 2389, 2550, 4460, 4470, 4490, 4503, 4510, 4520, 4532, 4533, 4537, 4538, 4542, 4561, 4572, 4598, 4599, 4607, 4608, 4609, 4611, 4626, 4656, 4659, 4660, 4670, 4680, 4681, 4687, 4689, 4695, 5621, 5629, 7502, 8030, 8034; PLA for males: 1450, 1601, 1610, 1620, 1750, 1812, 1900, 1920, 2050, 2070, 2165, 2170, 2235, 2260, 2299, 2303, 2360, 2370, 2388, 2501, 2530, 2550, 2650, 2660, 4614, 5000, 5001, 5010, 5020, 5030, 5200, 5831, 5891, 7080, 7325, 7340, 7545, 7900, 8330, 8497; PLA for females: 2000, 2010, 2037, 2152, 2260, 2299, 2304, 2311, 2360, 2370, 2388, 2395, 2398, 2501, 2510, 2530, 2540, 2598, 2620, 5000, 5010, 5020, 5030, 5200, 5520, 5551, 5611, 5631, 5711, 5720, 5750, 5760, 5764, 5779, 5800, 5811, 5891, 7039, 7340, 7545; UHA for males: 1525, 2681, 2683, 2688, 2730, 2811, 3000, 3010, 3015, 3030, 3053, 3060, 3068, 3069, 3071, 3080, 3100, 3102, 3110, 3120, 3130, 3150, 6230, 6250.1, 6300, 6313, 6350, 6510, 6540, 6550, 6560, 6570, 8485, 9040, 9252, 9410, 9630, 9635.1, 9810, 9902; UHA for females: 2683, 2691, 2730, 2981, 3000, 3010, 3015, 3030, 3051, 3053, 3063, 3064, 3068, 3069, 3071, 3080, 3100, 3102, 3110, 3120, 3140, 3150, 3168, 3170, 3191, 3225, 3266, 3400, 3500, 3530, 5971, 6021, 6022, 6190, 6200, 6210, 6212, 6230, 6243, 6250; ULA for males: 2095, 2100, 2141, 2200, 2205, 2206, 2210, 2214, 2375.1, 2393, 2399, 2440, 2490, 2570, 2700, 2715, 2722, 2750, 2753, 3017, 3301, 4490, 4510, 4550, 4561, 7006, 7025, 7031, 7150, 7170, 7187, 9220, 9265, 9280, 9290, 9331, 9360, 9421, 9571; ULA for females: 2399, 2490, 2491, 2590, 2722, 2750, 4001, 4210, 4230, 4233, 4240, 4290, 4635, 5120, 5130, 5534, 6010, 6241, 6800, 6930, 7031, 7036, 7044, 7046, 7054, 7060, 7130, 7150, 7180, 7184, 7211, 7224, 7234, 7484, 7491, 7700, 7705, 7920, 9000, 9080.

arousal (PLA), e.g., scenes of nature, neutral faces, (iii) unpleasant with high arousal (UHA), e.g., human violence, angry faces, attack and mutilation and (iv) unpleasant with low arousal (ULA), e.g., pollution, illness. We did not ask the participants to rate the stimuli during the MEG recordings to avoid the confounding effect of subjective stimulus evaluation interfering with the induced affective reactions. After the end of the experimental procedure, the participants viewed the stimuli and rated them on a scale of 1–9 with the use of the Self-Assessment Manikins model (Bradley and Lang, 1994). Thus, we measured the degree to which they perceived the stimuli as unpleasant/pleasant and low/high arousing. Differences between the participants' ratings and the normative IAPS ratings were found to be minimal ($p > 0.05$) with the use of a *t*-test (Table 1).

Balancing of stimuli

IAPS driven affective responses may vary with gender and arousal and involve both pleasant and unpleasant affect (Lang et al., 1993, 1998). For instance, males and females generally rate IAPS stimuli differently across arousal and valence (Lang et al., 1997). In order to effectively balance the stimuli for both genders, we formed gender-specific stimuli pools. Our strategy was to have a high number of common stimuli between the two pools but also make sure that a similar affective content level in terms of arousal and valence ratings was maintained. Therefore, we based our stimuli categorization on the gender-specific ratings provided by the IAPS collection in accordance with previous studies by our group (Lithari et al., 2010; Styliadis et al., 2014). We tested that the two sets of stimuli though different, were equal in terms of arousal and valence dimensions by conducting *t*-tests for both arousal and valence. The statistical analysis between the ratings of the stimuli used for males and those used for females did not reveal significant differences ($p > 0.05$). The gender-specific ratings for the selected stimuli as provided by the IAPS collection are presented in Table 1, accompanied by our own participants' group ratings.

The selected stimuli were also balanced for complexity, namely the picture's histogram entropy, overall Apparent Contrast (AC = (standard deviation of luminance matrix) / (mean of luminance matrix)) and AC for each color level between males and females ($p > 0.05$) (Delplanque et al., 2007). The stimuli were further controlled for the spatial frequencies and the AC of each picture for all the participants so as to avoid any possible effects of the physical properties of the stimuli confounding our findings. With respect to spatial frequency, spectral energies were computed for eight frequency bands (plus residuals) within each picture following the procedure described by Delplanque and colleagues (Delplanque et al., 2007) (http://www.affective-sciences.org/spatfreq). The AC associated with each frequency band was also considered (Delplanque et al., 2007). The effect of these spatial frequencies for the grayscale version and for each color level (red, green, blue) of each picture with respect to the experimental conditions (PHA, PLA, UHA, ULA) for both gender groups was not significant ($p > 0.05$). Also the effects of the overall AC and the AC for each color level within these spatial frequencies were also non-significant with respect to the experimental conditions for both gender groups ($p > 0.05$). Thus, the effects reported in the current study can be attributed to the emotional meaning of the stimuli and not to their incidental visual properties.

Table 1
Mean (S.D.) normative and participants' ratings for valence and arousal.

Males			
		Normative ratings	Participants' ratings
Valence	Pleasant	7.18 (±0.66)	6.97 (±0.61)
	Unpleasant	3.05 (±0.96)	3.45 (±1.30)
Arousal	High arousing	6.64 (±0.56)	6.52 (±0.83)
	Low arousing	3.51 (±0.80)	4.21 (±0.91)
Females			
		Normative ratings	Participants' ratings
Valence	Pleasant	7.15 (±0.67)	7.05 (±0.59)
	Unpleasant	2.83 (±1.29)	3.07 (±1.51)
Arousal	High arousing	6.46 (±0.62)	6.81 (±1.36)
	Low arousing	3.56 (±0.65)	4.12 (±0.67)

t-Tests were performed to ensure that there were no significant differences between pictures used for males and for females.

Experimental procedure

The experiments were performed at the Laboratory for Human Brain Dynamics (1998–2009), Brain Science Institute (BSI), RIKEN, Japan. The experimental procedure was performed in dim light in a magnetically shielded room (MSR). IAPS stimuli were back-projected onto a 10 inch (MEG compatible) screen, 55 cm away from the participant's eyes, at a visual angle of 4° horizontally and vertically via a DLP projector with a 96 Hz refresh rate (HL8000Dsx+, NEC Viewtechnology Ltd., Tokyo, Japan) located outside the MSR. The Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA) was employed to control the stimuli delivery. Markers within the MEG data for the onset and offset of the trials and the fixation cross were synchronized with luminance detection via an optical sensor of a white pixel, at 20 × 20 pixel resolution.

We employed a random design with two runs (80 trials per run, 20 trials per category). Stimuli and inter-stimuli (fixation cross) were projected centered on screen. Each run began with the projection of a fixation cross, at 40 × 40 pixel resolution for a pseudo-randomized interval of 1500 ± 200 ms. Trials were projected at 400 × 400 pixel resolution for 1000 ms along with the fixation cross (Fig. 1b). We considered the trial duration (1000 ms) long enough to engage processes that have a relatively fast time constant and elicit responses in the affective neural substrates. We considered the trial duration short enough so as not to produce considerable variability in the participants' responses. Each run lasted 220 s resulting in a total recording time of 440 s.

Data acquisition

We recorded the MEG signal at a sampling rate of 1250 Hz using a 151-channel CTF whole head MEG system (VSM MedTech Ltd). The CTF system is equipped with synthetic 3rd gradient balancing, an active noise cancelation technique that employs a set of reference channels for background interference subtraction. Each participant's head position was registered twice (beginning and end of each measurement) with localization coils placed at the nasion and the bilateral pre-auricular points. Head movements did not exceed 0.5 cm. We followed the coregistration procedure described in Papadelis et al. (2011). Special care was taken before each recording to ensure that each participant's head was placed in such a way that the cerebellum was fully covered. After performing the coregistration, we checked whether the cerebellum was well-covered by the system's gradiometers, and indeed this was the case for all individuals participating in the study. In addition, we made sure that the participants were positioned comfortably in order to reduce postural muscle artifacts. We instructed the participants to avoid movements, eye-blinks and eye movements during the trials and to focus on the fixation cross. We simultaneously recorded electro-oculogram (EOG) and electrocardiogram (ECG) signals by using four and five Ag/AgCl electrodes respectively. These signals facilitated the inspection of trials as well as the decomposition of the MEG data into independent components that were removed from source reconstructions (see below). Each participant's head was also scanned with a high-resolution anatomical MRI (1.5 T MRI, Model ExcelArt, Toshiba Medical Systems) using a T1-weighted volume acquisition sequence resulting in a voxel-size of 1 × 1 × 1 mm^3.

Data pre-processing

We initially removed the DC (direct current) offset. Raw data were then inspected offline for bad sensor recordings (two bad channels on average). Trials contaminated with muscle artifacts, signal jumps or distortions of the magnetic field were rejected off-line using automated threshold procedures applied to the MEG signals. On average 2 trials (2 to 4) were rejected. The remaining trials were kept for further analysis since none of them had field magnitudes greater than 1×10^{-11} T in any channel. Also, we inspected all MEG and EOG signals manually to ensure good artifact rejection performance. We then removed the line noise (50 Hz and its harmonics) by applying a 2nd order Butterworth notch filter. MEG data were then processed by using the Independent Component Analysis (ICA) in conjunction with the EOG and ECG recordings as implemented in the Brain Electrical Source Analysis software (BESA Research, version 6.0, Megis Software) so as to remove artifactual signal components. The inclusion of EOG signals in the ICA analysis has been shown to improve the removal of ocular artifacts (Klados et al., 2011). The average number of independent components removed from the original data was 5 (4 to 6) out of 20 components. The removed artifactual components consisted of facial muscle components, blinks, microsaccades and cardiac artifacts. MEG data from two male subjects were not further analyzed due to heavy artifact contamination. Following the data pre-processing, grand averages were estimated for each condition (PHA, PLA, UHA and ULA) and for each participant (see Supplementary Figure).

MEG sensor space time–frequency analysis (TFA)

TFA of MEG oscillatory activity was quantified by continuous Morlet wavelet transformation (factor 3) using Statistical Parametric Mapping 8 (SPM8 http://www.fil.ion.ucl.ac.uk/spm). Epochs were initially chopped from −500 to 1000 ms relative to the onset of the PHA, PLA, UHA and ULA stimuli. The wavelet decomposition was applied to each trial, sensor, and participant across the frequency range of 1−100 Hz, and this estimate of power was averaged to provide an analysis of non-phase-locked, induced information. The TFA was performed on recordings from nine[2] sensors covering the cerebellum in most of the cases. The resulting time–frequency spectrograms were rescaled to a percentage of the power in the baseline, and the control condition was subtracted from each affective condition. We performed the within-subjects statistical analysis of the time–frequency representations of power for the affective conditions and considered the effects significant at $p < 0.05$ (cluster level correction for multiple comparisons). Cluster level correction solves the multiple comparison problem by calculating a so-called cluster-based test statistic and its significance probability. It takes into account the correlation of the effect at neighboring time points and sensors in order to account for multiple correction. For more details see the publication by Maris and Oostenveld (2007).

Source analysis

A multisphere head model was created for each participant using their anatomical MRI. We used SAM (Robinson and Vrba, 1998) to analyze task-related activation differences in the gamma frequency band (30–100 Hz) (SAM pseudo-T source image statistics are described in detail in a number of sources (Hillebrand et al., 2005; Robinson and Vrba, 1998; Singh et al., 2002, 2003)). We employed dual-state SAM imaging, which estimates the task-related power change between the active and control time windows normalized by the noise variance, represented by a pseudo-t value. The SAM weights were computed using a different covariance matrix for each condition. The dual-state SAM output for the PHA, PLA, UHA and ULA conditions per participant was the difference between the active and the control state. SAM images from the two runs were averaged to generate a single SAM image per participant per condition (Singh et al., 2002, 2003). The resulting volumetric maps were overlaid on the individual MRI. Here, we followed two approaches both based on the dual-state SAM imaging; a static window and a sliding window analysis. Both approaches have been used before for the localization of active sources in the brain: static (Singh et al., 2002, 2003) and sliding (Luo et al., 2007, 2009, 2010).

The static window analysis provided a general overview on the spatial activity for the period of 1000 ms. The active state was defined as the 1000 ms time window following the stimulus onset and the control state (baseline) as the 1000 ms time window preceding the stimulus onset (Fig. 1c). The sliding window analysis provided the temporal sequencing (onset, peak, and offset) of the power changes in the source space. We obtained the time course activity in combination with the spatial activation maps across all of the time points starting from 0 to 1000 ms. The sliding window analysis (Fig. 1d) had an active window of 1000 ms sliding with a 10 ms step: −1000 to 0 ms, −990 to 10 ms, −980 to 20 ms, …, −10 to 990 ms, 0 to 1000 ms and a control state of 1000 ms before stimulus onset (or −1000 to 0 ms). The results for the sliding window analysis will be expressed in terms of the forward window of the active state (e.g., we will refer to the comparison of the active window (−900 to +100 ms) and the passive condition (−1000 to 0 ms) as the result at 100 ms).

Group space analysis of MEG source activity

We normalized the resulting SAM images into the Montreal Neurological Institute (MNI) space via the segmentation module of SPM8. SPM8 was further used for the statistical analysis of the normalized SAM images. Specifically, using the second level of analysis of SPM, a factorial model was designed to explore the main effects of arousal and valence as well as the valence × arousal interaction. The factorial model is SPM's equivalent analysis to a 2 × 2 model of repeated ANOVA measures with stimulus valence (pleasant/unpleasant) and arousal (high/low) as the within-subjects factors. Results were then constrained in cerebellar lobules using a spatially unbiased atlas template of the cerebellum (SUIT, http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm) (Diedrichsen et al., 2009) as an explicit mask, thereby keeping the search volume small and in related areas. We assessed the mean activation across participants for arousal, valence, and the valence × arousal interaction. Statistical maps had 32 degrees of freedom with a confidence level set at $p < 0.001$ uncorrected.

Cerebellar probabilistic maps

We identified the significant activation sites and volumes using the probabilistic atlas of the cerebellar lobules (Diedrichsen et al., 2009) available through the anatomy toolbox (Eickhoff et al., 2005). The use of probabilistic maps in the identification of underlying regions by using MEG has been shown for cortical (Barnikol et al., 2006; Papadelis et al., 2011; Prieto et al., 2007) and subcortical (Liu and Ioannides, 2010; Styliadis et al., 2014) areas. We assigned an anatomical identity to our activation sites based on the probabilities at the maxima of the activities. The assignment algorithm used (Eickhoff et al., 2006), is based on the assignment of each voxel to the most probable anatomical area at the position under investigation. The probability limit for assignment was set to ≥80%. In case the activity could be assigned to two distinct cerebellar lobules, we chose the one with the higher probability. We used the nomenclature of Schmahmann et al. (2000) to label the cerebellar lobules. Anatomically, the human cerebellum consists of the vermis and two hemispheres and is distinguished into ten lobules, grouped as the anterior lobe (lobules I through V), the posterior lobe (lobules VI through IX) and the flocculonodular lobe (lobule X) (Schmahmann et al., 2000).

[2] MLO31, MLO32, MLO41, MLO42, MRO31, MRO32, MRO41, MRO42, MZO02.

TFA at virtual sensors

Virtual sensors are defined as a weighted-sum of the sensor data that estimates the time-course of electrical activity at specific points in the source space via a spatial filter (Robinson and Vrba, 1998). Here, we estimated the virtual sensors for the static window analysis at locations indicating the local maxima derived from the group level analysis. We selected as local maxima the peak areas of difference: (i) between high and low arousal; (ii) between pleasant and unpleasant stimuli; and (iii) between the valence and arousal interaction. The virtual sensors were estimated for each subject at the locations derived by transforming the group analysis local maxima in MNI coordinates into the coordinate space of each subject. The same methodology that was used for the TFA at the sensor space was also used here for the virtual sensors.

Results

MEG TFA results

We found statistically significant effects ($p < 0.05$, cluster corrected) for arousal within the gamma band both at the sensor space (for a selection of sensors covering the cerebellum — Fig. 2a), as well as at the source space (for the virtual sensors placed at the maxima of the cerebellar lobules of interest, e.g., Crus II — Fig. 2b). At the sensor space, the arousal effect reached significance from ~400 to ~750 ms after the stimuli onset, while at the source space from ~530 to ~550 ms. Induced gamma-band activity was characterized by a steady-state response with a specific frequency content (~60–80 Hz) clearly visible only at the source space (see Fig. 2). No significant effects were observed for valence at the sensor space.

Static window analysis

Our results indicate significant cerebellar activity attributed to arousal (vermal VIIIa and hemispheric Crus II) and its interaction with valence (hemispheric V). Fig. 3 shows the group analysis MEG results of the static window analysis, for high arousal (Fig. 3a) and its interaction with pleasant valence (Fig. 3b). Table 2 presents the anatomical location of the maxima of statistical significant differences for all effects in the MNI space and their corresponding statistical value and cluster size. Cerebrum activities were also observed but these findings will be discussed elsewhere.

High arousal (PHA + UHA > PLA + ULA) was localized in the vermal VIIIa (peak coordinates: x = 0, y = −70, z = −40; t = 6.53; cluster size = 112 voxels; $p < 0.001$ uncorrected) and the left hemispheric Crus II (peak coordinates: x = −16, y = −86, z = −35; t = 6.34; cluster size = 254 voxels; $p < 0.001$ uncorrected) (Fig. 3a). The valence × arousal interaction (PHA + ULA vs UHA + PLA) was localized in the left hemispheric V (peak coordinates: x = −12, y = −50, z = −14; t = 5.29; cluster size = 68 voxels; $p < 0.001$ uncorrected) (Fig. 3b). The arousal effect for this neural area was larger for pleasant than for unpleasant pictures. We did not use a cluster correction threshold for the cerebellar mask in the static window analysis.

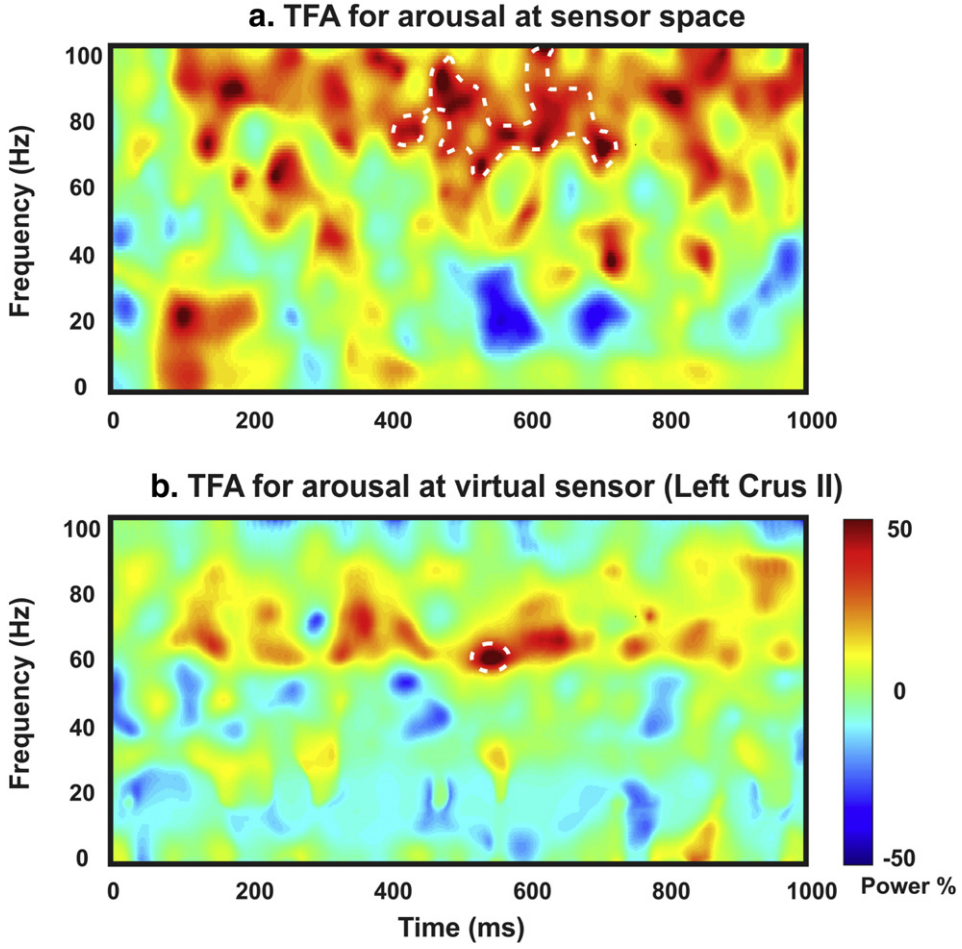

Fig. 2. TFA results: (a) Sensor space TFA results. Time–frequency changes of induced activity for arousal after onset for a representative set of MEG sensors that cover the cerebellum from 1 to 100 Hz (y-axis) over time from 0 to 1000 ms (x-axis) relative to the stimulus onset. Power changes (blue to red) significant at $p < 0.05$ level (cluster correction for multiple comparisons) indicated with dotted (white) lines. (b) Virtual sensor space TFA results. Time–frequency changes of induced activity for arousal after onset for left Crus II (−16, −86, −35). [Double column (full width)].

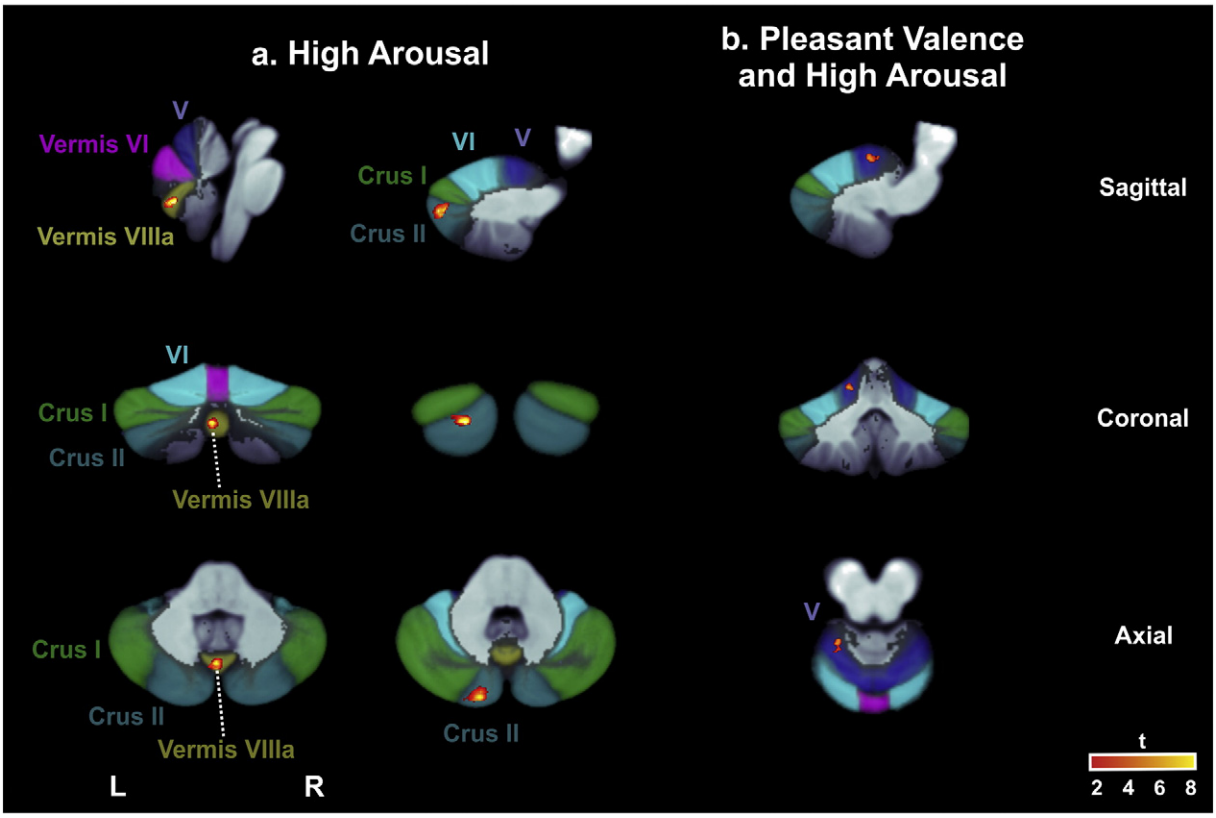

Fig. 3. Cerebellar activations for the static window analysis. Group analysis activations (red-yellow blobs, $p < 0.001$ uncorrected) superimposed on the PCM for cerebellar lobules for (a) high arousal, and (b) pleasant valence and high arousal stimuli. Red to yellow color scale, t-values. [Double column (full width)].

Sliding window analysis

Our results indicate cerebellar activity during emotional processing that was initially attributed to arousal (vermal VI, hemispheric Crus II), then valence (hemispheric VI) to be followed by their interaction (hemispheric V and Crus I), and finally again to arousal (vermal VIIIa). Fig. 4 shows the sliding window group analysis results for high arousal (Fig. 4a), unpleasant valence (Fig. 4b) and the interaction of pleasant valence by high arousal (Fig. 4c). Fig. 4d depicts the temporal evolution of the cerebellar emotional responses across time (for a period of 1000 ms) within the cerebellar lobules for high arousal, unpleasant valence, and the interaction of pleasant valence by high arousal. Table 3 presents the anatomical location of the maxima of statistically significant differences for all effects in the MNI space, their onset, peak, and offset, their corresponding statistical value, and cluster size at their peak. Cerebrum activities were also observed but these findings will not be discussed here.

Table 2
Local statistical maxima for static window analysis. Activated cerebellar regions for high arousal and pleasant valence by high arousal interaction at $p < 0.001$ uncorrected. Results are superimposed on standardized MNI coordinates; H, hemisphere; L, left; R, right; CS, cluster size in number of activated voxels; T, t-values for each peak.

	H	MNI coordinates (mm)			CS	T
		x	y	z		
High arousal						
Vermis VIIIa		0	−70	−40	112	6.53
Crus II	L	−16	−86	−35	254	6.34
Pleasant valence & high arousal						
V	L	−12	−50	−14	68	5.29

High arousal (PHA + UHA > PLA + ULA) was localized in the vermal VI for two different time instances (peak coordinates: x = 2, y = −72, z = −16; t = 4.06; cluster size = 64 voxels; $p < 0.001$ uncorrected, peak coordinates: x = 2, y = −72, z = −16; t = 3.97; cluster size = 70 voxels; $p < 0.001$ uncorrected) and the vermal VIIIa (peak coordinates: x = 0, y = −70, z = −40; t = 6.55; cluster size = 94 voxels; $p < 0.001$ uncorrected), as well as in the left hemispheric Crus II (peak coordinates: x = −10, y = −82, z = −40; t = 5.01; cluster size = 313 voxels; $p < 0.001$ uncorrected) (Fig. 4a). The effect of unpleasant valence (UHA + ULA > PHA + PLA) was localized in the left hemispheric VI (peak coordinates: x = −30, y = −54, z = −26; t = 4.39; cluster size = 169 voxels; $p < 0.001$ uncorrected) (Fig. 4b). The valence × arousal interaction (PHA + ULA vs UHA + PLA) was localized in the left hemispheric V (peak coordinates: x = −16, y = −46, z = −18; t = 3.93; cluster size = 127 voxels; $p < 0.001$ uncorrected), and the left hemispheric Crus I (peak coordinates: x = −38, y = −65, z = −32; t = 4.09; cluster size = 92 voxels; $p < 0.001$ uncorrected) (Fig. 4c). In these neural areas, the arousal effect was larger for pleasant than for unpleasant pictures. We did not use a cluster correction threshold for the cerebellar mask in the sliding window analysis.

High arousal was initially attributed to left Crus II activity, which had an early onset at 160 ms, peaked at 190 ms, and lasted up to 870 ms. High arousal was also attributed to vermal VI activity at two different time instances (170–370 ms, peak at 190 ms, and 640–910 ms, peak at 720 ms). Finally, high arousal was localized in the vermis of VIIIa lobule which had an onset at 920 ms, peaked at 950 ms, and had an offset at 980 ms (Fig. 4a, Table 3). Unpleasant spatiotemporal activity showed that left VI had an onset at 420 ms, peaked at 500 ms, and had an offset at 530 ms (Fig. 4b, Table 3). The spatiotemporal activity of valence × arousal interaction showed that left V and Crus I had a common onset at 570 ms, peaked at 590 and 600 ms, and had an offset at 640 and 630 ms respectively (Fig. 4c, Table 3).

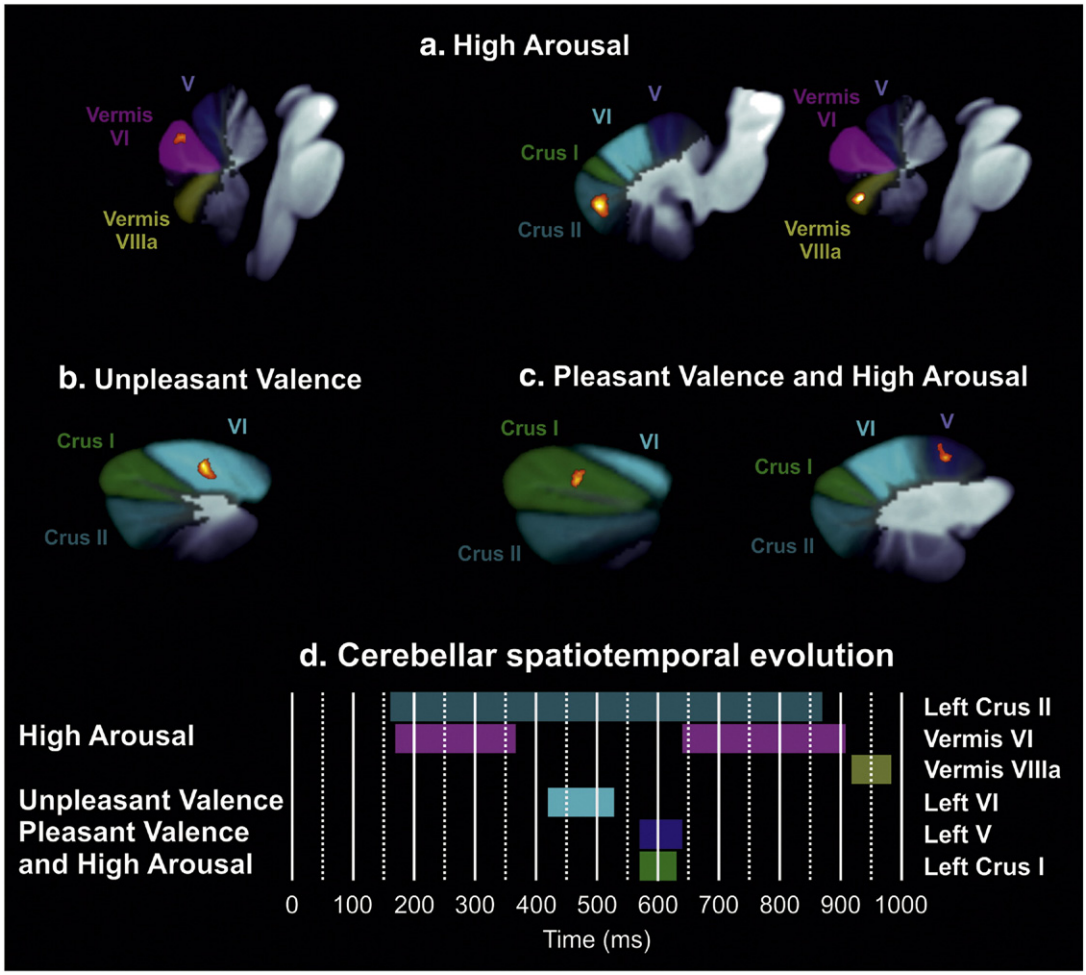

Fig. 4. Cerebellar activations for the sliding window analysis. Group analysis activations (red-yellow blobs, $p < 0.001$ uncorrected) superimposed on the sagittal PCM for cerebellar lobules for (a) high arousal, (b) unpleasant valence, and (c) pleasant and high arousal stimuli. Red to yellow color scale, t-values. (d) Temporal evolution of cerebellar emotional responses across time for a period of 1000 ms. [Double column (full width)].

Discussion

Our results reveal a novel spatiotemporal evolution of cerebellar activations for emotional processing showing that: (i) arousal, valence, and their interaction are processed in parallel within anatomically distinct cerebellar lobules, (ii) these processes unfold at well-defined latencies relative to stimulus onset following a temporal hierarchy, and (iii) cerebellar responses are organized into an early prioritization of high arousal, followed by an unpleasant valence effect, and later a pleasant valence by high arousal interaction.

Cerebellar lobules process in parallel arousal, valence, and their interaction

Our results point to separable roles for the cerebellar lobules in emotional processing and are in agreement with the previously reported cerebellar functional specificity for emotions (Colibazzi et al., 2010;

Table 3
Local statistical maxima for sliding window analysis. Activated cerebellar regions for high arousal, unpleasant valence and pleasant valence by high arousal interaction at $p < 0.001$ uncorrected. Results are superimposed on standardized MNI coordinates; H, hemisphere; L, left; R, right; CS, cluster size in number of activated voxels; T, t-values for each peak.

	H	MNI coordinates (mm)			Onset	Peak	Offset	CS	T
		x	y	z	(ms)	(ms)	(ms)	(at peak)	(at peak)
High arousal									
Crus II	L	−10	−82	−40	160	190	870	313	5.01
Vermis VI		2	−72	−16	170	190	370	64	4.06
		2	−72	−16	640	720	910	70	3.97
Vermis VIIIa		0	−70	−40	920	950	980	94	6.55
Unpleasant valence									
VI	L	−30	−54	−26	420	500	530	169	4.39
Pleasant valence & high arousal									
V	L	−16	−46	−18	570	600	640	127	3.93
Crus I	L	−38	−65	−32	570	590	630	92	4.09

Moulton et al., 2011; Posner et al., 2009). This notion is further extended by the cerebellar spatiotemporal profile demonstrated here. It is indicated that arousal, valence, and their interaction are processed in parallel and relatively independently within distinct cerebellar lobules. Thus, the cerebellum has characteristics that fit a parallel distributed processing model for emotions (Barrett et al., 2007). The basic idea of such a model is that the subcomponents of an emotional response (the processes of arousal, valence and their interaction) are sub-served by multiple brain circuits in parallel so as to reach a coherent (based on the context) instance of emotion. Cerebellar structures of multiple modules, each having discrete processing units, are ideal for processing tasks in a quick parallel and independent way (Apps and Garwicz, 2005). Considering the connections between the cerebellum and the limbic system, and the cerebello-thalamo-cortical projections that allow cognition and emotion interactions (Manto, 2006; Schutter and van Honk, 2005), it is conceivable these units may require different lengths of time to fully process their tasks. These connections may hence enable the cerebellum to integrate different information processing streams in parallel (Middleton and Strick, 1998).

Processing of arousal, valence, and their interaction follows a temporal hierarchy

Our findings further indicate that though arousal, valence, and their interaction seem to unfold in parallel, their processing is hierarchically organized with respect to time. Generally, the processing of the different levels of arousal and valence does not imply similar emotional responses and thus behavioral consequences; so it is plausible that not only a temporal hierarchy exists in the processing of these two emotional dimensions but it can also affect cerebellar functioning. This is consistent with the notion that the stimuli affective features may be processed in a prioritized manner as derived from behavioral (Ohman et al., 2001), electrophysiological (Stolarova et al., 2006) and neuroimaging studies (Bradley et al., 2003). In this sense, it is likely that the cerebellar lobules are engaged in emotional appraisal since they detect the extent to which the affective meaning of the emotional stimuli is potentially significant for the momentary hierarchy of goals and needs. The temporal hierarchy demonstrated here reveals that cerebellar responses manifest early in the processing of emotions and remain strong for a long period of time. These are organized into an early prioritization of high arousal followed by an unpleasant valence effect and later a pleasant valence by high arousal interaction effect. Cerebellar lobules are thus engaged in swift evaluations to highly arousing as well as unpleasant stimuli and slower evaluations to pleasant and highly arousing stimuli. Negative stimuli in particular are of critical urgency, as the failure to avoid a negative stimulus may be fatal (Estes and Adelman, 2008). From a decision making perspective, arousing stimuli are often considered negative until better evaluations present themselves; it is better to act quickly when a danger is present and relatively slowly when a potential reward is involved (Robinson, 1998).

Vermal and bilateral hemispheric lobules serve the processing of high arousal

The high arousal effect was localized in both vermal and hemispheric lobules. The vermal (VI and VIIIa) activation in response to high arousal is an expected result since the vermis is consistently implicated in processes related to motivation and emotion (Schutter, 2013). In healthy individuals, the vermis activity has been found to increase with arousing emotions (Colibazzi et al., 2010) and with autonomic processes elicited by the development of thirst (Parsons et al., 2000). In patients with vermal lesions, the vermis has been implicated in autonomic regulation and emotionally relevant memory (Schmahmann, 1991, 2000), as well as pronounced affective presentations (Schmahmann and Sherman, 1998). The vermis' role in arousal is based on its reciprocal connections to brainstem reticular nuclei (Brodal, 1975; Dietrichs and Walberg, 1979) as well as limbic and autonomic regions such as the hypothalamus (Haines et al., 1984). Previously, right hemispheric cerebellar activity has been found to be inversely associated to arousal, thus having a direct inhibitory influence on arousal (Posner et al., 2009). In contrast to these findings, here we observe that the left cerebellar hemispheric Crus II activity is directly associated with high arousal.

VI processes unpleasant valence

Unpleasant stimuli were processed in the left VI, while no cerebellar activity was identified for pleasant stimuli. This is in line with early findings reporting consistent cerebellar activation for negative compared to positive stimuli (Lane et al., 1997; Paradiso et al., 1999). Activity in VI has been associated with pain related processes (Moulton et al., 2010), empathy for another's pain (Singer et al., 2004) and emotional picture perception (Bermpohl et al., 2006) suggesting a (cerebellar) role in the control of emotions. Moulton et al. (2011) proposed that VI activity processes aversive stimuli in the form of associative learning. Schraa-Tam et al. (2012) suggested that VI may be more involved in the control of negative emotions contributing to the goal-directed behavior required for the observation and reaction to another person's negative expressions. Similarly, paravermal and hemispheric VI activity was associated with emotions such as anger, fear, disgust and sadness (Baumann and Mattingley, 2012).

V and Crus I code the interaction of emotional dimensions rather than arousal or valence per se

The interaction of arousal and valence has never been explored in the cerebellum so far. Our results indicate that the arousal effect on cerebellar activity is not the same at all levels of valence. Hemispheric V and Crus I responded only to highly arousing and pleasant stimuli. These results recast similar activities identified during emotional processing (E et al., 2014; Stoodley and Schmahmann, 2009) as an arousal by valence interaction effect: V and Crus I process neither arousal nor valence per se but their combination. Though both Crus I (Baumann and Mattingley, 2012; Moulton et al., 2011; Schraa-Tam et al., 2012) and V (E et al., 2014) were previously correlated with negative emotions, here these lobules process highly arousing pleasant stimuli. Crus I and V may adapt to the valenced (pleasant/unpleasant) information of the stimuli so as to influence the forthcoming evaluations either strongly (and possibly faster) or less strongly (and possibly slower).

Arousal processing is prioritized followed by valence and later their interaction

Our temporal results emphasize the timing capabilities of the cerebellum since the cerebellar activity responses are closely linked to the time at which these events are expected. Arousal processing was identified first at early latencies (~160 ms) and was long-lived (until 980 ms). In contrast, the processing of valence and its interaction to arousal was short lived at later stages (420–530 ms and 570–640 ms respectively). An exciting implication of our results is that in contrast to previous findings of very early valence (100–300 ms) and late arousal effects (200–1000 ms) for cerebrum (Olofsson et al., 2008), an inverted temporal relationship appears for the cerebellum in our study. This indicates that information about arousal of an incoming stimulus is extracted within the cerebellum before information about valence. The early and long-lasting arousal processing observed here was not surprising because the arousal influences on emotional responses emerge in general relatively early and last from 150 to 1000 ms with respect to stimulus onset (Olofsson et al., 2008). In contrast, our finding regarding the onset of the VI activity (at 420 ms for unpleasant valence) exceeds the periods during which valence processing is usually reported (100–300 ms) (Codispoti et al., 2007; Olofsson et al., 2008). We cannot rule out that other areas (e.g., prefrontal cortex) may have already processed

these very early valence effects, and fed their output to the cerebellum. This can be missed in the vast majority of the studies that focus only on cerebral sources and do not take into account cerebellar activity. In order to better elucidate how and when the cerebellum shows emotion-specific interactions with other brain regions, a whole head effective connectivity study is required. In line with this, a recent fMRI study revealed interesting cerebellar activation and coupling with the cerebrum regions (e.g., amygdala) relevant for the processing of happiness and disgust (Schienle and Scharmüller, 2013). However, due to the slow hemodynamic responses they were unable to elucidate the exact timing of these events.

The interaction requires the completion of initial modulations of arousal and valence (Delplanque et al., 2006; Dolcos and Cabeza, 2002; Gianotti et al., 2008). Thus, it is expected that it emerges late. Here, the interaction effects took place at ~600 ms after the stimulus onset, ~400 ms after the onset of arousal processing and ~150 ms after the onset of valence. Arousal by valence interaction is usually processed under further elaboration of the stimuli and aids in evaluating its emotional value (Robinson et al., 2004). Thus, the motivational qualities of the integrated emotional (pleasant and high arousal) information – processed within V and Crus I at ~600 ms – may contribute to slower responses.

Gamma-band responses in cerebellum

In terms of frequency, previous studies have revealed compelling MEG findings for the cerebellum including low (2 to 30 Hz) (Tesche and Karhu, 2000) and high-frequency oscillations (~60 to 150 Hz) (Dalal et al., 2008; Guggisberg et al., 2007). The cerebellum may primarily exhibit oscillatory modulations that are not necessarily phase-locked, precluding robust production of phase-locked evoked responses from natural stimuli (Dalal et al., 2013). Here, we analyzed the induced gamma-band activity, which usually occurs 200–300 ms after stimulus presentation or later, so as to exploit the phase information across trials. Induced analysis offers an insight into a different facet of the stimulus processing by being more sensitive to phase resets. Our focus on the gamma frequency band can be justified by the fact that gamma oscillations are considered of particular importance for emotion (Keil et al., 2001; Luo et al., 2007, 2009, 2010; Müller et al., 1999; Oya et al., 2002). Müller et al. (1999) suggested that the distribution of gamma oscillations is linked to neural areas engaged in binding emotional information. Keil et al. (2001) found that early mid gamma band activity (30–45 Hz) at 80 ms post-stimulus was enhanced in response to aversive stimuli only, whereas the higher gamma activity (46–65 Hz) at 500 ms showed an enhancement of arousing, compared to neutral pictures.

MEG ability to detect and localize gamma-band cerebellar responses

The study of induced gamma-band activity in the cerebellum by using MEG faces two main methodological challenges: (i) the cerebellum is traditionally considered a relatively deep brain source and MEG is limited in the recording and accurate localization of signals originating from deep structures, and (ii) the frequency spectrum of gamma-band neural activity overlaps with electromyogenic artifacts from cranial and ocular muscles.

For a long time the imaging community considered MEG incapable of identifying activity from deep brain areas in general and specifically from the cerebellum. However, there is an increasing number of recent demonstrations reporting MEG sensitivity to relatively deep source activity such as thalamus (Papadelis et al., 2012; Tenney et al., 2013), amygdala (Cornwell et al., 2008; Styliadis et al., 2014), hippocampus (Riggs et al., 2009) and cerebellum (Ioannides et al., 2005; Martin et al., 2006). In line with these findings, our previous phantom studies have shown the ability of MEG to detect and localize deep thalamic dipolar sources of weak high-frequency activity with an accuracy of 10–15 mm (Papadelis and Ioannides, 2007; Papadelis et al., 2009). The localization of these high-frequency thalamic generators is similarly challenging as the gamma-band cerebellar activity of the current study. Although a higher number of trials (360) was used in our phantom experiments compared to here (~160 in total, ~80 for each effect (arousal, valence), ~40 per affective condition), the active window in the SAM dual-analysis was of small length in the phantom studies (only 20 ms compared to 1000 ms here) containing 50 times less signal power compared to our current signals. Moreover, a weaker signal (in the amplitude range of human high frequency oscillations elicited by the stimulation of median nerve), compared to the gamma-band induced responses, was used to drive the phantom sources. Here, our task was to detect and localize accurately activity mainly in the posterior cerebellum, which is not as deep as the anterior cerebellum and thus its neural sources are closer to the sensor array. Considering the converging evidence from our previous phantom studies (Papadelis and Ioannides, 2007; Papadelis et al., 2009) as well as from human studies from both our and other groups (Ioannides et al., 2005; Tesche and Karhu, 2000) reporting indirect evidence of cerebellar activity with MEG, we are confident that our protocol and analysis methods were appropriate to capture the cerebellar spatiotemporal profile associated with emotional processing with a relatively good localization.

The contamination of MEG signals with cranial and ocular muscle activity is a major concern for MEG data in the gamma-band range. Here, we followed the most recent methodological recommendations for the collection, analysis, and presentation of high-frequency electrophysiological data (Gross et al., 2013; Hipp and Siegel, 2013; Muthukumaraswamy, 2013). Before and during the experiment: (i) we trained the participants to fixate on the screen and to avoid blinking, (ii) special care was taken that the participants sat comfortably in order to reduce postural muscle artifacts and relax their facial muscles, and (iii) we simultaneously collected EOG and ECG signals that facilitated the visual inspection and the ICA decomposition of the MEG data into artifactual and brain origin activity components. For the rejection of myogenic artifacts, we employed two complementary approaches suggested by Hipp and Siegel (2013): the epoch rejection, and the ICA. For the source localization, we employed a beamformer. Beamformer-based source localization techniques provide an efficient account for cranial muscle and saccadic spike artifacts in addition to high spatial specificity in the source space (Hipp and Siegel, 2013). The last notion is supported by our TFA results that present a "clear-cut" gamma-band steady-state response that is clearly visible only at the source space (see Fig. 2). Moreover, gamma-band activity at the source space does not extend to a broadband patchy-looking response that would be indicative of muscle artifacts occurring in a subset of trials (Muthukumaraswamy, 2013). Instead, it appears as a steady-state response with a very specific frequency content (~60–80 Hz). It is thus unlikely that the gamma-band activity observed at the source space represents activity of muscular origin.

Conclusions

Our findings advance the current knowledge on the cerebellar neurophysiological mechanism that underlies the emotional processing in the healthy population. Currently, very little is known about the spatiotemporal profile of emotional processing in the cerebellum. Here, we present evidence of a functional specificity of cerebellar lobules in the processing of arousal, valence, and their interaction. Our findings suggest that the emotional process does not depend only on the classic limbic cerebellum (i.e., vermis), but it also involves many of the hemispheric lobules. All these lobules seem to have separable roles in the processing of arousal and valence. Even though our study is limited by the relatively small number of participants, it provides for the first time the temporal component of emotional processing within the cerebellum. Our findings indicate that arousal, valence and their interaction are processed by distinct cerebellar lobules in a parallel manner

following a temporal hierarchy. The processing of high arousal takes place first and at early latencies. It is followed by the processing of unpleasant valence and later the interaction of pleasant and high arousal. This spatiotemporal profile indicates that cerebellar lobules are engaged in swift evaluations to highly arousing as well as unpleasant stimuli and slower evaluations to pleasant and highly arousing stimuli. The fast processing of negative stimuli is in particular of critical urgency in nature as failure to avoid them may be fatal. Since the temporal component of emotional processing plays a critical role in influencing vulnerability to psychopathology (Davidson, 1998), its study may prove to be a useful observation in accommodating the diagnosis of affective dysfunction with cerebellar disease populations.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.02.006.

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