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Baumann, Oliver; Mattingley, Jason B

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Title: Functional topography of primary emotion processing in the human cerebellum

Authors: Oliver Baumann & Jason B. Mattingley

The University of Queensland, Queensland Brain Institute & School of Psychology, St Lucia 4072, Australia

Correspondence should be addressed to:

Oliver Baumann
Queensland Brain Institute
The University of Queensland
St Lucia, Queensland, 4072
Australia

Ph: +61 7 3346 3305
Fax: +61 7 3346 6301
E-mail: o.baumann@uq.edu.au

Abstract

The cerebellum has an important role in the control and coordination of movement. It is now clear, however, that the cerebellum is also involved in neural processes underlying a wide variety of perceptual and cognitive functions, including the regulation of emotional responses. Contemporary neurobiological models of emotion assert that a small set of discrete emotions are mediated through distinct cortical and subcortical areas. Given the connectional specificity of neural pathways that link the cerebellum with these areas, we hypothesized that distinct sub-regions of the cerebellum might subserve the processing of different primary emotions. We used functional magnetic resonance imaging (fMRI) to identify neural activity patterns within the cerebellum in 30 healthy human volunteers as they categorized images that elicited each of the five primary emotions: happiness, anger, disgust, fear and sadness. In support of our hypothesis, all five emotions evoked spatially distinct patterns of activity in the posterior lobe of the cerebellum. We also detected overlaps between cerebellar activations for particular emotion categories, implying the existence of shared neural networks. By providing a detailed map of the functional topography of emotion processing in the cerebellum, our study provides important clues to the diverse effects of cerebellar pathology on human affective function.

Keywords: Cerebellum, Emotion, fMRI, Anger, Disgust, Fear, Happiness, Sadness

1. Introduction

In humans the cerebellum has long been recognized as being crucial for sensorimotor control (Holmes, 1917; Schmahmann, 2004). In recent years, however, a wealth of evidence from clinical, experimental and neuroimaging studies has led to the hypothesis that the cerebellum is also critically involved in perceptual, cognitive and, perhaps most intriguingly, emotional processes (Stoodley & Schmahmann, 2009; Bastian, 2011; Schmahmann, 2010). In a longitudinal follow-up study of 20 patients with cerebellar lesions, Schmahmann and Sherman (1998) observed prominent behavioral and affective changes, ranging from apathy to pathological crying and laughing, symptoms that they identified as a “cerebellar cognitive–affective syndrome”. Further support for a cerebellar role in emotional processes comes from anatomical studies in animals which have shown that the cerebellum has connections with other brain areas known to be involved in affective regulation, mood and higher cognition, including the hypothalamus, septum, amygdala, insula, basal ganglia, as well as the neocortex and brainstem nuclei (Anand et al., 1959; Snider & Maiti, 1976; Middleton & Strick, 2001; Schmahmann, 2001; Schutter & van Honk, 2005).

Surprisingly, despite the large literature on brain imaging of human emotions, potential contributions of the cerebellum have been largely ignored, or reported only as incidental to activity within the cerebrum (Fusar-Poli et al., 2009). One recent exception is a study by Moulton et al. (2011), which investigated aversion-related responses in the cerebellum to noxious heat and unpleasant images, and identified overlapping areas in the posterior cerebellum. By contrast, the authors found a distinct region of activation in response to pleasant images within right cerebellar hemispheric lobules VI and Crus II. These findings suggest a degree of neural specialization within the cerebellum for aversive (painful) stimuli as opposed to neutral or non-aversive stimuli.

Cognitive models predominantly consider emotions as being represented by just a small number of dimensions, and commonly conceptualize the affective space as a circle or circumplex (Russel, 1980). In contrast, neurobiological models of emotion have argued for the existence of a small set of discrete emotions that are instantiated by dedicated

neural systems (e.g. Ekman, 1992; Panksepp, 2005; 2008; 2011). This latter view is supported by a number of human neuroimaging studies, which have shown that different primary emotions activate, at least partially, distinct networks of cortical and subcortical structures (Phan et al., 2002; Murphey et al., 2003). Thus, for example, the amygdala is critically involved in mediating the so-called “threat-related” emotions of fear and anger (Davidson & Irwin, 1999; Adolphs, 2002), whereas the insula is involved in reactions of disgust (Wicker et al., 2003). Given the connectional specificity of the neural pathways that link the cerebellum with various cortical and subcortical structures involved in emotional processing (e.g. Anand, 1959), it is possible that such anatomical segregation and specialization for different emotional categories also exists within the cerebellum.

Here we employed functional magnetic resonance imaging (fMRI) to determine whether the human cerebellum is functionally segregated into distinct regions for processing the five primary emotions of anger, fear, disgust, sadness and happiness (Johnson-Laird & Oatley, 1989; Ekman, 1992).

2. Methods

2.1 Participants

Thirty healthy participants gave informed consent to the behavioral and brain imaging procedures, as approved by The University of Queensland Human Research Ethics Committee. The participants’ ages ranged from 18 to 30 years (mean age = 22.2, SD=2.9 years). Fifteen of the participants were female; all were right-handed.

2.2 Elicitation of emotions

Emotions were evoked by presenting participants with images from the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert, 1999), a standardized set of color photographs that includes affective ratings (along the dimensions of valence, arousal, and dominance) made by men and women (Lang, Bradley & Cuthbert, 1999). Instead of using the generic ratings to separate the images into categories of, for example, pleasant versus unpleasant, we asked participants to classify their emotional experience to

the stimuli into discrete categories of primary emotions, as per Mikels et al. (2005). By taking this approach, we aimed to isolate cerebellar activation patterns that are specific to each of the five primary emotions, and also to ensure that inter-individual differences in the predisposition to experience certain emotions could be quantified.

Each participant was presented with positive, negative and neutral affective pictures. The selection of the 240 pictures used in the experiment was based on the IAPS valence norms, which range from unpleasant (1) to pleasant (9): positive valence (40 pictures, mean IAPS valence norm 7.73), negative valence (160 pictures, mean IAPS valence norm 2.85), and neutral pictures (40 pictures, mean IAPS valence norm 5.02). We did not include any erotic picture stimuli, as there is disagreement as to whether sexual arousal should be classified as a positive emotion (Ekman, 1983), and due to the complicated patterns of emotion elicited by them for males and females, which may be contingent on sociocultural factors (Bradley et al., 2001).

Participants viewed the stimuli with a mirror that reflected the image from the projection screen placed at the head of the scanner bed. To reduce the requirement for exploratory eye movements, we utilized only those IAPS pictures in which the critical subject matter is contained within the centre of the image. To further control gaze, a fixation cross was presented in the center of the screen throughout the experiment.

2.3 Task

In every trial, an image was presented for 4 seconds, after which participants had 3 seconds to categorize their emotional reaction as happy, sad, angry, fearful, disgusted or neutral. Participants were instructed to withhold their response until the end of the stimulation period. To choose a category the participants pointed with an MR-compatible joystick (Current Designs inc., Philadelphia, USA) to one of six emotion labels (“angry”, “sad”, “disgusted”, “fearful”, “happy” and “neutral”), which were arranged at equal distances around a six-point star centered at fixation. The positions of the labels around the star were counterbalanced across participants. There were two experimental runs per participant, and each experimental run contained 120 trials. The trials were separated by

rest intervals of 3 seconds, in which the display contained the central fixation-cross alone. The temporal design of the stimulus sequence was optimized using the program optseq2 (Dale, 1999).

2.4 Pre-scan training and eye movement assessment

Participants were trained and assessed in the psychophysical laboratory prior to imaging to ensure that all individuals recruited into the fMRI study were able to maintain central fixation during the experiment. During the training session, participants undertook a 10-minute version of the experimental task (containing a different set of images than used in the main experiment), while eye movements were recorded to monitor fixation compliance using an Eyelink 1000 Gazetracker (SR Research Ltd., Mississauga, Ontario, Canada). The sampling frequency of the eye-tracker signal was 1000 Hz, the spatial resolution was 0.05° , and the accuracy was $\pm 0.125^\circ$. The eye-recording system was calibrated individually for each participant, to determine the exact deviation from central fixation. The eye tracker recording software was used to monitor the participants' fixation behavior and we provided immediate verbal feedback regarding their fixation performance. Participants were informed if their eye movements deviated more than $\pm 0.5^\circ$ from the central fixation spot. At the end of the training session all participants were able to maintain fixation during the task.

2.5 MRI acquisition

Brain images were acquired on a 3T MR scanner (Trio; Siemens, Erlangen, Germany) with a 32-channel head coil. For the functional data thirty-five axial slices (slice thickness, 3 mm) were acquired in an interleaved order, using a gradient echo echo-planar T2*-sensitive sequence (repetition time, 2.34 s; echo time, 30 ms; flip angle, 90° ; matrix, 64 x 64; field of view, 210 x 210 mm; voxel size, 3.3 x 3.3 x 3.0 mm). Per run 523 volumes were acquired for each participant. We also acquired a field map (same resolution/slices as the EPI, repetition time 468 ms, echo time 1 = 4.92 ms, echo time 2 = 7.38 ms) and a T1-weighted structural MPRAGE scan. A liquid crystal display projector back-projected the stimuli onto a screen positioned at the head of the participants in the end of the scanner gantry. Participants lay on their backs within the bore of the magnet

and viewed the stimuli via a mirror that reflected the images displayed on the screen. To minimize head movement, all participants were stabilized with tightly packed foam padding surrounding the head.

2.6 Image processing and statistical analysis of fMRI data

Image processing and statistical analyses were performed using SPM5 (Wellcome Department of Imaging Neuroscience, UCL, London, UK). Functional data volumes were slice-time corrected, unwarped using the individually acquired field maps and realigned to the first volume. A T2*-weighted mean of the images was co-registered with the corresponding anatomical T1-weighted image from the same individual. The individual T1-image was used to derive the transformation parameters for the stereotaxic space and to create an individual binary mask to exclude areas that were not part of the cerebellum, using the spatially unbiased infratentorial template (SUIT) for the cerebellum and the associated normalization procedure (Diedrichsen 2006). The transformation parameters and the mask were then applied to the individual co-registered EPI images. The binary mask and the resulting images were manually inspected using MRICron (<http://www.sph.sc.edu/comd/rorden/mricron>) to ensure that the automatic segmentation process functioned properly. Images were then smoothed with an 8-mm full-width half maximum (FWHM) isotropic Gaussian kernel.

Analyses using the general linear model (Friston et al. 1995) were conducted after applying high-pass filtering (cut-off: 128 s). In an event-related design analysis, responses during the 4 s stimulation periods were modeled with a boxcar function convolved with the hemodynamic response function separately for the 6 conditions, based on each individual's subjective categorization of their emotional experience (i.e., neutral, anger, disgust, fear, sadness and happiness). The relevant conditions were analyzed at the group level with SPM5 using t-tests to test for differences of the BOLD signal in each of the five evoked emotions with the neutral control condition, which was matched for visual input, attentional demands and motoric response requirements. We found that seven of the participants, of whom five were females, had very low reactions of anger (< 10 trials). Therefore, for the statistical contrast of anger > neutral, we only included data from

participants who experienced anger in at least 10 trials. Clusters surpassing a voxel-wise statistical threshold of $p = 0.05$ (t-contrast analysis, corrected for multiple comparisons, extent threshold = 5) were identified as active. A probabilistic atlas of the cerebellum (Diedrichsen et al., 2009; Diedrichsen et al., 2011) and MRICron (<http://www.sph.sc.edu/comd/rorden/mricron>) were used for the identification of anatomical locations. Figure 1 shows a detailed map of the human cerebellum, with key anatomical regions highlighted, following the nomenclature of Schmahmann et al. (2000).

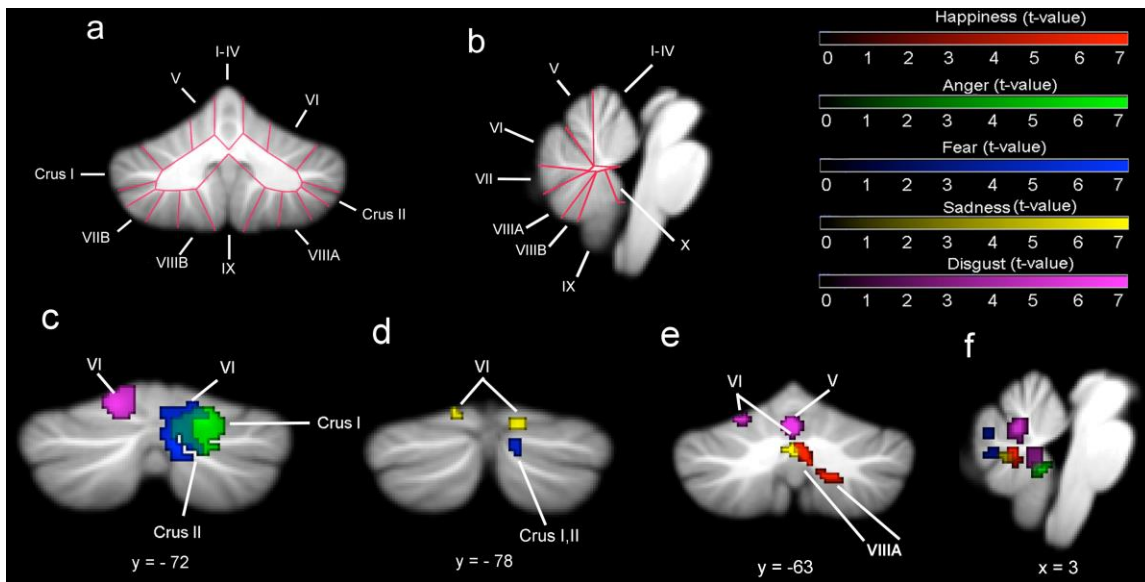


Fig 1: FMRI results. **a, b** Human cerebellar anatomy shown in sagittal and coronal planes (nomenclature according to Schmahmann et al., 2000), derived using the probabilistic atlas of the cerebellum by Diedrichsen et al. (2009). **c-f** MR brain slices showing mean BOLD activity from the random-effects analysis comparing emotion-specific effects (activation overlaps are indicated by intermediate colors).

3. Results

3.1 Behavioral data

Figure 2 shows the average relative frequencies of emotions elicited by the set of IAPS images. With the exception of anger, all emotions were well represented. We found that five of the female participants and two of the male participants rarely reported the experience of anger (<10 trials each), which explains the relatively low average frequency for this emotion (6.57%). This outcome is consistent with previous studies in which difficulties were noted in eliciting anger under artificial experimental conditions

(Gerrards-Hesse, Spies, & Hesse, 1994; Gross & Levenson, 1995; Mikels et al., 2005).

To examine sex differences in the ratings, we computed repeated-measures ANOVAs for each image, with the within-participant factor of emotion (anger, disgust, fear, sadness, happiness, and neutral) and the between-participants factor of sex (male, female). This analysis revealed that 20.0% of the 240 images had different categorical ratings between the sexes. Chi-square tests revealed that this difference arose principally because females tended to report the experience of fear (Chi-square = 9.875; $df = 1$; $p < 0.05$) or “no emotion” (neutral), (Chi-square = 12.004; $df = 1$; $p < 0.05$), whereas males tended to report anger (Chi-square = 207.792; $df = 1$; $p < 0.05$) or happiness (Chi-square = 9.888; $df = 1$; $p < 0.05$). There were no sex differences for the categories of disgust (Chi-square = 0.015; $df = 1$; $p > 0.05$) or sadness (Chi-square = 3.375; $df = 1$; $p > 0.05$).

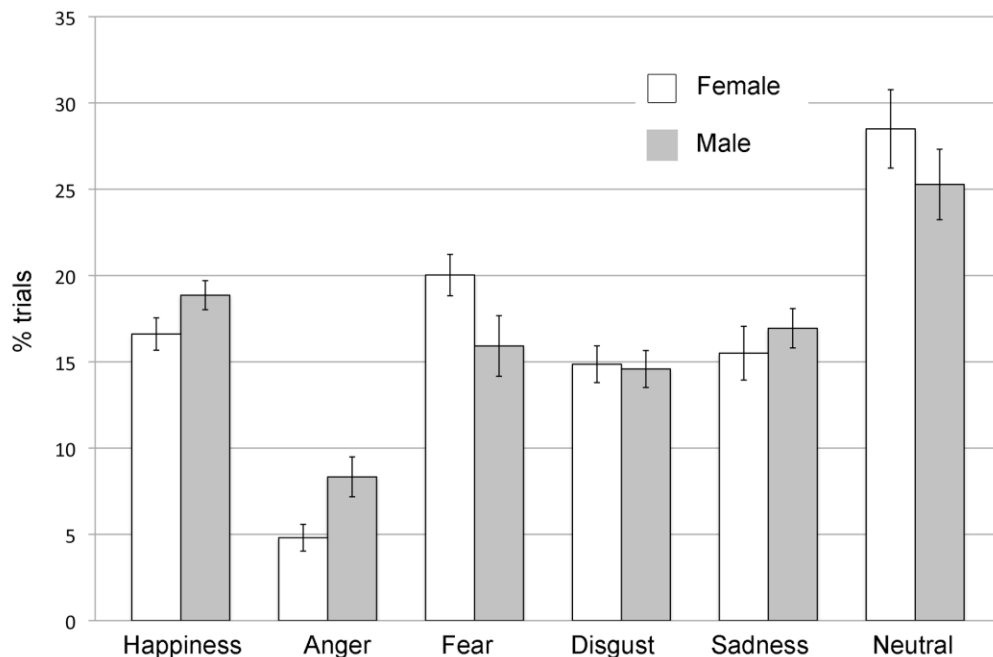


Fig 2: Relative frequency of the emotions elicited by the stimulus material (± 1 standard error) plotted separately for female and male participants.

3.2 Brain imaging data

When contrasted with the neutral condition, all five primary emotions led to activations that were located almost exclusively in the posterior lobe of the cerebellum (lobules VI –

IX; see Figure 1c-f). With the exception of disgust, which also evoked activation in vermal lobule V, there was no significant activation in the anterior or flocculonodular lobes (see Table 1).

Table 1 Summary of fMRI findings within the cerebellum for the contrasts of the five evoked emotions with the neutral control condition.

Region	Hemisphere	MNI coordinates			T-values / z-values of maxima
		X	Y	Z	
Anger					
Vermal lobule VI and VIIA, Paravermal lobule VI and Crus I,	R	18	-72	-24	7.12/5.08 (253)
Hemispheric lobule VI	R	32	-70	-22	5.57/4.35 (8)
Vermal lobule IX	L+R	4	-52	-38	5.56/4.35(26)
Fear					
Paravermal lobules VI, Crus I and Crus II; vermal lobules VI VIIA and VIIB	R	10	-72	-36	6.69/5.16(179)
Disgust					
Paravermal lobule VI	L	-16	-70	-20	6.86/5.25(130)
Vermal lobules V, VI, VIIIA, IX	L+R	-2	-52	-34	6.71/5.17(128)
Sadness					
Vermal lobule VI and VIIA, Paravermal lobules VI and Crus I	R	12	-76	-24	5.51/4.52(23)
Vermal lobules VIIB and VIIIA	L+R	0	-64	-32	5.37/4.44(20)
Vermal lobule VI, Paravermal lobule VI	L	-12	-78	-18	5.19/4.33(10)
Happiness					
Vermal lobules VIIIA	L+R	6	-62	-34	5.35/4.43(24)
Paravermal lobules VIIIA	R	20	-58	-46	5.10/4.27(36)

Spatial coordinates, anatomical locations and cluster-size of the local maxima in the group analysis, showing significant activations for all five emotions ($p \leq 0.05$, corrected for multiple comparisons). Abbreviations: L = left hemisphere, R = right hemisphere. Sagittal divisions were defined according to Luft et al. (1998); vermis: $-10 \text{ mm} \leq x \leq +10 \text{ mm}$; left and right paravermal region: $-24 \text{ mm} \leq x < -10 \text{ mm}$, $+10 \text{ mm} < x \leq +24 \text{ mm}$; left and right lateral hemispheres: $x < -24 \text{ mm}$, $x > +24 \text{ mm}$).

Each of the five emotions evoked activity in the cerebellar vermis as well as in the intermediate parts of the cerebellar hemispheres (i.e., the paravermis). For the emotion of

anger we also identified activity in the lateral aspect of the right cerebellar hemisphere. The extent of activity across the cerebellum was greater for anger, fear and disgust (179 - 287 voxels), compared with sadness and happiness (53 - 60 voxels).

Activity patterns for the five categories of emotion revealed both unique and overlapping areas across the two cerebellar hemispheres. In the right cerebellum, anger and fear evoked partly overlapping activations, predominantly in the paravermal lobules VI and Crus I (see Figure 1c). Happiness was also associated with right paravermal activations. However, these were located more inferiorly in lobule VIIIA and did not overlap with activity clusters for any of the other emotions (see Figure 1e). In the left cerebellum, activity to disgust and sadness was evident in paravermal lobule VI, but the extent of this activity was larger for disgust (see Figure 1c,d). In the vermal zone of the cerebellum, the experience of happiness and sadness led to partly overlapping activity in lobule VIIIA (see Figure 1e,f), whereas anger and disgust evoked partially overlapping activations in lobule IX (see Figure 1f).

In addition to analyzing activity within the cerebellum, we also performed exploratory whole-brain analyses to determine whether the stimuli we employed successfully activated cortical and subcortical brain regions commonly found to be involved in neural processes related to the experience of emotion (Wager et al., 2003; Phan et al., 2002). A statistical comparison of the BOLD signal from the five evoked emotional states with the neutral (control) condition revealed significant emotion-related activity in several key regions commonly found to be associated with emotional processing (e.g. Phan et al., 2002), including the amygdala, orbitofrontal cortex, dorsomedial and ventromedial prefrontal cortex, the striatum and the insula ($p=0.05$, corrected for multiple comparisons; see Table 2). Furthermore, as with the cerebellar activation patterns, we identified both unique and overlapping areas of activity for the five categories of emotion. For instance, whereas all five emotions were associated with activity in medial frontal and striatal areas, only fear and anger elicited activity in the amygdala, and only anger and disgust elicited activity in the insula.

Table 2 Summary of fMRI findings from the whole-brain analysis for the contrasts of the five evoked emotions with the neutral control condition.

Region	Hemisphere	Brodmann	MNI coordinates			T-values / z-
			X	Y	Z	
Whole Brain						
Disgust						
Middle cingulate gyrus	L+R	24/32	-6	4	44	8.30/5.89 (155)
Happiness						
Anterior cingulate/ DMPFC	L+R	9/10/11/32	-6	54	12	8.54/5.99 (224)
Anterior cingulate/ VMPFC	L+R	10/11/32	-4	44	-6	8.12/5.82 (170)
Sadness						
Middle cingulate gyrus	L+R	24/32	2	6	50	7.82/5.69 (223)
Additional significant ROI						
Anger						
Striatum	L	-	-14	4	14	6.37/4.74
DMPFC	L	10	-8	62	30	5.26/4.19
DMPFC	L	9	-6	52	32	4.55/3.78
OFC	L	47	-42	22	-6	5.54/4.34
OFC	L	47	-42	34	-4	5.52/4.27
Striatum	R	-	14	6	8	4.19/3.55
Insula	L	-	-38	20	-6	5.08/4.09
Insula	L	-	-32	22	-4	4.49/3.74
Insula	L	-	-40	22	0	4.13/3.52
Disgust						
Amygdala	R	-	26	-2	-12	3.57/3.23
DMPFC	L	32	-8	16	42	4.72/4.03
Insula	L	-	-34	26	6	4.02/3.55
Striatum	L	-	-22	6	-6	4.44/3.85
Fear						
Amygdala	L	-	-28	-4	-12	2.20/2.10
Striatum	L	-	-24	2	6	5.20/4.34
Striatum	L	-	-24	10	-2	4.45/3.85
Happiness						
Striatum	L	-	-6	16	2	4.21/3.69
Sadness						
DMPFC	L	10	-10	54	28	5.50/4.51
DMPFC	L	32	-6	16	42	5.50/4.51
DMPFC	R	9	6	54	30	5.38/4.45

Spatial coordinates, anatomical locations and cluster-size of the local maxima in the group analysis, showing significant activations for all five emotions ($p \leq 0.05$, corrected for multiple comparisons). Abbreviations: DMPFC = dorsomedial prefrontal cortex, L = left hemisphere, OFC = orbitofrontal cortex, R = right hemisphere, VMPFC = ventromedial prefrontal cortex.

Finally, to identify potential sex differences in emotion processing, we compared neural responses between males and females for the five different emotions. There were no significant differences in BOLD activity, either in the cerebellum or in other cortical or subcortical structures ($p \leq 0.05$).

4. Discussion

In recent years, clinical and neuroimaging studies have provided compelling evidence for a cerebellar role in the processing of emotion (Stoodley & Schmahmann, 2009). In the present study we tested the hypothesis that different primary emotions are associated with distinct patterns of cerebellar activity. While earlier work had already revealed different cortical and subcortical networks for distinct emotions (Phan et al., 2002; Murphey et al., 2003), it was not clear whether the same principle of organization might also apply to the cerebellum. In support of this hypothesis, we found that the primary emotions of anger, fear, disgust, sadness and happiness led to distinct patterns of cerebellar activity. However, we also detected localized regions of overlap in the activation patterns for individual emotions. Our results reveal for the first time that the cerebellum represents the five primary emotions in functionally distinct regions (see figure 1c-f), mirroring to some extent the segregation of emotion processing seen in the cerebrum (Phan et al., 2002; Murphey et al. 2003).

We also detected overlaps between the activation patterns of individual emotions. The experience of fear and anger led to large and substantially overlapping activations in the vermis and paravermis of the right cerebellar hemisphere (see Figure 1c). The emotions of fear and anger are both elicited by signals of threat (Cannon, 1915). It is therefore plausible that these two emotions share, in part, a neural network that subserves the processing of threat-related stimuli and mediates reciprocal autonomic responses for fear and anger (i.e. fight or flight). For the emotion of anger we also identified a separate cluster of activity in the lateral aspect of the right cerebellar hemisphere. It has been proposed that the lateral aspects of the posterior hemispheric lobules contribute to complex higher-level cognitive tasks (c.f. Stoodley & Schmahmann, 2009). In light of this theory, our observation of anger-related activation in the lateral zone of the right

cerebellar hemisphere might indicate involvement of neurons in this region in the regulation of cognitive components of emotional task performance, such as the appraisal of threat (Danesh, 1977; Fanselow, 1994), complementing the vermal-mediated autonomic response component for this emotion. Interestingly, anger was also the only emotion for which we observed significant activation in the orbitofrontal cortex, a region that, given its extensive connectivity with the dorsolateral prefrontal cortex and the amygdala, is thought to play a pivotal role in “linking” cognitive and emotional processes (Barbas, 2000). These findings might imply that the experience of anger is more associated with cognitive processing than the other four emotions.

Our findings also demonstrate that the emotions of happiness and sadness elicit partially overlapping activity in the vermis (see Figure 1e,f). Happiness and sadness are both mediated via opioid-based mechanisms (Panksepp, 1998). For instance, while the opioid system of young rats is active during play, social isolation is associated with low opioid-levels (Panksepp, 1998). In humans, happiness and sadness are also known to be associated with complementary patterns of activity in the anterior cingulate cortex (e.g. Damasio et al., 2000; Killgore & Yurgelun-Todd, 2004; Wager et al., 2003), a major node in the human endogenous opioid system (Zubieta et al., 2003). We therefore hypothesize that vermal lobule VIIIA is part of a neural network which, among other regions, comprises the cingulate cortex and mediates reciprocal autonomic responses for happiness and sadness.

Finally, we detected partial overlaps in the activation patterns for anger and disgust in vermal lobule IX (see Figure 1f). Most interestingly, we found that anger and disgust were also the only emotions that led to statistically significant activity in the insula, which tentatively points to a partially shared neural network. This finding might at first seem surprising, given that the prototypic forms of anger and disgust are rather distinct; whereas anger is commonly defined as a reaction to frustration or goal blockage (Plutchik, 1980), disgust reflects a mechanism that protects against ingestion of potential contaminants (Rozin & Fallon, 1987). However, among humans these two primary emotions are thought to have evolved into a more generic socio-moral affective state that

can be triggered by identical situations, such as sexuality, abuse of human bodies, and even betrayal or racism (Rozin et al., 2008). Alternatively, activation overlaps between anger and disgust might reflect the neural correlate of experiencing ‘mixed-emotions’, in this case anger and disgust at the same time (Panksepp, 1998; Larsen & McGraw 2011).

We found that all five emotions evoked activity in the cerebellar vermis as well as in the intermediate parts of the cerebellar hemispheres (i.e., the paravermis). Our findings therefore point to a key role of the medial cerebellum in emotional processing. They are concordant with earlier suggestions that the vermis, based on its connectivity with limbic brain structures, can be considered the “limbic cerebellum” (Heath et al., 1979; Schmahmann, 1991, 1996, 2004). This assumption is further corroborated by recent human fMRI evidence (Habas et al., 2009), suggesting that a region within vermal and paravermal lobule VI constitutes a node in a corticolimbic network, centered on the dorsal anterior cingulate and fronto-insular cortices, which is involved in detecting, integrating and filtering emotional information (Seeley et al., 2007). Several clinical studies have reported that the affective component of the cerebellar cognitive-affective syndrome is most notable when lesions involve the vermis and paravermis (c.f. Schmahmann & Sherman, 1998). Patients with lesions in this part of the cerebellum typically have striking deficits in emotion regulation, manifested as flattening or disinhibition of affect (Schmahmann, Weilburg & Sherman, 2007).

While many of the differences between men and women in the processing of emotions may be attributable to social factors and learned patterns of behavior (Hamann & Canli, 2004), previous neuroimaging studies have also suggested that sex differences in emotional responding might, at least partly, be subserved by differences in emotion related cortical and subcortical brain activity (Canli et al., 2002; Wrase et al., 2003). By including a relatively large sample of male and female participants in our study, we aimed to test the hypothesis that sex differences in emotion processing might also be reflected by differences in functional activity within the cerebellum. We found no evidence for any sex differences across emotion categories, either in the cerebellum or in relevant cortical and subcortical regions. By contrast, participants’ behavioral responses

indicated that females were more likely to report fear to the standardized images, whereas males had a greater predisposition to experience anger and happiness. Several previous studies that reported sex differences in emotion-related brain activity used IAPS images that had been divided into the categories of ‘pleasant’ and ‘unpleasant’, based upon generic ratings, rather than measuring the relative frequencies of different primary emotions elicited by the stimulus materials (e.g. Wrase et al. 2003). We therefore believe that earlier reports of sex differences in emotion-related brain activity might have been confounded by inter-individual differences in the predispositions of males and females to experience certain primary emotions.

Finally, it is important to note that the cerebellum also has a well-known role in the control of eye movements (e.g. Lynch & Tian, 2006; Leigh & Zee, 2006). For example, it has been shown that the execution of both smooth pursuit eye movements (Tanabe et al. 2002) and saccades (Dieterich et al., 2000) leads to an increased BOLD signal in the cerebellum. For this reason, we took great care to minimize eye movements that might confound our imaging results. To reduce the requirement for exploratory eye movements we utilized only those IAPS pictures in which the critical visual information was centered within the image, and trained all participants to maintain fixation using on-line eye monitoring prior to scanning.

Conclusions

We have provided the first evidence in healthy humans that distinct subregions of the cerebellum are responsive during the experience of happiness, anger, disgust, fear and sadness. Our findings also reveal overlaps between the activation patterns for selected emotions, indicating the existence of shared neural networks. For instance, we detected partial overlap in activations associated with fear and anger (paravermal lobules VI and Crus I), anger and disgust (vermal lobule IX), and happiness and sadness (vermal lobule VIIIA). While several recent MRI studies identified multiple cortico-cerebellar networks in humans (Habas et al., 2009; O’Reilly et al., 2010; Buckner et al., 2011), confirming its role in non-motor processes, they did not specifically investigate cerebellar connectivity with limbic networks. To advance our understanding of the cerebellum’s

role in emotion processing it will be essential to establish a comprehensive and detailed map of the cerebellar-limbic network. In future work, therefore, it will be important to conduct a dedicated analysis of the anatomical, functional and effective connectivity between key cerebellar regions and relevant cortical and subcortical limbic structures. Finally, whereas our study focused on stimulus-driven emotional responses, previous evidence indicates that emotions are also susceptible to top-down regulatory control by prefrontal areas (Ochsner et al., 2002; Phan et al., 2005). The fact that the cerebellum is reciprocally connected with a range of limbic structures, as well as the prefrontal cortex (c.f. Schmahmann, 2001), provides a strong neuroanatomical argument in favor of cerebellar involvement in emotion regulation. A further goal for future investigations should be to determine whether emotion related activity in the cerebellum can be modified by task instructions or other cognitive processes that are under voluntary control. In the meantime, the current findings provide important new clues to the likely effect of focal and diffuse cerebellar pathology on emotion processing, and may even facilitate the diagnosis of affective dysfunction in patients with cerebellar disease.

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