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Inability to Process Negative Emotions in Cerebellar Damage: a Functional Transcranial Doppler Sonographic Study

Michela Lupo · Elio Troisi · Francesca R. Chiricozzi · Silvia Clausi · Marco Molinari · Maria Leggio

Abstract Recent studies have implicated the cerebellum as part of a circuitry that is necessary to modulate higher order and behaviorally relevant information in emotional domains. However, little is known about the relationship between the cerebellum and emotional processing. This study examined cerebellar function specifically in the processing of negative emotions. Transcranial Doppler ultrasonography was performed to detect selective changes in middle cerebral artery flow velocity during emotional stimulation in patients affected by focal or degenerative cerebellar lesions and in matched healthy subjects. Changes in flow velocity during non-emotional (motor and cognitive tasks) and emotional (relaxing and negative stimuli) conditions were recorded. In the present study, we found that during negative emotional task, the hemodynamic pattern of the cerebellar patients was significantly different to that of controls. Indeed, whereas relaxing stimuli did not elicit an increase in mean flow velocity in any group, negative stimuli increased the mean flow velocity in the right compared with left middle cerebral artery only in the control group. The patterns by which mean flow velocity increased during the motor and cognitive tasks were similar within patients and controls. These findings support that the cerebellum is part of a network that gives meaning to external stimuli, and this particular involvement in processing negative emotional stimuli corroborates earlier phylogenetic hypotheses, for which the cerebellum is part of an older circuit in which negative emotions are crucial for survival and prepare the organism for rapid defense.

Keywords Cerebellum · Emotional task · Middle cerebral artery · Blood flow velocity · Focal cerebellar lesion

Introduction

For several decades, the debate over hemispheric asymmetries for emotion perception and identification has been going on.

In the last years of the nineteenth century, clinical evidence in patients with unilateral cortical damage suggested that the right hemisphere (RH) is specialized in perceiving, expressing, and experiencing emotions [1]. More recently, it has been advanced the hypothesis that the RH processes all basic emotions (positive and negative) and is the seat of subjective affect (feeling) [2–6]. In regard to the left hemisphere (LH), contradictory findings make its contributions to emotional processing highly debatable (i.e., whether the LH does not differentiate between emotional and neutral faces [7] or only processes positive emotions [2]).

Within this framework, interesting insights derive from neuroimaging studies that showed a widespread distribution of neural activity associated with emotional tasks and involving both hemispheres (i.e., see meta-analysis [8, 9]).

Elizabeth Shobe (2014) proposed a qualitatively different involvement of each hemisphere in emotional processing. According to her model, the RH directly mediates the identification and comprehension of positive and negative emotional stimuli, whereas the LH contributes to higher level processing of emotional information that has been shared via the corpus

M. Lupo · F. R. Chiricozzi · S. Clausi · M. Leggio
Department of Psychology, Sapienza University of Rome,
00185 Rome, Italy

M. Lupo · F. R. Chiricozzi · S. Clausi · M. Leggio (✉)
Ataxia Laboratory, IRCCS Santa Lucia Foundation,
00179 Rome, Italy
e-mail: maria.leggio@uniroma1.it

E. Troisi
IRCCS Santa Lucia Foundation, 00179 Rome, Italy

M. Molinari
Neurological and Spinal Cord Injury Rehabilitation Department A,
IRCCS Santa Lucia Foundation, 00179 Rome, Italy

callosum, so that “the complex processing of and responding to emotions require a cross-hemispheric collaboration that originates in the RH, and this is particularly true for negative emotions” [6].

It is worth noting that Shobe’s model makes the claim that emotional processing arises at a more basic level that begins with subcortical networks and their influence on cortical activity. The right amygdala–pulvinar–colliculus pathway would subserve automatic or unconscious processing of emotional stimuli and subsequent activation for physiological preparation. The cortico-pulvinar–cortical pathway would provide “the preliminary link between the immediate fast and coarse subcortical processing and the cortical processing of emotion”, enabling a cross-callosal transfer of emotional information from the RH to the LH [6].

The subcortical and cortical networks, involved in tasks that require emotional stimuli to be processed, have been extensively investigated by fMRI studies. It has been described that happiness activates the middle temporal gyrus, parahippocampal gyrus, hippocampus, claustrum, inferior parietal lobule, cuneus, and middle frontal gyrus, whereas negative emotions activate the posterior cingulate gyrus, fusiform gyrus, and cerebellum [10].

Neuroimaging evidences of cerebellar involvement in emotional processing confirm previous findings from anatomical and clinical studies that the cerebellum is part of the circuitry that is necessary for modulating higher order and behaviorally relevant information in the emotional domains [11, 12].

Very recently, Baumann and Mattingley (2012) provided the first evidence that specific and distinct subregions of the cerebellum are involved in the processing of different primary emotions. Indeed, all five primary emotions, happiness, anger, disgust, fear, and sadness, evoke spatially distinct patterns of activity in the posterior cerebellar lobe [13]. Furthermore, for selected emotions, such as fear and anger, anger and disgust, happiness and sadness, cerebellar areas of activation overlap indicating the existence of shared neural networks [13].

The results of this important study have been replicated by Schienle and Scharmüller (2013) that also performed a functional connectivity analysis to identify cortical as well as subcortical brain regions that interact with the cerebellum during the emotions of disgust and happiness. Increased connectivity of the cerebellum with limbic regions was observed for both emotions, indicating the existence of widespread connections of the cerebellum with regions involved in emotion experience. According to the authors, this cerebellar network might explain the pronounced changes of affective experience described in patients affected by cerebellar damage [14].

The introduction of investigation techniques such as positron emission tomography and functional magnetic resonance imaging has led to the development of a new approach to the study of emotions [15–17].

However, even though these methods provide high spatial resolution, they are not as suitable for analyzing rapid sequential events because of the relatively low sampling frequency [18]. On the other hand, with transcranical Doppler ultrasound (TCD), it is possible to detect instantaneous changes in blood flow velocity of large cerebral arteries. Even if such information cannot be used for describing the absolute value of cerebral blood flow (CBF), it is a reliable indicator of a rapid flow change in the areas supplied by the large intracerebral arteries [19, 20]. Thus, TCD has a high temporal resolution providing information about the time course of CBF changes. On the other hand, the main disadvantage of TCD is its low spatial resolution, determined by the size of the cerebral area supplied by the artery being studied.

This technique has been widely employed in the investigation of cerebral perfusion changes during mental activity [21–23] and in emotional stimulation [18, 24].

Troisi and collegues (1999) demonstrated that TCD is suitable for detecting rapid changes in mean blood flow velocity (MFV) of the middle cerebral arteries (MCAs) during emotional stimulation in healthy subjects [24]. Their results suggest that the processing of negative emotional stimuli clearly evokes a general predominance of the RH. The specificity of the side-to-side asymmetry in cerebral activation during processing of negative stimuli is confirmed by the fact that non-emotional stimulation produced a bilateral and symmetrical effect on MFV.

The aim of the present study was to investigate the involvement of the cerebellum in processing of negative emotions by analyzing whether a cerebellar damage affects the cortical activity during emotional tasks.

To this end, changes in mean blood flow velocity of the MCAs in patients affected by cerebellar damage were analyzed by TCD.

Changes of MVF were measured in MCAs, which supply the limbic, parietal, and frontal areas—all of which are involved in emotional processing.

Materials and Methods

We enrolled cerebellar patients—six affected by right focal cerebellar lesions (RCb) and seven affected by idiopathic cerebellar ataxia (ICA)—who had been hospitalized at Santa Lucia Foundation Rehabilitation Hospital and 13 matched control subjects (Ct). The demographics of each group are reported in Table 1. Figures 1 and 2 describe the localization of the focal cerebellar lesions. The diagnosis of ICA was based on clinical indications of a purely cerebellar syndrome and on evidence from magnetic resonance imaging (MRI) of atrophic pathology restricted to the cerebellum.

All patients underwent a neurological examination, and their motor impairments were quantified using a modified

Table 1 Characteristics of cerebellar and control groups; means and standard deviation (SD)

Groups	No. of subjects	Age (years)	Education level	Motor score	IQ
RCb	6	45.8 (13.3)	13.1 (2.8)	6.3 (4.4)	95.5 (10.1)
ICA	7	44.7 (15.6)	8.8 (4.9)	19.6 (11.7)	85.0 (9.2)
Ct	13	46.5 (12.8)	10.8 (4.6)	–	106.8 (9.5)

RCb right cerebellar group, *ICA* idiopathic cerebellar ataxia, *Ct* control group, *IQ* intelligence quotient

version of the Appollonio cerebellar motor deficit scale [25], which ranges from 0 (absence of any deficit) to 42 (presence of all deficits to the highest degree) (Table 1).

The experimental procedures were approved by the ethical committee of IRCCS Santa Lucia Foundation (CE-PROG.2-AG4-187), and written consent was obtained from each subject per the Helsinki Declaration.

All patients performed the battery of tests for mental deterioration [26] to exclude the presence of global cognitive impairments and took the Wechsler Adult Scale–Revised [27] to match patients and controls with regard to IQ (Table 1).

Experimental paradigm was carried out according to the protocol described by Troisi and colleagues [18, 24].

Experimental sessions were performed in a quiet room with the subjects in a comfortable sitting position without any visual stimulation. Subjects were instructed to close their eyes, relax, and breathe regularly. Right and left MCA mean flow velocity was continuously and simultaneously monitored by a Multi-Dop X/TCD7 transcranial Doppler instrument (DWL Elektronische Systeme GmbH, Esaote Biomedica).

Two dual 2-MHz transducers fitted on a headband and placed on the temporal bone were used to obtain a continuous bilateral measurement. The highest signal was sought at a depth ranging from 46 to 54 mm. This unit allows for continuous Doppler recording of the intracranial artery with online calculation of MFV in centimeters per second. By activating the "record" function, it is possible to save the Doppler spectra during the entire period of each study and then to calculate the MFV of any test period (rest phase and activation phase). For each subject, recording was made during a 2-min rest phase and during the whole performance of different tasks; before each recording, a return to the baseline values of flow velocity was documented. MFV changes were calculated as percentage

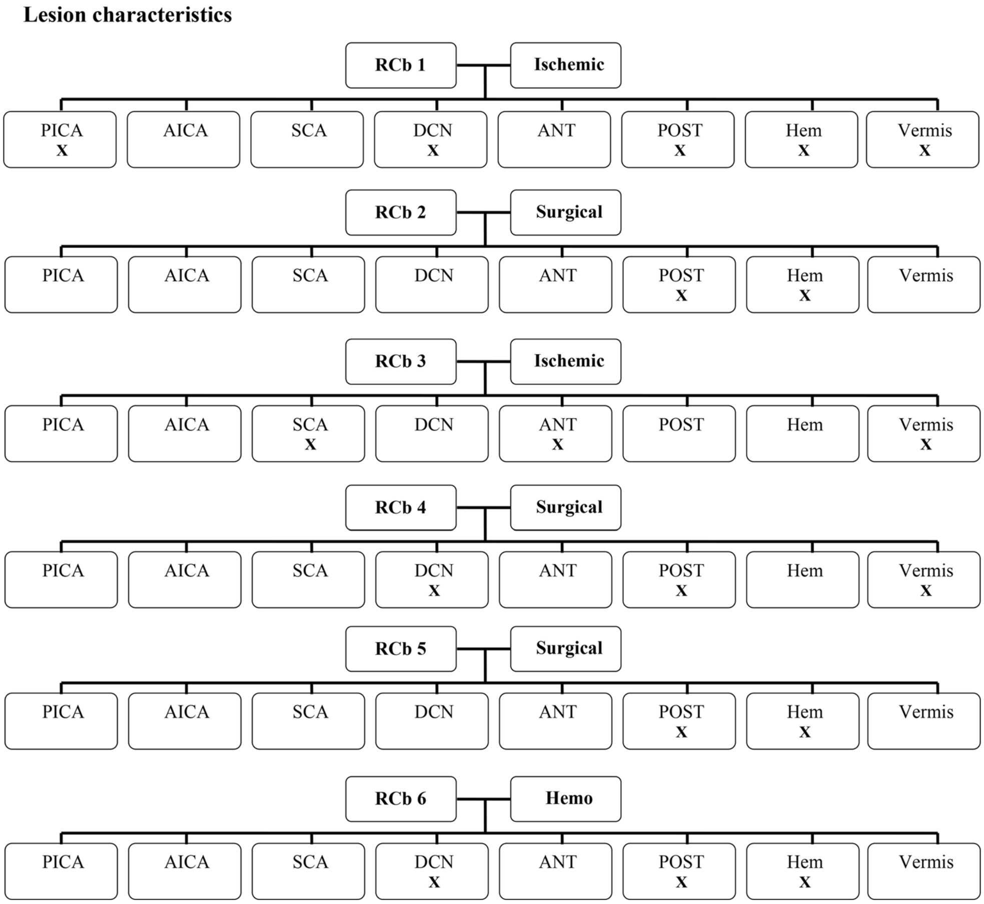

Fig. 1 Lesion characteristics in subjects with focal cerebellar lesion. The extent of focal cerebellar damage is summarized for each patient, evaluated on individual T1-weighed volumes in stereotaxic space with the Schmahmann 3D MRI atlas of the human cerebellum [35] and the 3D MRI atlas of human cerebellar nuclei as references [36]. *Ischemic* ischemic lesion, *Surgical* surgical lesion, *Hemo* hemorragic lesion, *PICA* posterior inferior cerebral artery, *AICA* anterior inferior cerebral artery, *SCA* superior cerebral artery, *DCN* dentate nucleus, *ANT* anterior lesion, *POST* posterior lesion, *Hem* hemisferic lesion, *Vermis* vermis lesion

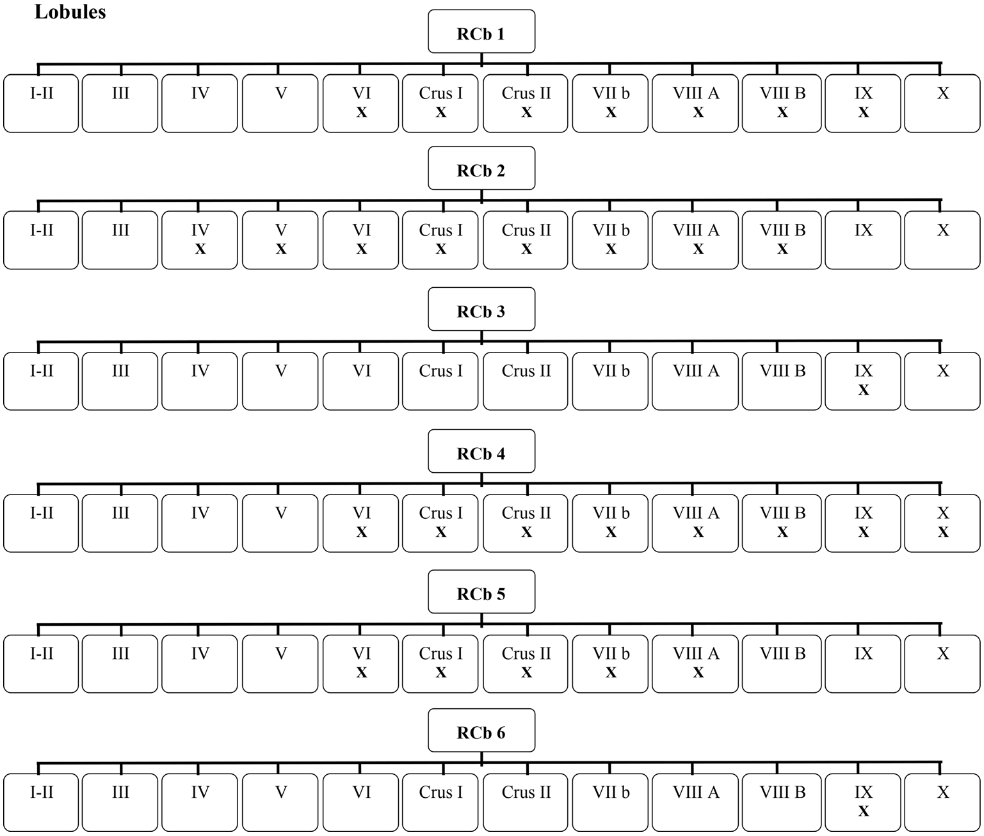

Fig. 2 Affected lobules in subjects with focal cerebellar lesion. The extent of focal cerebellar damage is summarized for each patient, evaluated on individual T1-weighed volumes in stereotaxic space with the Schmahmann 3D MRI atlas of the human cerebellum [35] and the 3D MRI atlas of human cerebellar nuclei as references [36]

Lobules

RCb 1	I-II	III	IV	V	VI X	Crus I X	Crus II X	VII b X	VIII A X	VIII B X	IX X	X
RCb 2	I-II	III	IV X	V X	VI X	Crus I X	Crus II X	VII b X	VIII A X	VIII B X	IX	X
RCb 3	I-II	III	IV	V	VI	Crus I	Crus II	VII b	VIII A	VIII B	IX X	X
RCb 4	I-II	III	IV	V	VI X	Crus I X	Crus II X	VII b X	VIII A X	VIII B X	IX X	X X
RCb 5	I-II	III	IV	V	VI X	Crus I X	Crus II X	VII b X	VIII A X	VIII B	IX	X
RCb 6	I-II	III	IV	V	VI	Crus I	Crus II	VII b	VIII A	VIII B	IX X	X

increase from rest phase to task performance. To evaluate the possible dysfunctioning of cerebrovascular reactivity of MCAs, all patients and controls were examined by calculating the breath holding index (BHI) [28]. This index is obtained by dividing the percent increase in MFV occurring during breath holding by the length of time (seconds) the subjects hold their breath after a normal inspiration. The length of apnea was arbitrarily chosen as 30 s.

To elicit disparate emotional responses, subjects were shown three series of 15 pictures in random order each for a period of 1 min (each picture was presented for 4 s) [24]. Two series were composed of relaxing stimuli (seascapes and mountain scenery). Another series was composed of negative emotion-related stimuli (images of plastic surgery).

The latter stimulation technique was chosen because a previous study [24] showed this method to be able to induce intense tonic emotional arousal in healthy subjects that is high enough to show hemisphere asymmetry and to measure lateralized control of emotional behavior.

Finally, to reveal a possible deficit in the ability to activate both hemispheres in response to non-emotion related stimuli, the protocol study included a motor task (finger tapping) and two cognitive tasks (verbal fluency and design discrimination) that were performed by both patients and controls. The motor task was a 2-min sequential thumb-to-finger opposition performed with right hand at a rate of two oppositions every 3 s. The cognitive task included (1) a verbal task requiring subjects to produce as many words as possible beginning with the letter “S” (word fluency) in 1 min; (2) a design discrimination task in which 10 pairs of abstract geometric designs, identical or different due to a small detail, were presented simultaneously for 5 s. Subjects had to decide whether the pairs were identical or different and to push a button with the right hand if they were identical or do nothing if they were different. Before each recording, a return to the baseline values of flow velocity was documented. The sequence of kinds of tasks was changed randomly. The efficacy of the breath holding was checked by means of a respiratory activity monitor (Normocapoxy, Datex).

In the present study, patients’ performances were similar to control ones in both cognitive tasks (see Table 2).

Based on a previous study that measured changes in MFV during mental activity, we expected a task-specific (motor or cognitive) increase in MCA [23].

One-way ANOVA was used to compare BHI values between groups (RCb, ICA, and Ct).

The effects of the motor, cognitive, and emotional tasks on flow velocity were analyzed by one-way ANOVA within and between groups (RCb, ICA, and Ct). When appropriate, the analyses were corrected by Duncan post hoc test (P_{Dunc}).

Results

By one-way ANOVA between the RCb, ICA, and Ct groups, BHI did not differ between groups ($F_{2,19}=2.929$; $p=0.078$).

Further, the patterns by which MFV increased during the motor and cognitive tasks were similar within groups, independent of the existence of cerebellar pathology (Table 2). In particular, during finger tapping with the right hand, the two groups of cerebellar patients and Ct subjects showed significantly greater reactivity in the left versus right MCA (RCb $p=0.010$; ICA $p=0.000$; Ct $p=0.000$). As expected, based on previous studies [23], the verbal fluency task effected a significant rise in MFV on the left side (RCb $p=0.001$; ICA $p=0.010$; Ct $p=0.000$), whereas the design discrimination task induced the opposite pattern (RCb $p=0.001$; ICA $p=0.011$; Ct $p=0.000$) (Table 2).

Notably, patient and control subjects differed specifically in MCA reactivity to the emotional task. Only in Ct subjects, negative emotion-related stimuli increased the MFV in the right MCA significantly more than in the left MCA ($p=0.000$). No modification in right MFV was detected in cerebellar subjects with negative emotion-related stimuli (RCb $p=0.136$; ICA $p=0.436$) (Table 2).

This disparate pattern of reactivity was selective for negative emotion-related stimuli. As expected [24], relaxing stimuli did not have significant effects in either MCA in control subjects or cerebellar patients (RCb $p=0.326$; ICA $p=0.886$; Ct $p=0.466$) (Table 2).

By one-way ANOVA between groups (RCb, ICA, and Ct), there was no difference in the motor task or verbal fluency task for the left MCA ($F_{2,23}=0.221$; $p=0.803$ and $F_{2,23}=0.242$; $p=0.786$, respectively) or in the design discrimination task for the right MCA ($F_{2,23}=0.301$; $p=0.742$). With regard to emotional stimuli, right and left MCA activation was similar for relaxing stimuli ($F_{2,23}=1.525$; $p=0.239$ and $F_{2,23}=1.785$; $p=0.190$, respectively). A significant effect between groups was detected only for negative emotion-related stimuli ($F_{2,23}=22.762$; $p=0.000$). Duncan post hoc comparisons showed that the percentage of MFV rose significantly in control right MCA but not those of patients (RCb vs Ct $P_{\mathrm{Dunc}}=0.000$; ICA vs Ct $P_{\mathrm{Dunc}}=0.000$).

Discussion

According to a previous study, changes in flow velocity in large cerebral arteries can be interpreted as a consequence of modifications in brain perfusion and then of cerebral activation [29, 30]. Thus, increases in flow velocity during task presentation can be interpreted to reflect enhanced neural activity in the MCA-supplied regions of the brain [18, 23, 24].

It is worth noting that the asymmetry of MFV in MCAs is associated with information processing in the cortex, and it is not an indicator of good or bad performances. Indeed, in the present study, changes in MVF of patients affected by cerebellar lesion were detected in right or left MCA accordingly to the specific task, as a consequence of motor or cognitive processing, independently from the performance level.

Table 2 Percentage of MFV changes from rest to performance of each task in the right and left MCAs in cerebellar and control groups; means and standard deviation (SD)

Groups	No. of subjects	BHI average	% Increment of MFV in specific side of MCA									
			Motor task		Cognitive tasks				Emotional tasks			
			Right	Left	Verbal		Design		Relaxing		Negative	
					Right	Left	Right	Left	Right	Left	Right	Left
RCb	6	1.1	3.1 (2.9)	10.6 (3.7)	1.7 (1.2)	8.1 (2.2)	8.8 (3.8)	3.6 (2.6)	1.9 (0.6)	2.6 (1.3)	1.4 (0.9)	3.0 (1.9)
ICA	7	1.2	2.5 (2.0)	9.4 (3.0)	2.4 (2.0)	7.1 (3.0)	9.2 (6.0)	3.4 (4.0)	3.0 (4.0)	3.1 (3.0)	3.2 (4.0)	3.6 (3.0)
Ct	13	1.3	1.8 (1.0)	9.8 (2.6)	1.2 (1.3)	7.9 (2.7)	10.2 (2.8)	2.8 (1.0)	3.9 (1.9)	4.4 (1.7)	9.1 (1.8)	2.8 (1.2)

MFV mean flow velocity, *MCA* middle cerebral artery, *RCb* right cerebellar group, *ICA* idiopathic cerebellar ataxia, *Ct* control group, *BHI average* breath holding index average, *Verbal* verbal fluency task, *Design* design discrimination

The main result of our study is that there are significant differences in hemodynamic patterns of and patients affected by cerebellar damage and Ct subjects during negative emotional tasks.

Whereas relaxing stimuli did not elicit an increase in MFV in any group, negative stimuli increased the MFV in the right compared with left MCA only in the control group. These data suggest that cerebellar lesions cause selective impairments in the ability to activate the right hemispheric areas during negative emotional stimulation.

This result allows us to hypothesize that when negative stimuli are presented to patients affected by cerebellar lesions, they do not perceive the negative value of the images or do not process their emotional content. In other words, the absence of MFV reaction in both MCAs in cerebellar patients is probably to indicate the "non-processing" of negative emotional stimuli. On the contrary, during motor and cognitive tasks, changes in MVF were detected in right or left MCA accordingly to the specific task. This means that cerebellar patients were elaborating the motor as well as the cognitive information regardless of the performance accuracy.

All in all, the present data indicates that in cerebellar patients, negative emotional stimuli do not cause an increase of MFV in right MCA (as controls do), probably because they do not detect the negative emotional content of the images observed.

Because the comparison between patients and Ct groups failed to demonstrate a significant group effect in tasks processing motor and cognitive stimuli—and considering the similarity in their BHI values—the lack of response to negative emotional stimuli cannot be attributed to general impairment of vascular reactivity. Notably, cerebellar damage affects negative emotional processing independently if it involves the entire cerebellum (see ICA) or the hemicerebellum which is not linked anatomically to the right cerebral hemisphere (see RCb). We consider this a strong element of our results. We already demonstrated that spatial and verbal information in visuomotor and verbal fluency tasks are altered bilaterally in unilateral cerebellar lesions [31, 32]. As previously said, based on the present results, we hypothesize that unilateral cerebellar lesions affects the capacity to detect the emotional component of images independently from the side of the cerebral cortex that processes such information.

The present study confirm the hypothesis that the cerebellum participates in elaborating negative emotions [10] and support earlier proposals, according to which the cerebellum belongs to a widespread network that determines the meaning of external stimuli by mediating facilitatory cortical processes during the processing of emotional information [12, 33]. These data are consistent with studies that have implicated the cerebellum as a part of an older circuit in which negative emotions, such as anger and sadness, are crucial for survival and prepare the organism for rapid defense [34].

In conclusion, this preliminary study demonstrates that cerebellar lesions create difficulties in encoding and processing negative stimuli.

A limit of the study is the absence of additional clinical, neuropsychological, and psychophysiological data, confirming the impairment of the cerebellar patients in negative emotions.

Moreover, the absence of patients affected by left focal cerebellar lesions and the focus exclusively on negative emotions are further limitations of this study and will be addressed in future research aimed to identify the precise lobular localizations that subserve negative emotional processing and determine cerebellar function in other types of emotions.

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Conflict of interest The authors have no conflict of interest to declare.

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