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A B S T R A C T

Clinical and neuroimaging data indicate a cerebellar contribution to emotional processing, which may account for affective-behavioral disturbances in patients with cerebellar lesions. We studied the neurophysiology of cerebellar involvement in recognition of emotional facial expression. Participants comprised eight patients with discrete ischemic cerebellar lesions and eight control patients without any cerebrovascular stroke. Event-related potentials (ERP) were used to measure responses to faces from the Karolinska Directed Emotional Faces Database (KDEF), interspersed in a stream of images with salient contents. Images of faces augmented N170 in both groups, but increased late positive potential (LPP) only in control patients without brain lesions. Dipole anaylsis revealed altered activation patterns for negative emotions in patients with cerebellar lesions, including activation of the left inferior prefrontal area to images of faces showing fear, contralateral to controls. Correlation analysis indicated that lesions of cerebellar area Crus I contribute to ERP deviations. Overall, our results implicate the cerebellum in integrating emotional information at different higher order stages, suggesting distinct cerebellar contributions to the proposed large-scale cerebral network of emotional face recognition.

1. Introduction

The cerebellum has a role in affective regulation and behavior. Reports in patients with cerebellar lesions have noted affective blunting, disinhibition or lability, even with little cognitive or other behavioral change (Schmahmann and Sherman, 1998). Neurofunctional research has identified neuroanatomical connections between the cerebellum and circumscribed cerebral areas, subserving distinct cognitive and affective processes (Habas et al., 2009; Strick et al., 2009). In topographic analyses, the posterior lobes of the cerebellum are involved in both cognitive and emotional processing, particularly lobule VI, vermal lobule VII implicated in cerebellar-limbic circuits, and Crus I (Stoodley and Schmahmann, 2009).

Emotional recognition of facial expression, highly relevant to social cognition and behavioral responses, is an important topic in contemporary neuroscience research. One area of interest understands how emotional processing is involved in simple and complex motor tasks, as well as higher order cognitive decision tasks (Adolphs, 2004). Neuroanatomical and functional neuroimaging data suggest that evolution has favoured development of complex visual strategies that recruit large-scale networks of the brain, though details of the supratentorial brain pathways involved remain uncertain (Fusar-Poli et al., 2009; Pessoa, 2008).

Whilst the subordinate role of the cerebellum in motor task execution is well recognized, reviews of clinical and functional imaging studies indicate little is known about cerebellar involvement in processing emotional components to support behavioral and motor responses (Leiner et al., 1989; Stoodley and Schmahmann, 2009; Strick et al., 2009; Timmann et al., 2009). Several reports have identified the cerebellum as recognizing and discriminating emotional facial expressions, in particular for negative emotions (Turner et al., 2007; Fusar-Poli et al., 2009; Ferrucci et al., 2012; Adamaszek et al., 2014). These observations suggest that in addition to its recognized motor tasks, the cerebellum is involved in the integration of emotional responses in social behaviors. In spite of neuroimaging observations outlining topographical aspects of cerebellar contributions to emotional face recognition (Fusar-Poli et al., 2009), its temporal characteristics are less defined. In healthy subjects, several studies of event-related potentials (ERP) have indicated that perception of faces *per se* occurs early, manifested in an augmented N170, whereas the later processing of specific face details such as emotional expressions usually displays augmented late positive potentials (LPP), indicating that higher order neocortical pathways are tasked with analyzing the details of facial cues and selection of adaptive behavioral responses (Eimer and Holmes, 2007).

The present study investigated disturbances of emotional processing in patients suffering from ischemic cerebellar lesions. We aimed to evaluate whether patients suffering an ischemic cerebellar lesion, compared to controls, show specific impairments in their ability to comprehend facially communicated emotion as indexed by ERP. We hypothesized that patients with a cerebellar lesion would show reduced amplitudes of late positive potentials, the neurophysiological correlate of deficient recognition of the emotional information in facial expressions. Further, that dipole analysis of the ERP would clarify topographical regions of the cerebellum that are supporting generators of the ERP and therefore involved in the cerebral network for recognition of emotional facial expressions. We also administered the Tübingen Affect Battery, a standardised tool for assessing recognition anddiscrimination of emotional facial expressions, to study any correspondence between observed ERP differences and clinically obtained neuropsychological impairments.

2. Results

2.1. Patient sample

The cerebellar lesion group had only slight to moderate ataxia or dysarthria, and none of the patients had disturbances of ocular movement. Thus, movement or ocular gaze disturbance interfering with the performance of the patients in our tasks were not likely. All participants were right-handed. The

lesion volumes of the cerebellar infarctions were small to moderate
(mean 16.9 cm^3, SD 9.5). The cerebellar lesion and control groups did not differ in sex [cerebellar group mean = 1.11, SD = 0.33, control group mean = 1.25, SD = 0.46, $t(15) = -0.716$, $p = 0.485$],age [cerebellar group mean = 57.22, SD = 15.67, control group mean = 66.00, SD = 10.07, $t(15) = -1.389$, $p = 0.196$] or years of education [cerebellar group mean = 12.22, SD = 1.39, control group mean = 11.75, SD = 1.16, $t(15) = 0.760$, $p = 0.464$]. No cases of concurrent ICD10 depressive disorder were found at a clinicalscreening interview.

2.2. Tuebingen affect battery

Compared to previously published normative data (Bowers et al., 1999), both cerebellar lesion and control groups showed high rates for discriminating the identity of non-emotional faces as probed by subtest 1, with no significant difference between groups. On subtests 2 to 5 scores were lower in the cerebellar than control group but this was statistically significant only for subtest 5, facial affect matching, cerebellar lesion group mean = 73.33, SD = 20.27, control group mean = 90.0, SD = 6.17, t(15)= –2.228, p= 0.042, mean difference= –16.67, standard error of difference= 7.48. Other scores were in detail: subtest 1, cerebellar lesion group mean = 95.37, SD = 8.45, control group mean = 98.96, SD = 2.95, t(15)= –1.138, p= 0.273, mean difference =–3.58, standard error of difference = 3.01; subtest 2, 82.15(12.08), 89.28(12.07), t(15)= –1.433, p= 0.172, –7.14; –7.14; subtest 3, 83.7 (12.07), 87.5(8.31), t(15)= –0.745 p= 0.468, –3.79, 5,09; subtest 4, 85.92 (7.78), 91.67(7.77), t(15)= –1.520, p= 0.149, –5.74, 3.15.

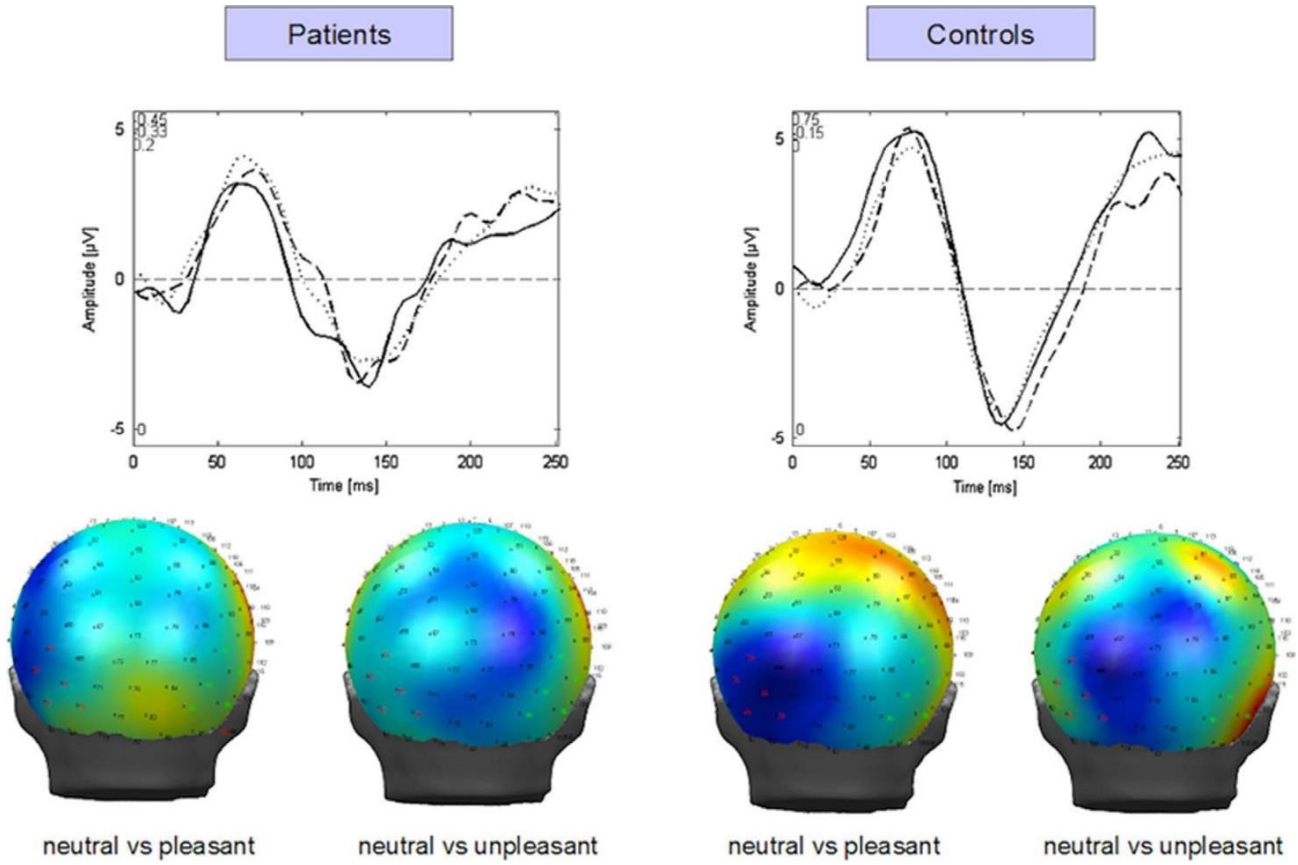

Fig. 1 – Comparison of N170 in patients with cerebellar lesions and controls. In the top row are representative ERP curves for each emotional valence of the facial expressions (neutral facial expressions =solid line; pleasant facial expressions =dashed line; unpleasant facial expressions =dotted line). Below are corresponding subtraction maps portraying the topographic distribution of ERP differences between neutral and pleasant, and neutral and unpleasant facial expressions (amplitudes charted in range - 5 to 5 μV, maps in power range -2 (blue) to 2 (red) μV).

2.3. ERP measurements

The N170 amplitude indexing early perception of faces, was pronounced in all participants for faces compared to non-face neutral images (e.g., household objects) from the IAPS, indicating preserved recognition of faces in comparison to non-facial stimuli. On more detailed analysis, both patient samples also evoked a strong N170 to emotional as well as neutral faces of the KDEF (see top row of Fig. 1). The N170 started around 120 ms and lasted nearly 200 ms post-stimulus, with distribution centered over temporo-occipital regions (see lower row of Fig. 2). There was no statistically significant difference in N170 amplitude between neutral face and each of the four emotional facial expressions [$F(1,15) = 1.178, p = 0.258$].

Analyzing the late ERP responses, the LPP from around 452 ms to 752 ms showed clear augmentation to faces compared to non-facial neutral stimuli (e.g., household objects) of the IAPS, in both cerebellar lesion [$F(1,7) = 2.259, p = 0.040$] and control groups [F (1,8) = 2.259, $p = 0.032$]. In a detailed analysis of responses to emotional vs. neutral face expressions, how- ever, late ERP in parietal areas was only significantly increased for faces with an emotional expression compared to neutral faces in the control group [$F(1,15) = 2.264, p = 0.027$] (see the ERP curves of the LPP in the top row, and the corresponding subtraction power maps indicating the power differences of the LPP to emotional vs. neutral face expressions in the lower row of Fig. 2).

Analyzing each facial emotional expression, the cerebellar lesion group showed diminished LPP for anger [left parietal cluster: F(1,15) = 5.616, $p = 0.035$; right parietal cluster: $F(1,15) = 4.148$, $p = 0.064$] and particularly for fear [left parietal cluster: $F(1,15) = 5.224, p = 0.041$; right parietal cluster: $F(1,15) = 6.518, p = 0.025$]. The other emotions showed only a trend:happiness [$F(1,15) = 3.680$, $p = 0.079$] and sadness [$F(1,15) = 3.336, p = 0.093$], at the left parietal cluster (see illustrative sample averaged ERP curves and corresponding power maps for cerebellar lesion group in Fig. 3, and controls in Fig. 4: in both figures, ERP curves of each emotion are depicted in the top row, and the subtraction power maps displaying the differences of LPP power in the middle row). These findings were confirmed by calculating the within-subject effect of the LPP between both groups by repeated measures ANOVA, indicating a significant interaction between emotional recognition, as indexed by LPP, and group over centro-parietal recording sites [emotional facial expressions ~ group: $F(1,15) = 2.5568, p = 0.011$]. However, analysis of laterality effects in the LPP data did not reveal a difference between the groups [laterality ~group: $F(1,15) = 0.0350, p = 0.851$].

The L2 minimum-norm analysis indicated different topo- graphical sources of the LPP in each patient group. In the control group there was a stronger generation source in the right PFC for the emotions anger and fear (see the distribution maps at the lower row of Fig. 4). In the cerebellar lesion group the dipole source of LPP for these two emotions was predominantly located in the left PFC (see the distribution maps at the lower row of Fig. 3). Furthermore, the L2 minimum-norm analysis of the LPP for happiness showed a predominant source in the left PFC in the control group (depicted at the lower row in Fig. 4), and the right PFC for the cerebellar lesion group (depicted at the lower row in Fig. 3). Finally, whereas the control group displayed a more pronounced right prefrontal center of LPP generation for sadness (also the lower row in Fig. 4), cerebellar patients showed a slight dipole at the left PFC (see lower row in Fig. 3).

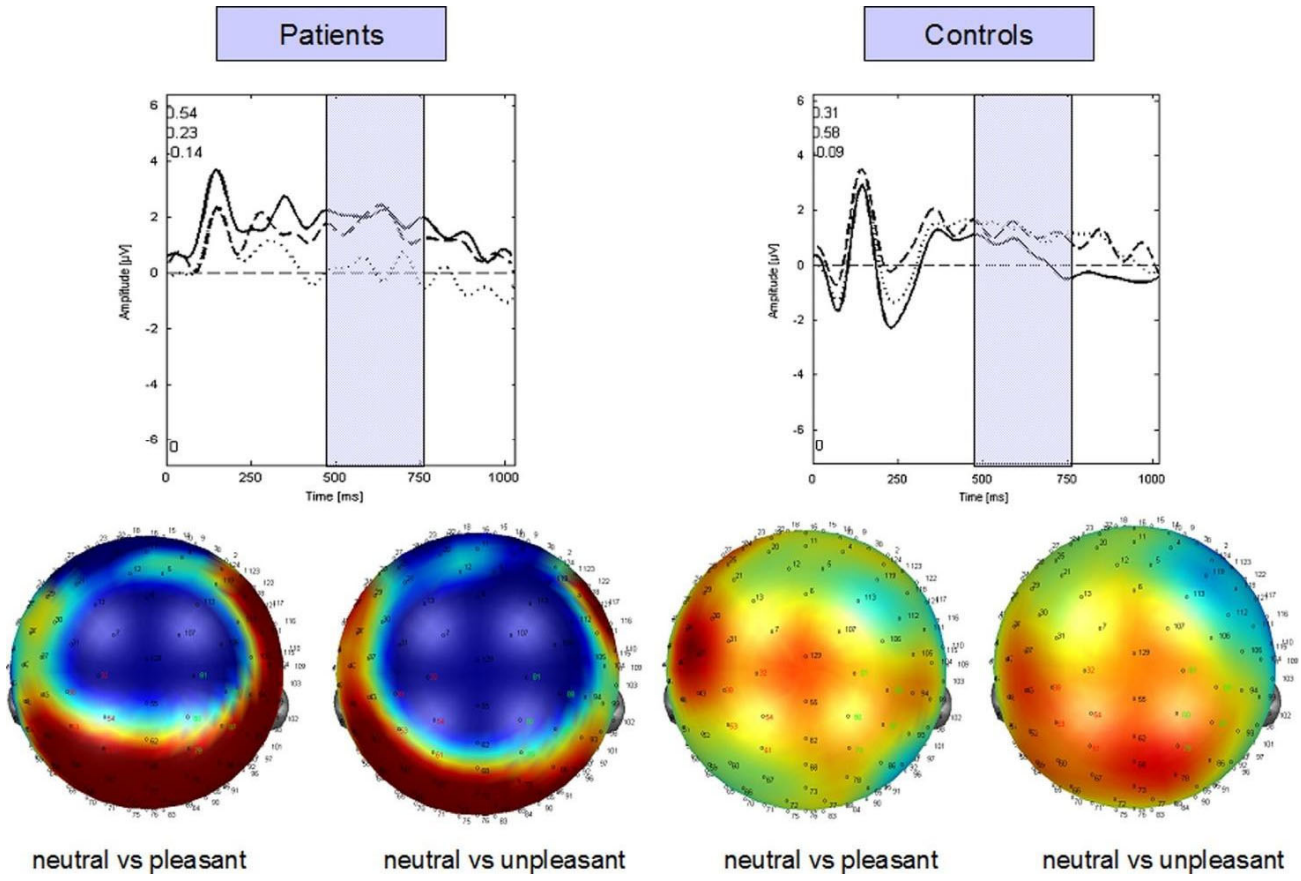

Fig. 2 — Comparison of LPP in patients with cerebellar lesions and control subjects. In the top row are representative ERP curves for each emotional valence of the facial expressions (neutral facial expressions =solid line; pleasant facial expressions =dashed line; unpleasant facial expressions =dotted line). Below are corresponding subtraction maps portraying the topographic distributions of ERP differences between neutral and pleasant, and neutral and unpleasant facial expressions (amplitudes charted in range — 6 to 6 µV, maps in power range–2,5 (blue) and 2,5 (red) µV).

2.4. Correlation analysis

Evaluating correlations of TAB subtest score and group, patients with cerebellar lesions revealed a negative correlation to scores on subtest 5 of the TAB [r(15) =— 0.499, p = 042]. Separate correlational analysis of the event-related potentials showed a negative correlation between the volume of cerebellar infarction and LPP for fear at both parietal sensor clusters [left cluster: r(5) =-0.837, P = 0.019; right cluster: r(5) =-0.868, p = 0.011]. The LPP results for fear were also influenced by topographic location, i.e. if the left Crus I was damaged, there were significant correlations between the diminished LPP to fear in both hemispheres [left parietal cluster: r(12) =— 0.824, p = 0.023; right parietal cluster: r(12) = -0.787, p = 0.036], and also to angry faces in the left hemisphere [r(12) =-0.885, p = 0.008]. The clinical data of TAB performance also showed strong negative correlations between diminished LPP to fear in cerebellar patients and their TAB scores in subtest 4 [left parietal cluster: $r(12) = -0.763, p = 0.002$; right parietal cluster: $r(12) = -0.637, p = 0.014$] and subtest 5 [left parietal cluster: $r(12) = -0.663$, $p = 0.010$; right parietal cluster: $r(12) = -0.675$, $p = 0.008$]. However, the scores of TAB subtests 1 to 5 showed no statistically significant correlation to the infarction volume or the infarction location.

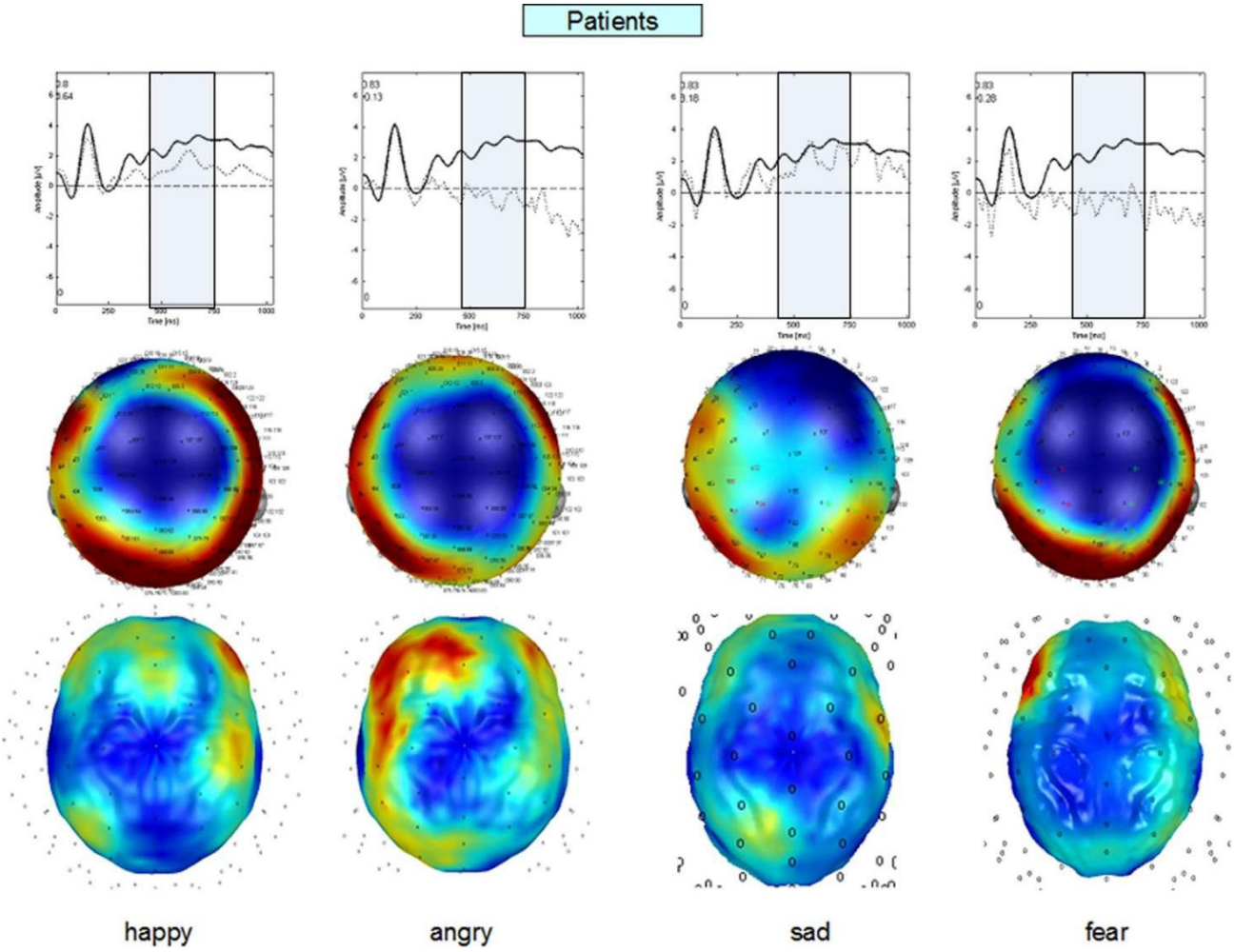

Fig. 3 – Patients with cerebellar lesions. Comparison of LPP for the four emotional expressions displayed, happiness, sadness, anger and fear. In the top row are representative ERP curves for each emotional expression (solid line =neutral facial expression; dotted line =emotional facial expression). In the middle row are subtraction maps comparing the respective emotional and neutral expression. In the lowest row, the corresponding dipole source estimation as obtained by a L2 minimum norm analysis are displayed (amplitudes of ERP curves charted in range - 6 to 6 μV, maps in power range –2,5 (blue)to 2,5 (red) μV, and dipole strengths between 1000 (blue) and 12000 (red) nA/mm).

3. Discussion

Our study delineates neurophysiological correlates of impaired recognition of emotional facial expression in patients with circumscribed cerebellar lesions. Principal findings are impaired neural responses to emotional facial expressions, shown by diminished LPP over centroparietal cortex areas in patients with cerebellar lesions. This contrasts with LPP augmentation in control subjects. The ERP data indicate a particular disturbance of the LPP to the two basic emotions fear and anger, whereas happiness and sadness show only a statistical trend. Dipole source estimations of the LPP demonstrated increased activation of the prefrontal cortex (PFC) with a stronger representation of fear and angerat the left than the right PFC, whereas control subjects showed a stronger activation of the right PFC to these same emotions. However, we found a strong N170 in both groups toemotional facial expressions, indicating preserved encoding in early recognition, as opposed to later higher order processing stages. According to the additional clinical information of TAB performance, patients with cerebellar lesions had lower performances on subtests 2, 3, 4 and 5, but the difference between groups only reached statistical significance on subtest 5, facial affect matching.

In regard to brain processing of emotional face expressions, perception of facial expression has been attributed to the fusiform gyrus as the neuronal area for the early visual perception of faces (Kanwhisher

et al., 1997), whereas the recognition of emotional aspects of facial expression is mainly processed within a large-scale cerebral network including temporal, parietal and prefrontal cortex with extensive reciprocal connections between temporal visual regions and subareas of the PFC (Bowers et al., 1999; LeDoux, 2000; Adolphs, 2004; Pessoa, 2008). The PFC seems to play an important role in processing emotional facial expressions, especially in response to aversive (sad, fearful or angry) expressions (Sprengelmeyer et al, 1998), whereas the amygdala (LeDoux, 2000) and insula (Pessoa, 2005) are involved in appraisal of emotional significance.

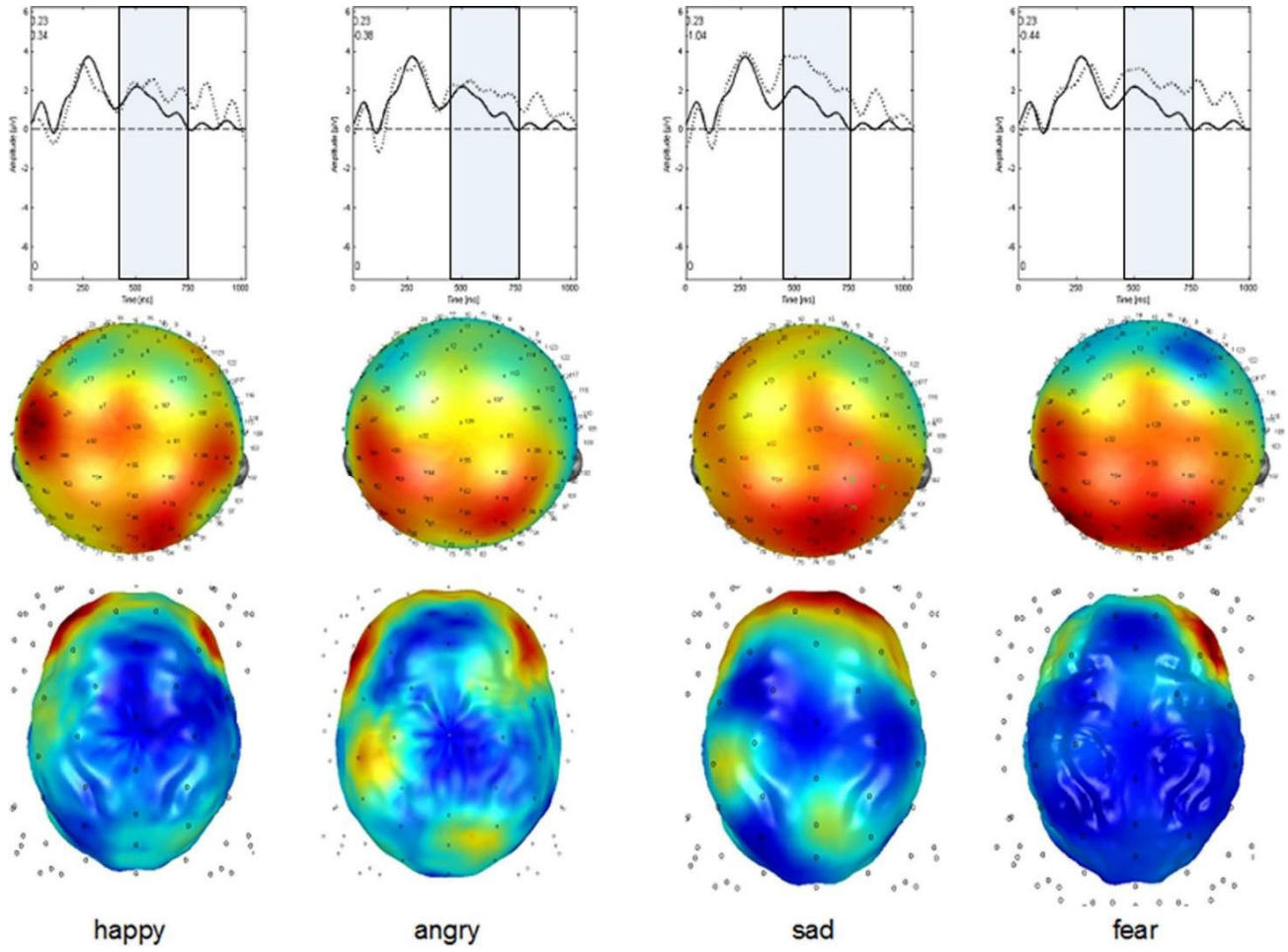

Fig. 4 – Control subjects, for comparison with Fig. 4. LPP for the four emotional expressions displayed, happiness, sadness, anger and fear. In the top row are ERP curves for each emotional expression (solid line=neutral facial expression; dotted line=emotional facial expression). In the middle row are subtraction maps comparing the respective emotional and neutral expression. In the lowest row, the corresponding dipole source estimations as obtained by a L2 minimum norm analysis are displayed (amplitudes of ERP curves charted in range - 6 to 6 μV, maps in power range -2,5 (blue) to 2,5 (red) μV, and dipole strengths between 1000 (blue) and 8000 (red) nA/mm).

However, there is limited knowledge or even awareness ofinvolvement of subcortical structures such as the cerebellum. A meta-analysis of neuroimaging studies of emotional facial expression pointed to consistent findings that the cerebellum is part of the large-scale cerebral network that serves recognizing and discriminating emotional facial expressions (Fusar-Poli et al., 2009). As regards precise localization, a study by Habas analyzing the functional connectivity of the human cerebellum using a defined MRI protocol identified lobule VI, VII and Crus I of the posterior lobe to be involved in emotional processing (Habas et al., 2009). Studies applying well defined neuropsychological test inventories showed impairment of emotional recognition in cerebellar disorder (Sokolovsky et al., 2010; D'Agata et al., 2011; Adamaszek et al., 2014). Neurofunctional approaches have demonstrated

cere bellar involvement in recognizing and forwarding information of negative facial emotions such as fear or anger to mainly prefrontal and temporal areas (Turner et al., 2007; Ferrucci et al., 2012).

Our ERP finding of impaired recognition of the negative emotional facial expressions, fear and anger, is in line with previous clinical and neuroimaging observations. Sacchetti reported disturbed subsequent emotional trace storage in an animal fear conditioning model (Sacchetti et al., 2002), and also Ferrucci found enhanced processing of negative facial expressions after transcranial direct current stimulation (tDCS) of the cerebellum (Ferrucci et al., 2012). The observation, in our and other studies, that the cerebellum is strongly involved in recognizing predominately negative emotions, especially fear, may be explained by the crucial role of the cerebellum in preparation of motoric responses to emotional cues, thus facilitating adaptive behavior in specific social situations (Stoodley and Schmahmann, 2009; Strick et al., 2009; Moulton et al., 2011). However, in the emerging under- standing of the role of the cerebellum in processing the emotional content of facial expression, little is known about temporal details. This can be researched using ERP to study the time course and functional properties of emotional face processing stages. ERP results indicate that N170 indexes the early surface EEG signal over occipital areas, related to perception of faces and reflecting the pre-categorical perceptual encoding of faces in face-specific visual areas (Krolak- Salmon et al., 2004). The LPP in the range 550–900 ms over occipito-temporal, frontal and right temporal areas reflects the analysis of categorical aspects of facial expressions at higher order stages (Bentin et al, 1996; Eimer and Holmes, 2002, 2007). Indeed, lesion of the PFC were accompanied with disrupted ERP after 200 ms, emphasizing the PFC and their attentional resources as crucial to recognition of emotional facial expression at late processing stages (Suwazono et al., 2000; Yago and Knight, 2000). Therefore, LPP reflects neural correlates of this later neocortical stage, processing emo tional facial expression for the purpose of generating intentional control of behavior in a strategic and task-dependent fashion (Eimer and Holmes, 2007; Wong et al., 2009).

So the presented neurophysiologic alterations of late ERP responses to emotional facial expressions in patients with cerebellar lesions substantiate the assumed involvement of neuroanatomical and neurofunctional pathways of the cere- bellum in emotional processing, an exhaustive interpretation of these findings is limited since the fine details of these pathways are subject to debate. Of note, efferents from the central nuclei of the cerebellum project to multiple divisions of the ventrolateral thalamus, forwarded on to multiple cortical areas, including the frontal, prefrontal, and posterior parietal cortex (Habas et al., 2009; Strick et al., 2009). So the thalamus stratifies cerebellar output to cerebral areas, impaired activity of these circuits may result in altered affective network processing of such discrete information regarding emotional facial expression from the visual cortices passing through the thalamus and on to other substantial hubs in the amygdala and the PFC (LeDoux, 2000; Pessoa, 2008). More specifically, non-motor subregions of the cerebellar dentate nucleus are engaged in pre-attentive encoding and forwarding of event-based temporal sensory information to the parietal, frontal and temporal cortex via the thalamus, forming complex neuronal circuits engaged in early and late processing stages of incoming signals (Timmann et al., 2009; Aso et al., 2010; Kotz and Schwartze, 2010; Leggio et al., 2011). According to the proposed pre-attentive detection of emotional facial expression (Palermo and Rhodes, 2007), the cerebellum may integrate event-based temporal information, derived from attending to emotional facial expressions through feed-forward computation to the cerebral large-scale processing system. Thus, cerebellar lesions may result in impaired temporal coordination and decreased recall of established internal representations of features of emotional facial expression. This in turn, results in a critical delay of cerebral processing stages as may be illustrated by the missing augmentation of LPP to emotional facial expression in our cerebellar lesion patients.

A key role of the cerebellum in decoding emotional facial expression is feasible given the multiple cerebellar regions that interact with PFC subterritories (Ramnani, 2006; Habas et al., 2009; Krienen and Buckner, 2009; Strick et al., 2009). The lateral neocerebellum is mainly connected to associative cortices, and frontoinsular and prefrontal cortices have been identified as preferentially linked with lobules VI and Crus I (Habas et al., 2009). Interestingly, activation of lobule VI and Crus I was

observed during evaluation of facial expression, suggesting a defined role in estimating the valence of emotional cues of facial expressions to enable selection of appropriate behavior responses (Stoodley and Schmahmann, 2009). These observations are in keeping with our findings of a prefrontal activity shift for fear and anger and the strong correlation of the LPP response to both emotions with lesions of Crus I. Our finding of impaired LPP but preserved N170 to emotional facial expressions is consistent with recent findings of strong connectivity of cerebellar areas to the prefrontal, but less to the occipital cortex (Buckner et al., 2011). This corresponds to our results of a preserved N170 with its main source within the visual cortex, and an impaired LPP with its source at prefrontal, temporal and centroparietal regions. The conclusion that the cerebellum subserves higher order processing stages of emotional facial expressions is also consistent with the preservation of discrimination of face identities but impairment of facial affect recognition and discrimina tion on TAB subtests. Subtests 4 and 5 of the TAB require additional cognitive effort to select or match emotional expressions, requiring stronger engagement of the responsi ble large-scale cerebral network that handles emotional facial expressions (Breitenstein et al., 1996; Adamaszek et al., 2014). We found that recruitment of the lateral PFC in response to presentations of facial expressions of fear and anger, was on the opposite side in the cerebellar lesion group compared to controls. The inferior frontal gyrus (IFG) is considered an important node of a mirror neuron system which has been suggested to contribute to emotion mirroring mechanisms (Shamay-Tsoory et al., 2009; Prochnow et al., 2013). Thus, it could be argued that the increased activity of the left PFC to fear and also anger in the cerebellar lesion group in our study may represent enhanced allocation to the mirroring left prefrontal cortex, substituting for the interrupted cerebellar input to the right PFC. This would be consistent with Turner's premise that the default network that processes emotional-laden stimuli, attempts to adapt by engaging alternative nodes, when a cerebellar lesion has disrupted the established connectivities to cerebral cortex (Turner et al., 2007). Interestingly, in a previous study, investigating performance on recognition of syntax deviations in focal cerebellar lesion patients, using an ERP paradigm, strong activation was found of homologous areas of the cerebral cortex, pointing to the cerebral cortex compensating for deficient cerebellar contributions (Adamaszek et al., 2012). The finding of augmented activation of the left PFC in our cerebellar lesion sample may also reflect that the left PFC handles approach-related positive cues, whereas the right PFC is deemed to be involved in behavioral inhibition to negative cues (Davidson et al., 2003). This supports the assumption of compensatory contralateral activation due to disrupted cerebellar contribution to the PFC, Kirchner recently reported involvement of the left inferior frontal gyrus (IFG) in cognitive processing of negative affect, suggesting that such cognitive components may be allocated to compensate for the connectivity loss in the default cerebellar-cerebral loop to the later alized PFC (Kircher et al., 2013). This adds weight to the notion that diaschisis of cerebellar–cerebral
pathways is substantially responsible for the observed clinical and associated neurophysiological impairments, and may be of particular relevance inexplaining our findings.

The small sample size may account for limited findings regarding lateralization within the cerebellum. However, the statistically significant reduced ERP responses to negative cues at higher order stages, and also the correlation of Crus I with impaired recognition of negative facial expressions are in agreement with prior reports on cerebellar contributions. The small sample size may also account for the lack of significant differences between lesion and control patients on TAB subtests 2 to 4, though reduced matching of facial emotional expression was found on TAB subtest 5 in the cerebellar lesion group. Indeed, significant impairments of facial affect selection on subtests 3 and 4 were previously found in larger but otherwise comparable samples of patients suffering from ischemic lesions of the posterior lobe (Adamaszek et al., 2014, unsubmitted).

It may be argued that the discrepancies between the observed ERP changes, and the clinically significant impairmenton a single subtest of the TAB, facial affect matching on subtest5, are contradictory. It is noted that we administered the TAB to collect clinical information, for comparison with subclinical information from brain imaging. The ERP results indeed suggest that performance impairment related to emotional facial expressions is detected by ERP at a greater level of sensitivity than clinical

performance as probed by the TAB. This is particularly so if one compares ERP results to clinical performance in those TAB subtests that require less secondarycognitive input, as it is true for subtests 2 and 3. Also, participants had no time restrictions in performing the TAB tasks, whereas each face presentation in ERP trials was restricted to a time window of 1200 ms. The late positive potentials capture pre-attentive brain responses prior to secondary mechanisms of cognitive attention that may compensate for possible deficits in recognition or discrimination of emotional facial expression. Moreover, we could show strong negative correlations between diminished LPP to fear in cerebellar patients and their TAB scores in subtests 4 and 5, both subtests that require a secondary cognitive component. Thus, as outlined above, the ERP results register pre-attentive stages of the recognition or discrimination of emotional facial expressions, even capturing subsidiary areas of the cerebral cortex for presumably compensation of lacking pre-attentive cerebellar contributions, whereas the TAB assesses clinical performance, emphazising the greater value in capturing the initial phase of brain responses to emotional facial expressions by ERP.

3.1. Conclusions

Our study supports a growing consensus in the literature thatthe cerebellum plays a specific role in the emotional recogni tion and discrimination of facial expression. The finding of impaired LPP as a robust ERP component of recognition and discrimination of emotional facial expressions emphasizes that distinct parts of the neocerebellum subserve higher order levels of the large-scale inter-connected network responsible for processes of attending to and evaluating emotional facial expressions. In addition, the neurophysiological avenue of capturing disturbed function of the responsible large-scaled network appears to provide more information on impairments in recognizing and discriminating emotional facial expressions than do established clinical test inventories such as the TAB. Emotional expressions via facial gestures powerfully influence social behavior requiring the engagement of neural response systems to react most appropriately. This perspective enriches the classical neuro- logic view of the cerebellum as a pure motor player, adding a function of the cerebellum as an interface in higher order processing of perceptions, discernments and behavioral responses subserving social cognition. Further electrophysiological and functional brain imaging studies, utilizing larger samples of patients with cerebellar disorders, may elucidate more detail of the pathways involved, in both normal and impaired recognition of emotional facial expression.

4. Experimental procedures

4.1. Participants

Eight patients with documented ischemic cerebellar damage (1 female, 7 males; mean age 55.1þ12.8) and eight control patients (2 females, 6 males; mean age 57.6þ8.2) were enrolled (see Table 1 for more details of patients). All participants had normal or corrected to normal vision. All patients were recruited from the Department of Neurology of the University of Greifswald. Control patients had a comparable comorbidity (arterial hypertension, diabetes mellitus or transient ischemic attack of the cerebrovascular system) but no history of cerebrovascular stroke. We examined all participants clinically, and recorded medical and educational history in detail. Exclusion criteria were any of: a psychiatric history; Mini Mental State Examination (MMSE) score less than 26 out of 30; Hamilton Rating Scale for Depression (HAMD) greater than 10 out of 66. All participants were informed about the design and aims of the study and gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki as formulated by the Word Medical Association in 2013 and was approved by the Ethics Committee of the University of Greifswald.

Table 1 – Characteristics of 8 patients with cerebellar lesions: demographics comprising age, sex, years of education; handedness; neuroimaging findings comprising topography (lobules I to IX and Dentate Nucleus (DN)), and volume (cm^3) ofcerebellar lesions.

Patient	*Topography*	*Lesion size*	*Age*	*Sex*	*Handedness*	***Education (years)***
C1	VI (right)	9.79	62	M	right	**12**
C2	VI (left)	8.28	67	M	right	**11**
C3	I,II,VI,DN (left)	25.54	55	M	right	**11**
C4	I,VI,VII (right); II (left)	13.17	70	M	right	**13**
C5	I,II,VI,VII,DN (right); II,VI (left)	34.62	51	M	right	**13**
C6	VII (left)	8.61	50	F	right	**11**
C7	I,VII (left)	9.47	52	M	right	**13**
C8	I,II,VI,DN (right)	22.08	59	M	right	**15**

4.2. *Measures*

4.2.1. *Cerebral imaging*

Computer Tomography (CT), or Magnetic Resonance Imaging (MRI) was conducted to record the location and extent of the ischemic cerebellar lesion in patients, as assessed by a specialist neuroradiologist. The location of lesions was classified according to neuroanatomic area of the cerebellum, a method used in several recent neuroimaging trials (Habas et al., 2009; Krienen and Buckner, 2009). In addition, a lesion overlap map was derived, as follows. Where available, multiple image contrasts were used to confirm lesion location and extent. Lesions were first manually outlined in Medical Imaging Processing, Analysis and Visualization (MIPAV; McAuliffe et al., 2001) and converted to native space binary lesion masks. CT and MR images were then registered to the MNI152 template using a 12 dof affine transform to create individual linear transforms (Jenkinson et al., 2002). Individual lesion masks were transformed into Montreal Neurological Institute (MNI) space by applying the calculated transformation matrix and then summed to create the lesion overlap map (see Fig. 5).

4.2.2. Tübingen affect battery (TAB)

The TAB (Breitenstein et al., 1996) is a German translated version of the Florida Affect Battery (FAB) (Bowers et al., 1999). It measures recognition and discrimination of emotional facial expression and of emotional prosody (tone of voice), two elementary components of social cognition. Of the ten subtests, we applied subtests1–5, which present series of photographs of female faces, probing the recognition and discrimination of emotional facial expression with respect to five emotions, happiness, sadness, anger, fear, and neutral. Subtest 1 probes discrimination of facial identity. Subtests 2 to 5 study capacity to recognize and discriminate specific emotional cues in facial expressions with each subtest comprising 15 trials, delivering three to five instances of each emotion. Subtest 2 probes facial affect discrimination (whether two faces depict the same or different emotional expressions), subtest 3 facial affect naming (name the emotion depicted by an individual face), subtest 4 facial affect selection (point to the face corresponding to the emotion named by the examiner) and subtest 5 facial affect matching (match the emotion of one face with its counterpart face emotion on a multiple response card). The TAB shows a high reliability with an internal consistency of 0.97 (Cronbach's Alpha), and validity calculated at 71.9% in patients suffering from cortical damage (Bowers et al., 1999). Of note, the participant was not restricted by a time limit for responding to each task in a subtest. Scores on each subtest of the TAB of patients with a cerebellar infarction and patients without a brain lesion were analyzed by Student's t-test.

4.2.3. *ERP procedures*

Event-related potentials (ERP) indexed early and late stages of emotional recognition of visually

displayed faces, varying in five basic emotional facial expressions: happiness, sadness, anger, fear, and neutral. We used images from the Karolinska Directed Emotional Faces Database (KDEF) (Lundqvist et al., 1998) comprising male and female faces expressing these five emotions and interspersed these pictures in a pseudorandomized order within a stream of 579 pictures from the Inter- national Affective Picture System (IAPS) (Lang et al., 1999). Based on standardized ratings of arousal, pictures of the IAPS display real objects or situations varying in emotional arousal, i.e. high arousing examples of pleasant (e.g., erotica or family scenes) or unpleasant (e.g. mutilation, pollution) con- tent, or low arousing examples depicting neutral contents (e. g., household objects). We utilized the pseudorandomized display of IAPS images for demonstrating a preserved recognition of faces at the initial phase of visual encoding (N170), but also as distracting cues to emotional perception, in order to interfere with the use of compensatory cognitive strategies by patients with impaired discrimination of emotional face expressions at the following phase of processing visually perceived emotional face expressions (LPP). Thus, after analyzing a preserved N170 to non-emotional faces and non- facial cues with a low arousing content as delivered by images of IAPS, we compared as a first step the early and late ERP response to clustered emotional, i.e. pleasant (happy) and unpleasant (sad, angry, fearful) face expressions versus neutral face expressions in order to calculate if patients evoke an ERP augmentation for overall pleasant or unpleasant valences of facial expressions. As a second step, we analyzed differences between patients and controls on ERP response to each basic emotional facial expression, irrespective of their valence (pleasant, unpleasant).

All images were presented for 1200 ms, with no interstimulus interval, in random sequences, constructed as a movie. Therefore, watching the displayed images conforms to an appropriate time range in order to analyze early negative potential (N170) in the usual time window from 140 up to 200 ms, and late positive potentials (LPP) in the usual time window from 452 up to 752 ms. Participants were instructed to watch the images, inspect each face shown and to make a mental note of the emotion displayed. To minimize stimulus novelty effects, patients were familiarized with five representative pictures before the experimental session. The images were presented on a 20″ computer monitor located 1.5 m in front of the
viewer (11° visual angle). Subjects were seated in a reclining chair in a sound-attenuated, dimly lit room. Before starting the image stream, participants were requested to minimize eye blinks and body movements during ERP measurement.

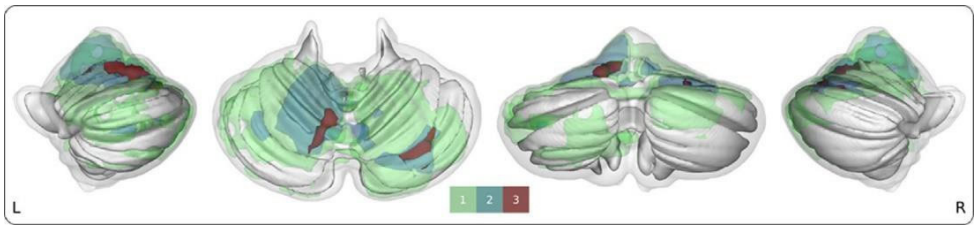

Fig. 5 – Overlap map of cerebellar lesions in the patient sample, superimposed on coronal (middle) and sagittal (left and right) slices of the cerebellum of a healthy subject. The number of overlapping lesions is indicated by colors ranging from 1 (dark blue) to 6 (darkred).

At the end of testing, participants were ask to rate their comfortduring the session.

4.2.4. Data collection, reduction and analysis

For ERP responses to presented images, EEG signals were continuously recorded from the scalp using a 129-channel system (Electrical Geodesics, Inc., Eugene, OR). Scalp impedancefor each sensor was kept below 30 kΩ. EEG was digitized at a rate of 250 Hz using Netstation software and EGI amplifiers (Electrical Geodesics, Inc., USA), using the vertex sensor (Cz) as the reference electrode. All channels were

preprocessed on-line by bandpass filters from 0.01 to 100 Hz. Off-line analysis of ERP was performed by Electro Magneto EncephaloGraphy Software (EMEGS; Jungh fer et al., 2006), written in Matlab programming language, handling EEG and MEG data alike (Version 1.9; University of Konstanz, Germany). Whereas continuous EEG data were on-line bandpass filtered from 0.01 to 100 Hz and sampled at 250 Hz, continuous EEG data were off-line low pass filtered at 40 Hz using digital filtering before stimulus synchronized epochs were extracted from baseline, corrected 108 ms before and 1200 ms after picture onset, i.e. eliminating electrical components which represent technical artifacts. A two-step procedurewas used for artifact detection and correction. The raw EEG epochs were first passed through a computerized artifact detection algorithm that uses statistical parameters (e.g., absolute value over time, standard deviation over time, etc.) to detect and reject channels and trials with artifacts. In a second step, basedon the average referenced data, sensors containing artifact- contaminated activity were replaced using spherical interpolation on the basis of all remaining sensors for the given trial. ERPs were computed for each sensor and participant. Statis- tical analyses were performed by averaging a group of sensors over the area where each ERP component showed maximal amplitude. As already mentioned earlier, the amplitude of N170 was assessed over temporo-occiptial sensors in a 140–200 msec time window. The late positive potential (LPP) was assessed from centro-parietal sensors, within a 452–752 msec time window, following onset of images displaying an emotional facial expression. The mean averages of each ERP trial in each subject wereused in the calculation of a grand average, i.e. the displayed ERPresults constitute the data of the ERP component for each basic emotion in the patient sample as a whole. Thus, the ERP analysis and therefore the display of data results were not restricted to one representative subject. Mean ERP amplitudes in the above time window for the temporo-occipital and the centro-parietal cluster were analyzed by repeated measures Analysis of Variance (ANOVA) including the factors Emotional Facial Expression (happiness, sadness, anger, fear, and neutral) and Laterality (left vs. right) as within-subject factors and Group (cerebellar lesion vs.controls) as a between-subjects factor. For effects involving repeated measures, the Greenhouse-Geisser procedure was used to correct violations of sphericity.

For source analyses of the ERPs, L2 minimum-norm solu- tions (MN) were calculated separately for both experimental groups to provide neural source estimations for the ERP difference potential between the emotions studied. Calcula- tions were based on a spherical four-shell isotropic volume conductor head model with 3 (radial, azimuthal, and polar direction) ~ ~ 197 evenly and spherically distributed dipoles as a source model. A source shell radius of 6 cm was chosen as trade off between depth sensitivity and spatial resolution, as previously reported (Hauk et al., 2002).

Cerebellar lesion volumes were derived from neuroimaging (CT in three and MRI in five patients) and calculated semi-quantitatively using Image J, a highly reproducible threshold technique (Rasband, 2002). Lesions were segmented on computer displayed slices by delineating regions of interests (ROI). Lesion volume was calculated by multiplying total ROI area by slice thickness. Additionally, we determined the topography of each cerebellar lesion in a neuroanatomic classification (Habas et al., 2009; Krienen and Buckner, 2009). Associations between neurophysiological, neuropsychological and brain scan data were examined using Spearman's testof correlation coefficients.

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