The embodied emotion in cerebellum: a neuroimaging study of alexithymia

ARTICLE *in* BRAIN STRUCTURE AND FUNCTION · MAY 2014

Impact Factor: 5.62 · DOI: 10.1007/s00429-014-0790-0 · Source: PubMed

9 AUTHORS, INCLUDING:

Daniela Laricchiuta
Foundation Santa Lucia
26 PUBLICATIONS **208** CITATIONS
SEE PROFILE

Laura Petrosini
Sapienza University of Rome
149 PUBLICATIONS **3,166** CITATIONS
SEE PROFILE

Chiara Chiapponi
Foundation Santa Lucia
24 PUBLICATIONS **143** CITATIONS
SEE PROFILE

Gianfranco Spalletta
IRCCS Santa Lucia Foundation
247 PUBLICATIONS **5,557** CITATIONS
SEE PROFILE

Brain Struct Funct
DOI 10.1007/s00429-014-0790-0

ORIGINAL ARTICLE

The embodied emotion in cerebellum: a neuroimaging study of alexithymia

Daniela Laricchiuta · Laura Petrosini · Eleonora Picerni · Debora Cutuli · Mariangela Iorio · Chiara Chiapponi · Carlo Caltagirone · Fabrizio Piras · Gianfranco Spalletta

Received: 28 January 2014 / Accepted: 28 April 2014

Abstract Neuroimaging studies have indicated that people with alexithymia show structural and functional alterations in brain areas associated with emotional awareness, as amygdala, insula, anterior cingulate cortex, fusiform gyrus and parahippocampal gyrus, and only occasionally alterations in the cerebellar activity were reported. The main goal of the present study was to investigate the associations between gray and white matter cerebellar macro- (Voxel-Based Morphometry) and micro- (Mean Diffusivity and Fractional Anisotropy) structural measures (evaluated by means of a 3-T high-resolution structural Magnetic Resonance Imaging and a Diffusion Tensor Imaging scan protocol) and the presence of alexithymia (evaluated by means of 20-item Toronto Alexithymia Scale), in a sample of 60 healthy subjects having low, borderline or high alexithymia. As a corollary aim, the associations between volumes of amygdala, insula, anterior cingulate cortex, fusiform gyrus or parahippocampal gyrus and alexithymia scores have been investigated. Cerebellar gray matter volumes were positively associated with alexithymia scores. The subjects with high alexithymic traits had larger volumes in the bilateral Crus 1 in comparison to the remaining subjects. Volumes of right amygdala, left insula and left parahippocampal gyrus were negatively associated with the alexithymia scores. Thus, alexithymia scores were linked directly with cerebellar areas and inversely with limbic and para-limbic system, proposing a possible functional modality for the cerebellar involvement in emotional processing. The increased volumes in Crus 1 of subjects with high alexithymic traits may be related to an altered embodiment process leading to not-cognitively interpreted emotions.

Keywords Voxel-based morphometry · Diffusion tensor imaging · Gray matter · Limbic system · Emotion regulation · Embodiment

D. Laricchiuta · L. Petrosini · E. Picerni · D. Cutuli · M. Iorio · C. Chiapponi · C. Caltagirone · F. Piras · G. Spalletta
IRCCS Fondazione Santa Lucia, via Ardeatina 306, 00142 Rome, Italy

D. Laricchiuta (✉) · L. Petrosini · E. Picerni · D. Cutuli
Dipartimento di Psicologia, Facoltà di Medicina e Psicologia, Università "Sapienza" di Roma, via dei Marsi 78, 00185 Rome, Italy
e-mail: daniela.laricchiuta@uniroma1.it

C. Caltagirone
Dipartimento di Neuroscienze, Università Tor Vergata, Via Montpellier 1, 00135 Rome, Italy

Introduction

Neuroanatomical, physiological and functional imaging studies described the cerebellar action in integrating motor, somato-visceral, cognitive and emotional information (Andreasen et al. 1999; Schmahmann 2004; Zhu et al. 2006). Cerebellar functional topographic organization indicates that while the anterior cerebellum (lobules I–V) and lobule VIII sustain motor and sensory-motor functions, the posterior cerebellum (lobules VI and VII, including Crus 1 and 2 and lobule VIIb) is the anatomical substrate of cognitive functions, and the posterior vermis, the so-called limbic cerebellum (lobules VI, VII, VIIb and VIII, Crus 1 and 2), is involved in the emotional regulation (Stoodley and Schmahmann 2010; Stoodley et al. 2012).

The description of behavioral changes in the presence of posterior and vermian lesions has led to the definition of the clinical entity known as the "cerebellar cognitive-affective syndrome" (Schmahmann and Sherman 1998),

Published online: 20 May 2014

characterized by executive dysfunction, behavioral disinhibition and blunting of affect. Magnetic Resonance Imaging (MRI) studies showed structural and functional cerebellar abnormalities in patients with depression, anxiety and personality disorders (Baldaçara et al. 2011; De Bellis and Kuchibhatla 2006; Fitzgerald et al. 2008). Even data obtained in healthy subjects indicated reduced capacities of emotional regulation following inhibitory repetitive transcranial magnetic stimulation over the cerebellum (Schutter and Van Honk 2009). More recently, the cerebellar involvement in some personality dimensions has been advanced. Namely, analyzing the relationships between the amplitude of spontaneous low-frequency oscillations and personality traits using resting-state functional MRI (fMRI), behavioral inhibition appeared to be correlated negatively with the cerebellum and positively with the middle frontal gyrus (Kunisato et al. 2011). Cerebellar neuronal activity positively co-varied with approach temperament (Wei et al. 2011), and cerebellar volumes negatively co-varied with avoidance temperament (Schutter et al. 2012). Recently, using a Region of Interest (ROI)-based approach, we reported cerebellar volumes associated positively with Novelty Seeking (NS) and negatively with Harm Avoidance (HA) by Cloninger's model (1986) (Laricchiuta et al. 2012). Subsequently, using a Voxel-Based Morphometry (VBM) analysis and a Diffusion Tensor Imaging (DTI) scan protocol, we reported NS associated positively with the cerebellar Gray Matter (GM) volumes (lobules VIIb, VIII and Crus 2) and White Matter (WM) Fractional Anisotropy (FA) (lobules IV, V, VI and IX), and negatively with GM Mean Diffusivity (MD) (lobules IV, V, VI, VIII, IX, and Crus 1 and 2) (Picerni et al. 2013).

Given the cerebellar contribution in personality traits and emotional processing, we sought to investigate the cerebellar involvement even in alexithymia, construct of personality characterized by impairment in cognitive-emotional and affective processing. It describes people with deficiencies in identifying, processing, or describing subjective feelings or emotional aspects of social interaction, difficulty in distinguishing between feelings and bodily sensations of emotional arousal, and limited affect-related fantasy and imagery. People with alexithymic traits have a tendency to focus on facts without affective involvement rather than inner experiences (Bagby et al. 1994a, b; Franz et al. 2004; Sifneos 1972; Taylor 2000). Although alexithymia is not a psychological disorder in itself, it is associated with enhanced risk of psychological impairment and is present in a broad spectrum of psychiatric and psychosomatic disorders, as chronic pain, somatoform disorders, addictive disorders, anxiety and depression (Dorard et al. 2008; Honkalampi et al. 2000; Larsen et al. 2003; Taylor and Bagby 2004). Neuroimaging studies have indicated that people with high alexithymic traits show less activation in brain areas associated with emotional awareness, as anterior cingulate cortex (ACC), fusiform gyrus, amygdala, parahippocampal gyrus and insula (Kano et al. 2003; Pouga et al. 2010; Reker et al. 2010) (Fig. 1). Volumetric variations promoting the functional and behavioral differences in people with high alexithymic traits were searched for in most of these areas. Namely, negative correlations between alexithymia scores and amygdala and insula volumes were described (Borsci et al. 2009; Ihme et al. 2013), while no correlation between alexithymia scores and fusiform gyrus volumes was found (Ihme et al. 2013). Conversely, controversial findings showing negative (Borsci et al. 2009; Ihme et al. 2013), positive (Gündel et al. 2004) or even no correlation (Heinzel et al. 2012) between alexithymia scores and ACC volumes were reported. Occasionally, in the presence of alexithymia some alterations in the cerebellar activity (but not in the volumes) were reported (Kano et al. 2003; Moriguchi et al. 2007, 2009), even if these reports have not been taken into account in the new conceptualization of the limbic cerebellum. Our hypothesis that the altered cognitive experience of emotion in the subjects with high alexithymic traits may be associated with cerebellar volumetric alterations is in line with the most recent reports on cerebellar functionality (Kh et al. 2012; Wolf et al. 2009).

The main goal of the present study was to investigate the associations between the presence of alexithymia, evaluated by means of 20-item Toronto Alexithymia Scale (TAS-20) (Bagby et al. 1994a, b), and bilateral cerebellar macro- (VBM) and micro- (FA and MD) structural measures, using a 3-T high-resolution structural MRI and a DTI scan protocol in a sample of 60 healthy subjects. DTI measures the diffusion of water molecules through tissues, detects brain micro-structural variations, and provides physiological information not available using conventional MRI (Basser and Pierpaoli 1996). The indirect observation of the displacements of diffusing water molecules provides valuable information on size of the pores between cells as well as structure, density, surface and orientation of cells (Le Bihan 2007). Among DTI indices we used the MD for GM and the FA for WM. In particular, MD measures the average extent of water diffusion, providing information on restrictions (e.g., high density of cells) that water molecules encounter. If these obstacles have coherent alignment, on average the water tends to diffuse more along a certain axis. Although traditionally used to study WM features, MD allows studying even GM variations (Laricchiuta et al. 2013; Müller et al. 2007; Picerni et al. 2013; Piras et al. 2010, 2011; Spalletta et al. 2012). Since unlike WM, GM has a less organized orientation, the use of MD is limited to the GM structures with high directionality in diffusion.

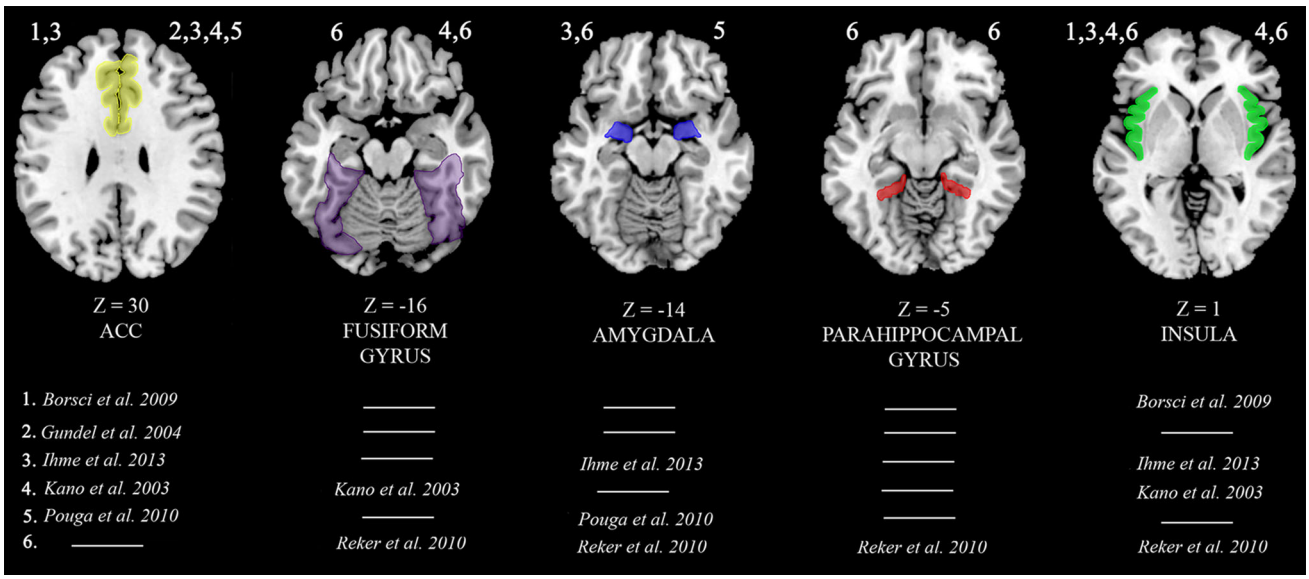

Fig. 1 Neural correlates of alexithymia. Representative axial slices (Montreal Neurological Institute template, *MNI*) showing the brain areas [anterior cingulate cortex (*ACC*), fusiform gyrus, amygdala, parahippocampal gyrus and insula] whose volumetric or functional variations have been associated to alexithymia by the quoted studies. References are positioned according to area and side (*right* or *left*) described by the authors. References are fully reported in the main text. The *right side* of the brain is shown on the *right side*

Cerebellar GM meets such a condition. FA measures anisotropy of water diffusion and it is positively linked to fiber density, axonal diameter and myelination in WM. Low FA values stand for isotropic diffusion (i.e., unrestricted in all directions), while high FA values indicate diffusion fully restricted along one axis. Thus, FA is high when the density of the ordered structures (axonal fibers) is high (Pierpaoli et al. 1996).

As a corollary aim, we verified that the structural patterns of limbic and para-limbic regions of our sample fitted with the above-reported ones in the presence of alexithymia (Fig. 1). Namely, we analyzed the associations between TAS-20 scores and volumes of structures determined a priori, as amygdala, insula, ACC, fusiform gyrus and parahippocampal gyrus.

Materials and methods

Ethics statement

The study was approved by the Local Ethics Committee of the IRCCS Fondazione Santa Lucia and written consent was obtained from all participants after full explanation of study procedures.

Participants

The 60 participants of present study were selected from a large ($n = 258$) sample of subjects scored on TAS-20. All participants were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). Inclusion criteria were age between 18 and 70 years and suitability for MRI scanning. Exclusion criteria included (1) suspicion of cognitive impairment or dementia based on Mini Mental State Examination (MMSE) (Folstein et al. 1975) scores $\leq$24 (Measso et al. 1993), and confirmed by clinical neuropsychological evaluation using the Mental Deterioration Battery (Carlesimo et al. 1996) and the NINCDS-ADRDA criteria for dementia (McKhann et al. 1984); (2) subjective complaint of memory difficulties or of any other cognitive deficit, regardless of interference with daily activities; (3) major medical illnesses, e.g. diabetes (not stabilized), obstructive pulmonary disease, or asthma; hematologic and oncologic disorders; pernicious anemia; clinically significant gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases; newly treated hypothyroidism; (4) current or reported psychiatric (assessed by SCID-I and the SCID-II) (First et al. 1997, 2002) or neurological (assessed by clinical neurological evaluation) disorders (e.g. schizophrenia, mood disorders, anxiety disorders, stroke, Parkinson's disease, seizure disorder, head injury with loss of consciousness, and any other significant mental or neurological disorder); (5) known or suspected history of alcoholism or drug dependence and abuse, evaluated by structured interviews (SCID I or SCID II) (First et al. 1997; Spitzer et al. 1992); (6) MRI evidence of focal parenchymal abnormalities or cerebro-vascular diseases: for each subject, a trained neuroradiologist and a neuropsychologist expert in neuroimaging co-inspected all the available

clinical MRI sequences (i.e. T1- and T2-weighted and FLAIR images) to ensure that the subjects were free from structural brain pathologies and vascular lesions (i.e. FLAIR or T2-weighted hyper-intensities and T1-weighted hypo-intensities).

Psychological instruments

TAS-20 is a 20-item self-administered questionnaire with good internal consistency and test–retest reliability (Bagby et al. 1994a, b). The items are scored on a five-point scale ranging from "strongly disagree" to "strongly agree". The TAS-20 has a three-factor structure. Factor 1 (F1) assesses Difficulty in Identifying Feelings (e.g. "I am often confused about what emotion I am feeling", and "I have feelings that I can't quite identify"). Factor 2 (F2) assesses Difficulty in Describing Feelings (e.g. "I find it hard to describe how I feel about people" and "It is difficult for me to reveal my innermost feelings, even to close friends"). Factor 3 (F3) assesses Externally Oriented Thinking [e.g. "I prefer to just let things happen rather than to understand why they turned out that way" and "I find examination of my feelings useful in solving problems" (reverse-scored)]. TAS-20 total scores can range from 20 to 100.

Because of the known association between alexithymia and depression (Honkalampi et al. 2000), although healthy, all participants were also evaluated by means of Beck Depression Inventory (BDI) (Beck et al. 1988). The BDI is a 21-item multiple-choice self-report inventory rated on a four-point scale ranging from 0 to 3 that assesses the presence of depressive symptoms. Scores can range from 0 to 63. The questionnaire is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex.

Furthermore, all subjects completed the scale 2 of State-Trait Anxiety Inventory (STAI-2) (Spielberger 1989). STAI-2 has 20 items rated on a four-point scale ranging from 1 to 4 assessing trait anxiety. Scores can range from 20 to 80.

Italian versions of the psychological scales were used in this study.

Sampling

As mentioned above, in the present study we screened a large ($n = 258$) sample of participants with TAS-20 to obtain a final sample of 60 healthy subjects. Participants reaching TAS-20 scores ≥ 61 were classified as participants with high alexithymic traits (A group; $n = 20$); participants reaching scores between 51 and 60 were classified as participants with borderline alexithymic traits (BA group; $n = 20$); and participants reaching scores ≤ 50 were classified as participants with low alexithymic traits (LA group; $n = 20$). The categorization was based on the cut-off scoring indicated by the scale developers (Bagby et al. 1994a, b).

Demographic variables (age, gender and education years) and scores of psychological scales [TAS-20 (total and factors); BDI; STAI-2] of the participants (total sample and three groups, separately) are reported in Table 1.

Image acquisition

Participants underwent an imaging protocol that included standard clinical sequences (FLAIR, DP-T2-weighted), a volumetric whole-brain 3D high-resolution T1-weighted sequence, and a DTI scan protocol, performed with a 3 T Allegra MR imager (Siemens, Erlangen, Germany). Volumetric whole-brain T1-weighted images were obtained in the sagittal plane using a modified driven equilibrium Fourier transform (MDEFT) sequence (Echo Time/Repetition Time $-$TE/TR$-$ $=$ 2.4/7.92 ms, flip angle 15°, voxel size $1 \times 1 \times 1$ mm^3).

Diffusion tensor images were acquired using echo-planar imaging (TE/TR = 89/8,500 ms, bandwidth = 2,126 Hz/vx; matrix size 128×128; 80 axial slices, voxel size $1.8 \times 1.8 \times 1.8$ mm^3) with 30 isotropically distributed orientations for the diffusion-sensitizing gradients at one b value of 1,000 s mm^2 and two $b = 0$ images. Scanning was repeated three times to increase the signal-to-noise ratio.

All planar sequence acquisitions were obtained in the plane of the anterior–posterior commissure line. Since the posterior cranial fossa usually falls at the lower limit of the field of view, particular care was taken to center subject's head in the head coil, to avoid possible magnetic field dishomogeneities or artifacts at cerebellar level.

Image processing

T1-weighted and DTI images were submitted to several processing steps. First, T1-weighted images were processed and examined using the SPM8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), specifically the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) running in Matlab 2007b (MathWorks, Natick, MA, USA). The toolbox extends the unified segmentation model (Ashburner and Friston 2005) consisting of MRI field intensity inhomogeneity correction, spatial normalization and tissue segmentation at several pre-processing steps to further improve data quality. Initially, to increase the signal-to-noise ratio, an optimized blockwise nonlocal-means filter was applied to the MRI scans using the Rician noise

Table 1 Demographic variables (gender, age and years of formal education) and scores of psychological scales [TAS-20 (total and factors); BDI; STAI-2] of the participants (total sample and LA, BA and A groups, separately)

Groups	No. (Males)	Age Mean, years (±SD)	Education Mean, years (±SD)	Total TAS-20 Mean (±SD)	F1 TAS-20 Mean (±SD)	F2 TAS-20 Mean (±SD)	F3 TAS-20 Mean (±SD)	BDI Mean (±SD)	STAI-2 Mean (±SD)
Total sample	60 (25)	58.0 (±17.2)	11.9 (±3.7)	51.3 (±14.7)	15.9 (±6.6)	14.8 (±5.4)	20.7 (±5.9)	6.7 (±4.7)	37.5 (±8.9)
LA	20 (10)	57.8 (±12.7)	12.9 (±2.6)	33.2 (±6.6)	9.4 (±3.0)	9.1 (±3.7)	14.7 (±3.4)	3.4 (±2.8)	34.2 (±7.6)
BA	20 (9)	59.1 (±19.1)	11.3 (±4.4)	54.6 (±2.3)	16.2 (±3.8)	15.6 (±3.6)	22.9 (±3.1)	8.0 (±4.9)	38.5 (±7.8)
A	20 (6)	57.1 (±19.6)	11.7 (±3.8)	66.2 (±5.5)	22.1 (±5.4)	19.7 (±2.0)	24.5 (±5.3)	8.9 (±4.4)	40.8 (±10.5)

LA Low alexithymic traits (TAS-20 scores ≤50), *BA* borderline alexithymic traits (TAS-20 scores 51–60), *A* high Alexithymic traits (TAS-20 scores ≥61)

adaption (Wiest-Daesslé et al. 2008). Then, an adaptive maximum a posteriori segmentation approach extended by partial volume estimation was employed to separate the MRI scans into GM, WM and cerebro-spinal fluid. The segmentation step was finished by applying a spatial constraint to the segmented tissue probability maps based on a hidden Markow Random Field model to remove isolated voxels which unlikely were members of a certain tissue class and to close holes in clusters of connected voxels of a certain class, resulting in a higher signal-to-noise ratio of the final tissue probability maps. Then, the iterative high-dimensional normalization approach provided by the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner 2007) toolbox was applied to the segmented tissue maps to register them to the stereotaxic space of the Montreal Neurological Institute (MNI). The tissue deformations were used to modulate participants' GM and WM maps to be entered in the analyses. Voxel values of the resulting normalized and modulated GM and WM segments indicated the probability (between 0 and 1) that a specific voxel belonged to the relative tissue. Finally, the modulated and normalized GM and WM segments were written with an isotropic voxel resolution of 1.5 mm^3 and smoothed with a 6-mm Full-Width Half Maximum (FWHM) Gaussian kernel. The segmented, normalized, modulated and smoothed GM and WM images were used for analyses.

Subsequently, DTI images were processed using FSL 4.1 (www.fmrib.ox.ac.uk/fsl/). Image distortions induced by eddy currents and head motion in the DTI data were corrected by applying a 3D full affine (mutual information cost function) alignment of each image to the mean no diffusion weighting ($b = 0$) image. After corrections, DTI data were averaged and concatenated into 31 (1 $b0$ + 30 $b1{,}000$) volumes. A diffusion tensor model was fit at each voxel and maps of FA and MD were generated. FA was non-linearly transformed into standard space using the tool FNIRT (Andersson et al. 2007) and the transformation matrix was then applied to the MD maps which were subsequently smoothed using a Gaussian kernel with a 6-mm FWHM.

Analyses restricted to cerebellar GM and WM were determined as follows: (1) GM mask was achieved by meaning all GM probability maps obtained in the VBM8 processing steps, thresholding the relative image to a value of 0.3 (i.e. removing all voxels having a probability to belong to GM lower or equal to 29 %) and manually removing all the non-cerebellar structures using the MNI-oriented atlas of the human brain (Automated Anatomical Labeling Atlas, AAL) (Tzourio-Mazoyer et al. 2002) as reference; (2) similarly, WM mask was obtained by meaning all VBM8 WM probability maps, thresholding the relative image to a value of 0.3 and manually removing all the non-cerebellar structures using the AAL template. To obtain the precise anatomical localization of results, we superimposed statistical maps onto Diedrichsen's probabilistic atlas of the human cerebellum, which subdivides the cerebellum into ten different regions (Diedrichsen et al. 2009).

We did not explore the volumetric variations of deep cerebellar nuclei (dentate, emboliform, globose, and fastigial nuclei) in association with TAS-20 scores, primarily because our MRI protocol did not include the sequences (e.g. T2* or susceptibility-weighted imaging) necessary to segment such nuclei and map their volumetry.

We analyzed the associations between TAS-20 scores and GM volumes of ACC, fusiform gyrus, parahippocampal gyrus, amygdala and insula, defined by the Wake Forest University PICKATLAS templates.

Statistical analysis

Parametric associations between scores of psychological scales [TAS-20 (total and factors); BDI; STAI-2], age and years of formal education were analyzed by Pearson's product moment correlations (Fisher's r to z). Differences

in age, gender, education years and scores of psychological scales were assessed by unpaired t test among the three groups of participants. Alpha level for significance testing was Bonferroni corrected at $p < 0.005$.

Relationships between regional volumes, MD, FA values and scores of psychological scales [TAS-20 (total and factors); BDI; STAI-2] were tested at the voxel level using SPM8 within the framework of the General Linear Model. Multiple-regression analyses were computed by singularly using the measures of volumes, MD and FA as dependent variables, the scores of psychological scales [TAS-20 (total and factors) or BDI or STAI-2] as regressors, and age, education years and gender as well as the psychological variables not used as regressors in a given analysis as covariates. This statistical model was used to evaluate the associations between brain structural measures and psychological variables as well as to control for the effects of the socio-demographic and psychological variables on the main effects (e.g. we used cerebellar or para-limbic GM volumes as a dependent variable, total scores of TAS-20 as a regressor, BDI scores, STAI-2 scores, age, education years and gender as covariates). Gender was always considered a "dummy variable" given its dichotomic nature.

Finally, the mean values of cerebellar volumes significantly associated with TAS-20 scores were extracted and used to create scatterplots. Differences in cerebellar volumes among the three groups were evaluated using one-way ANOVA. Pair-wise post hoc comparisons were performed to assess differences between groups.

We reported relationships whose voxels were part of a spatially contiguous cluster size of a minimum of ten voxels and that survived ($p < 0.05$) at the random field theory-based method from the Family-Wise Error (FWE) corrections (Nichols and Hayasaka 2003). However, to avoid the risk of false negatives, in the limited instances reported in the "Results", an uncorrected statistical level of $p < 0.0001$ was accepted.

Results

Differences in socio-demographic and psychological variables

No correlation emerged between age, education years and psychological variables (Table 2). Significant correlations were found between BDI and total ($r = 0.48$; $p < 0.0001$), F1 ($r = 0.48$; $p < 0.0001$) or F2 ($r = 0.45$; $p < 0.0001$) TAS-20 scores, while no significant correlation was found between BDI and F3 ($r = 0.25$; $p = 0.05$) TAS-20 scores (Fig. 2a). No significant correlations were found among STAI-2 and total ($r = 0.38$; $p = 0.01$), F1 ($r = 0.37$; $p = 0.01$), F2 ($r = 0.39$; $p = 0.007$) and F3 ($r = 0.19$; $p = 0.20$) TAS-20 scores (Fig. 2b). Significant correlation was found between BDI and STAI-2 ($r = 0.47$; $p < 0.0001$) scores.

Table 2 Parametric associations between age or years of formal education and scores of the psychological scales [TAS-20 (total and factors); BDI; STAI-2]

Variables	Total TAS-20	F1 TAS-20	F2 TAS-20	F3 TAS-20	BDI	STAI-2
	r	*r*	*r*	*r*	*r*	*r*
	p	*p*	*p*	*p*	*p*	*p*
Age	−0.14	−0.04	−0.11	−0.06	0.08	−0.29
	0.32	0.77	0.40	0.64	0.58	0.04
Education years	−0.08	−0.18	−0.07	−0.15	−0.19	0.008
	0.59	0.16	0.58	0.26	0.18	0.95

No significant differences emerged in terms of age, gender, and education years among the three groups of participants. A and BA groups significantly differed from LA group in TAS-20 (total and factors) and BDI but not in STAI-2 scores. A group differed from BA group in TAS-20 (total and F1, F2) but not in BDI and STAI-2 scores (Table 3).

Psychological variables and cerebellar measures

Cerebellar GM volumes were positively associated with TAS-20 (total and factors) scores (Fig. 3).

Namely, positive associations were found between bilateral volumes in Crus 1 (MNI coordinates, left: −34, −61, −38; Z score = 2.86, $p_{FWEcorr}$ <0.05; right: 34, −69, −35; Z score = 2.95, $p_{FWEcorr}$ <0.05) and TAS-20 (total and factors) scores. One-way ANOVA on cerebellar GM volumes of the three groups revealed a significant group effect in two clusters located in bilateral Crus 1 (MNI coordinates, left: −34, −60, −38, Z score = 6.85, $p_{FWEcorr}$ <0.05; right: 38, −60, −38; Z score = 6.74, $p_{FWEcorr}$ <0.05). In particular, as revealed by post hoc comparisons the A group showed volumes in bilateral Crus 1 greater than BA (MNI coordinates, left: −34, −60, −38, Z score = 6.45, $p_{FWEcorr}$ <0.05; right: 36, −64, −36, Z score = 6.64, $p_{FWEcorr}$ <0.05) and LA (MNI coordinates, left: −34, −60, −38, Z score = 6.6, $p_{FWEcorr}$ <0.05; right: 38, −60, −38, Z score = 6.35, $p_{FWEcorr}$ <0.05) groups.

No significant associations were found between cerebellar WM volumes and TAS-20 (total and factors) scores. The measures of GM MD and WM FA also failed to reveal any significant micro-structural variation in relation to TAS-20 (total and factors) scores.

No significant association emerged between cerebellar GM or WM volumes, GM MD, or WM FA and BDI and STAI-2 scores, indicating no significant relationship

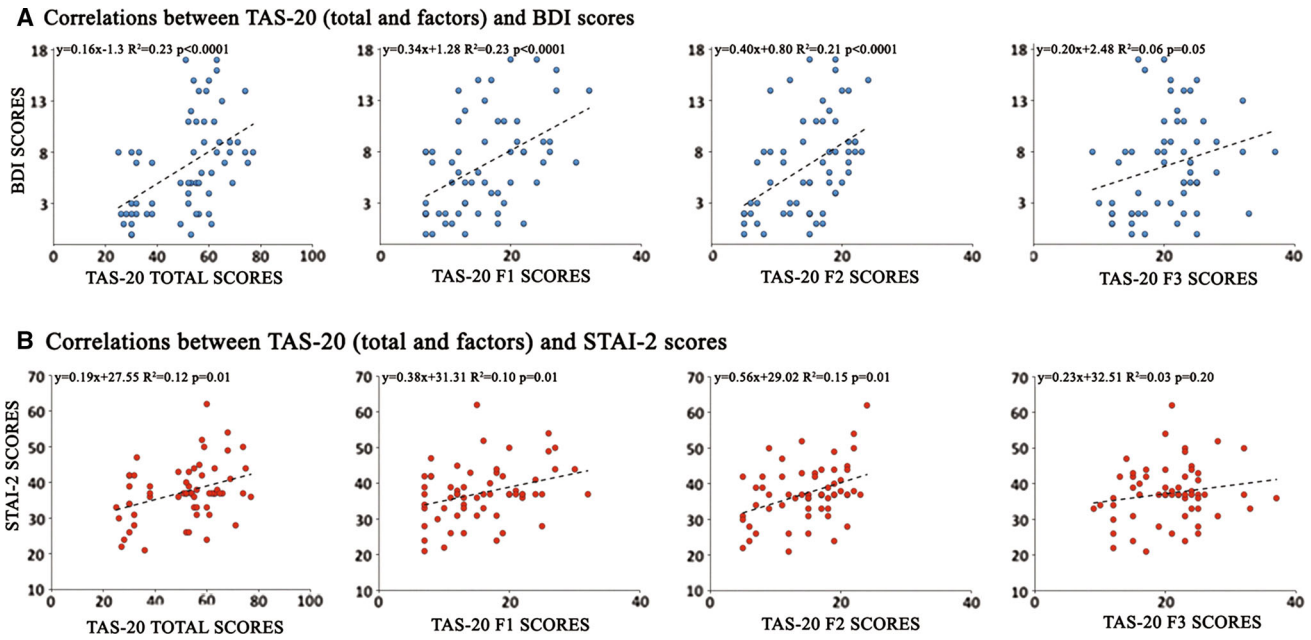

Fig. 2 Correlations between TAS-20 (total and F1, F2, F3) scores and BDI (**a**) or STAI-2 (**b**) scores. Equation, R^2, and *p*-value, as well as linear fit (*dotted line*) are reported

Table 3 Differences in scores of the psychological scales [TAS-20 (total and factors); BDI; STAI-2] among the three groups of participants

Groups	Total TAS-20 *t* (d.f. 38) *p*	F1 TAS-20 *t* (d.f. 38) *p*	F2 TAS-20 *t* (d.f. 38) *p*	F3 TAS-20 *t* (d.f. 38) *p*	Total BDI *t* (d.f. 38) *p*	STAI-2 *t* (d.f. 38) *p*
LA vs. BA	−13.7	−6.2	−5.6	−7.9	−3.6	−1.6
	<0.00001	**<0.00001**	**<0.00001**	**<0.00001**	**<0.001**	0.11
LA vs. A	−17.2	−9.2	−11.3	−7.0	−4.7	−2.1
	<0.00001	**<0.00001**	**<0.00001**	**<0.00001**	**<0.00001**	0.043
BA vs. A	−8.7	−4.0	−4.4	−1.2	−0.6	−0.6
	<0.00001	**0.0003**	**<0.0001**	0.23	0.54	0.52

Significant results are reported in bold

LA Low alexithymic traits (TAS-20 scores ≤50), *BA* borderline alexithymic traits (TAS-20 scores 51–60), *A* high alexithymic traits (TAS-20 scores ≥61)

between cerebellar measures and depression or anxiety in our sample of healthy subjects.

Psychological variables and limbic and para-limbic volumes

Volumes of parahippocampal gyrus, amygdala and insula were negatively associated with TAS-20 scores, while no significant associations were found between ACC or fusiform gyrus volumes and TAS-20 scores. Namely, negative associations were found between left parahippocampal gyrus (MNI coordinates, −16, −10, −32 *Z* score = 3.58; p_{uncorr} <0.0001) or left insula (MNI coordinates, −36, −9, −11, *Z* score = 3.89; p_{uncorr} <0.0001) volumes and TAS-20 total scores. Furthermore, a powerful significant negative association was found between right amygdala (MNI coordinates, 16, −6, −14; *Z* score = 4.48; $p_{FWE\text{-}corr} = 0.002$) volumes and TAS-20 total scores. No significant association emerged between volumes of the reported structures and BDI or STAI-2 scores.

Discussion

In the present sample of healthy subjects categorized according to their TAS-20 scores, the repeatedly described contribution of limbic structures to high alexithymic traits was confirmed. Namely, volumes of the right amygdala, left insula and left parahippocampal gyrus were negatively associated with TAS-20 scores, supporting the view that the altered processing of emotional stimuli featuring alexithymia is accompanied by a reduction of reactivity

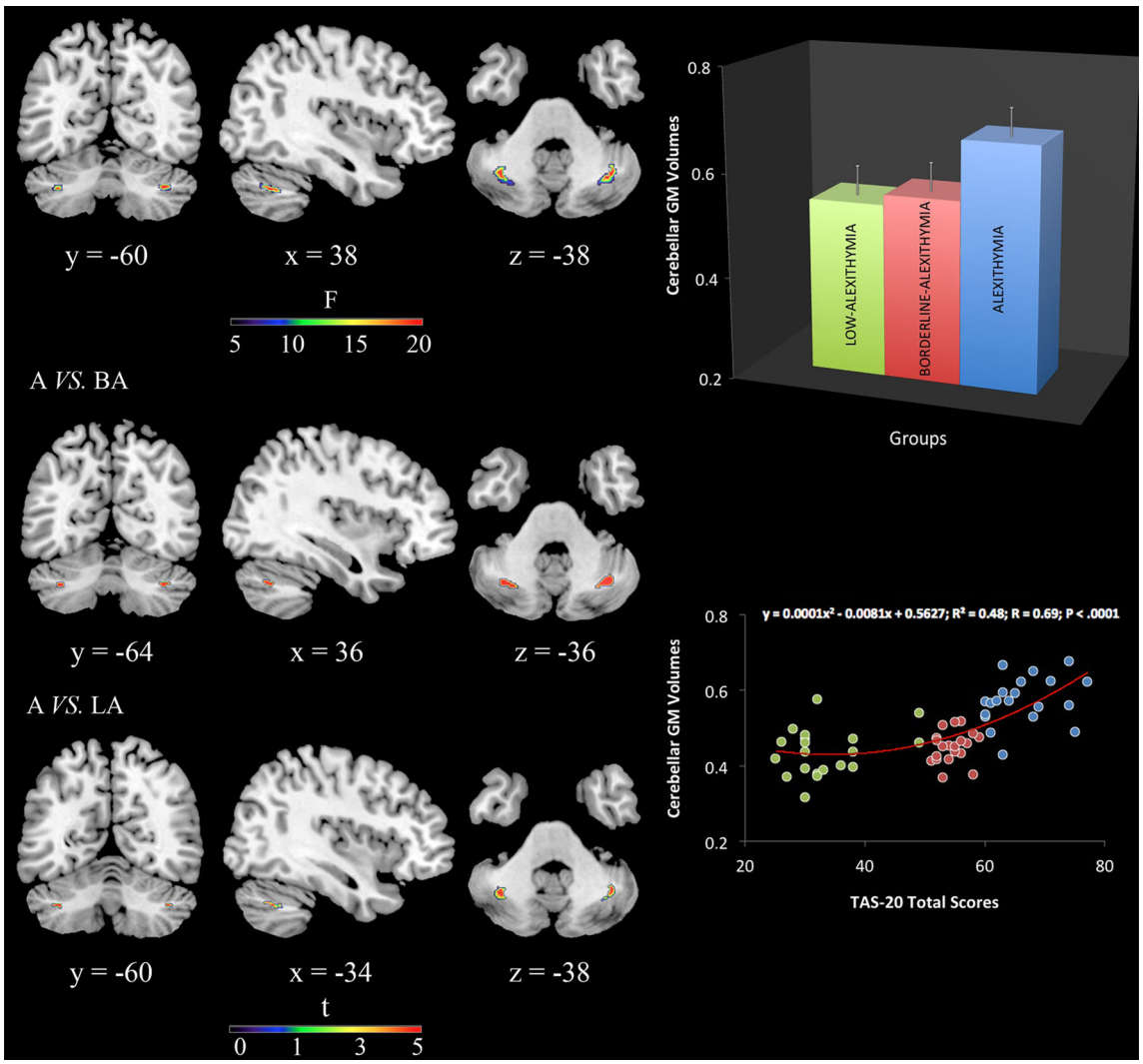

Fig. 3 Cerebellar Gray Matter (*GM*) correlates of alexithymia. A group showed greater volumes in bilateral Crus 1 than BA and LA groups. Above colorbars *F* and *t* values are indicated. Bilateral volumes in Crus 1 associated with TAS-20 scores were used as regions of interest (*ROI*) to extract raw data and create histograms (mean ± SEM) and *scatterplot*, where equation, R^2, *r*, and *p* value, as well as quadratic fit (*solid line*) are reported. The *right side* of the brain is shown on the *right side*. Coordinates are in MNI space. *LA* Low alexithymia (TAS-20 scores ≤50) group, *BA* borderline alexithymia (TAS-20 scores 51–60) group, *A* Alexithymia (TAS-20 scores ≥61) group

(Kano et al. 2003; Pouga et al. 2010; Reker et al. 2010) and volume (Borsci et al. 2009; Ihme et al. 2013) in limbic and para-limbic structures. No association between ACC or fusiform gyrus and TAS-20 scores was observed.

More importantly, we found positive associations between TAS-20 scores and cerebellar GM volumes in right and left Crus 1. Peculiarly, the subjects with high alexithymic traits (TAS-20 scores ≥61) had larger volumes in the bilateral Crus 1 in comparison to the remaining subjects. The increased volumes in Crus 1 were not accompanied by significant alterations in density, surface and orientation of cells as indicated by MD and FA values, showing thus that no micro-structural variation in Crus 1 as well as in other cerebellar areas was related with alexithymic traits. Also cerebellar WM volumes did not correlate with TAS-20 scores.

Assuming that alexithymia is a normally distributed continuous personality construct and that bio-psycho-pathological susceptibility exists in healthy individuals, the present research was performed on a sample of healthy subjects without psychiatric diagnosis to minimize the influence of disease-related and environmental confounders, as previously suggested (Laricchiuta et al. 2013; Westlye et al. 2011). Being alexithymia expressed with variable intensity in the healthy population, we expected an effect size of alexithymia on brain morphology to be small. Conversely, the associations of TAS-20 scores with cerebellar and amygdala volumes were powerfully significant,

and we needed to lower the significance threshold only for the associations of TAS-20 scores with insula and parahippocampal gyrus volumes. Furthermore, we chose the tripartite sample categorization proposed by the TAS-20 scale developers (Bagby et al. 1994a, b) to evaluate whether the eventual associations between cerebellar volumes and TAS-20 scores implied gradual transition or discontinuity among groups classified as having different degrees of alexithymia. Interestingly, the present data emphasized the specificity of the association between cerebellar volumes and TAS-20 scores only in the presence of a definite alexithymia (A group), indicating thus that the enlargement of volumes in Crus 1 was not distributed along a continuum.

Although healthy, all participants were also evaluated by BDI (Beck et al. 1988). As expected, a positive correlation between TAS-20 and BDI scores was found, strengthening the already-documented relationship between alexithymia and depression (Assogna et al. 2012; Bossù et al. 2009; Honkalampi et al. 2000; Spalletta et al. 2001). However, the lack of any significant association between BDI scores and cerebellar structural measures (as well as the outcomes of the statistical model with BDI scores used as regressor) demonstrated that the association between cerebellar volumes and alexithymia scores was independent from depression, confirming that alexithymia and depression are two distinct dimensions (Parker et al. 1991). While in some studies alexithymia scores were significantly associated with anxiety levels (Devine et al. 1999; Karukivi et al. 2010; Marchesi et al. 2005), in the present study no significant relations were found between STAI-2 and TAS-20 scores, between STAI-2 and cerebellar GM volumes, as well as between STAI-2 and cerebellar WM volumes, MD or FA values.

The enlarged volumes in Crus 1 occurring in subjects with high alexithymic traits sustain the cerebellar involvement in cognitive, emotional and affective processes and fit with the consistent activation unique to emotional processing described in bilateral Crus 1 in recent reports (Kh et al. 2012; Stoodley and Schmahmann 2010). Neuroanatomical (Bostan et al. 2013) and fMRI studies (Dimitrova et al. 2003; Habas et al. 2009) indicate that Crus 1 and lobule VI constitute a node in the cortico-limbic network centered on the dorsal ACC and fronto-insular cortex, and involved in detecting, integrating and filtering emotional information. Furthermore, it has been reported that aversive stimuli in the form of noxious heat and unpleasant images produce increased activation in Crus 1 and lobule VI (Moulton et al. 2011) and negative emotional faces evoke prominent activation in Crus 1 and Crus 2 as well as in lobules VI and IX (Schraa-Tam et al. 2012). Even the act of identifying emotional intonation (affective prosody) produces activation in Crus 1 and lobule VI, VII (Imaizumi et al. 1997; Wildgruber et al. 2005).

In investigating from a structural point of view a brain region likely associated with a given function, a basic question is how the structure relates to that function. Human and experimental evidence favors the larger-is-more-powerful position: training on particular tasks or experiencing complex environment do increase the volume of the brain structures related to specific functions (Boyke et al. 2008; Di Paola et al. 2013; Pangelinan et al. 2011). Thus, it seems reasonable to assume that volume positively co-varies with function. We found that volumes in bilateral Crus 1 were positively related to TAS-20 scores that in turn were negatively related to volumes of some limbic and para-limbic structures. These results are consistent with the activation of Crus 1 and lobules VI and VIIb demonstrated to be negatively correlated with the activation of limbic and para-limbic areas, as parahippocampal gyrus, ACC, and hypothalamus (Moulton et al. 2011). The inverse link between cerebellum and limbic system suggests a possible functional modality for the cerebellar involvement in emotional processing (Fusar-Poli et al. 2009; Konarski et al. 2005; Murphy et al. 2003). Although it has not yet been clarified the mechanism underlying the functional relations between cerebellar and limbic regions, it is possible to advance that the increased volumes of Crus 1 could result in an enhanced inhibitory output of Purkinje cells, the only efferents of the cerebellar cortex, on the deep cerebellar nuclei, modulating thus their excitatory activity. Cerebellar nuclei then project to extra-cerebellar targets including the limbic system (Bostan et al. 2013). The inhibited nuclear activity could have as consequence a reduced excitatory input to limbic and para-limbic structures that in turn could undergo a volumetric reduction because of the diminished activation level. Such a mechanism, however to date hypothetical, is in line with classical electrophysiological evidence indicating that cerebellar nuclear stimulations have suppressive effects on limbic sites, including ACC and amygdala (Anand et al. 1959; Snider and Maiti 1976). In the same vein, smaller ACC volumes and greater posterior cerebellar volumes have been very recently demonstrated in patients with Cushing's disease reporting depressive and anxiety symptoms as well as cognitive, affective and personality disorders (Andela et al. 2013). Structural neuroimaging studies on patients affected by obsessive–compulsive disorder also indicate smaller ACC volumes associated with greater cerebellar GM volumes (de Wit et al. 2014), offering additional insights into such a reciprocal structural relation between cerebellum and limbic and para-limbic areas.

Intriguingly, our structural findings are nicely compatible with the functional findings reported by Moriguchi and Komaki (2013). In their recent review, the authors

advance that people with high alexithymic traits show *reduced* neural response in the limbic system to external and internal emotional stimuli and in contrast *increased* neural response in somato-sensory and sensorimotor areas to stimuli closely associated with physical information. The authors report that subjects with high alexithymic traits exhibit hypersensitivity to physical sensations associated with a tendency to rely on or to amplify physical symptoms. The network comprising cerebellum and limbic system (and also the somato-sensory, sensorimotor and prefrontal cortices) is involved in sensing and monitoring the physiological bodily condition (Critchley et al. 2003), in representing the internal viscero-sensory state within the context of ongoing activities (D'Angelo and Casali 2012) as well as in feeling self- and externally induced emotions (Anders et al. 2004). It has been advanced that in the condition of efficient functioning subjects have internal models of their internal or external environment that serves the function of representing it, even when they are not causally determined by current stimuli. The internal models form embodied representations grounded in sensorimotor control loops, and these representations in turn are internally manipulated before or instead of acting directly on environment, even if the final goal of this form of embodied emotion and cognition is acting on the environment (Barsalou 2008; Niedenthal et al. 2005; Pezzulo and Castelfranchi 2007, 2009a, b). This concept of embodiment fully fits Ito's seminal proposal (2008) advancing that the cerebellum forms internal models of the body to control motor, cognitive and emotional activities both on-line and off-line. The increased volumes in Crus 1 of subjects with high alexithymic traits thus could be related to an altered embodiment process leading to not-cognitively interpreted emotions. On this vein, alexithymia may be considered an embodiment process related to altered perception of physiological correlates (viscero- and somato-motor responses) of the emotional activation resulting in a deficit in the emotional awareness. In this framework, in subjects with high alexithymic traits the enlarged volumes in Crus 1 would be associated to a lacking relocation (from the embodied internal state to the symbolic representation) of the emotional signals that thus remain embodied (F1 of TAS-20 scale), not-cognitively described (F2 of TAS-20 scale) and not mentalized (F3 of TAS-20 scale). Accordingly, a somato-sensory amplification has been described in the presence of definite alexithymia (Lumley et al. 2002, 2005). Kano et al. (2007) describing the aberrant manner of perceiving body signals of subjects with high alexithymic traits reported positive associations between TAS-20 scores and cerebellar regional cerebral blood flow (rCBF) following visceral stimulation. Furthermore, high cerebellar rCBF was reported in subjects with high alexithymic traits when viewing emotional facial expressions (Kano et al. 2003), recalling emotional autobiographic traces (Huber et al. 2002) or observing a classic mirror neuron task, as the observation of goal-directed hand actions (Moriguchi et al. 2009). Further fMRI analyses on subjects with alexithymic traits performing specific emotional and somato-sensory tasks will be useful for tracing a better correlation between anatomical and functional alterations in the presence of alexithymia.

In conclusion, the increased volumes in bilateral Crus 1 we found associated with high alexithymic traits throw a new light on alexithymia and its conceptualization as related to the "alexisomia", intriguing phenomenon describing the difficulty in the awareness of somatic sensations (Ikemi and Ikemi 1986; Moriguchi and Komaki 2013). Considering the bottom-up component of emotional control (LeDoux 2013), the altered awareness of bodily states featuring the alexisomia might be the primitive level of altered emotional awareness featuring alexithymia.

Acknowledgments The authors would like to thank Prof. Fabio Ferlazzo for his kind and expert support in statistical analyses.

Conflict of interest The authors declare that they have no conflict of interest.

References

Anand BK, Malhotra CL, Singh B, Dua S (1959) Cerebellar projections to limbic system. J Neurophysiol 22:451–457

Andela CD, van der Werff SJ, Pannekoek JN, van den Berg SM, Meijer OC, van Buchem MA, Rombouts SA, van der Mast RC, Romijn JA, Tiemensma J, Biermasz NR, van der Wee NJ, Pereira AM (2013) Smaller grey matter volumes in the anterior cingulate cortex and greater cerebellar volumes in patients with long-term remission of Cushing's disease: a case–control study. Eur J Endocrinol 169:811–819. doi:10.1530/EJE-13-0471

Anders S, Lotze M, Erb M, Grodd W, Birbaumer N (2004) Brain activity underlying emotional valence and arousal: a response-related fMRI study. Hum Brain Mapp 23:200–209

Andersson J, Jenkinson M, Smith S (2007) Non-linear registration, aka spatial normalisation. FMRIB Technical report TR07JA2. www.fmrib.ox.ac.uk/analysis/techrep

Andreasen NC, O'Leary DS, Paradiso S, Cizadlo T, Arndt S, Watkins GL, Ponto LL, Hichwa RD (1999) The cerebellum plays a role in conscious episodic memory retrieval. Hum Brain Mapp 8:226–234

Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 38:95–113

Ashburner J, Friston KJ (2005) Unified segmentation. Neuroimage 26:839–851

Assogna F, Palmer K, Pontieri FE, Pierantozzi M, Stefani A, Gianni W, Caltagirone C, Spalletta G (2012) Alexithymia is a non-motor symptom of Parkinson disease. Am J Geriatr Psychiatry 20:133–141. doi:10.1097/JGP.0b013e318209de07

Bagby RM, Parker JD, Taylor GJ (1994a) The 20-item Toronto Alexithymia Scale-I. Item selection and cross-validation of the factor structure. J Psychosom Res 38:23–32

Bagby RM, Taylor GJ, Parker JD (1994b) The 20-item Toronto Alexithymia Scale-II. Convergent, discriminant, and concurrent validity. J Psychosom Res 38:33–40

Baldaçara L, Nery-Fernandes F, Rocha M, Quarantini LC, Rocha GG, Guimarães JL, Araújo C, Oliveira I, Miranda-Scippa A, Jackowski A (2011) Is cerebellar volume related to bipolar disorder? J Affect Disord 135:305–309. doi:10.1016/j.jad.2011.06.059

Barsalou LW (2008) Grounded cognition. Annu Rev Psychol 59:617–645

Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111:209–219

Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck Depression Inventory. 25 years of evaluation. Clin Psychol Rev 8:77–100

Borsci G, Boccardi M, Rossi R, Rossi G, Perez J, Bonetti M, Frisoni GB (2009) Alexithymia in healthy women: a brain morphology study. J Affect Disord 114:208–215. doi:10.1016/j.jad.2008.07.013

Bossù P, Salani F, Cacciari C, Picchetto L, Cao M, Bizzoni F, Rasura M, Caltagirone C, Robinson RG, Orzi F, Spalletta G (2009) Disease outcome, alexithymia and depression are differently associated with serum IL-18 levels in acute stroke. Curr Neurovasc Res 6:163–170

Bostan AC, Dum RP, Strick PL (2013) Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci 17:241–254. doi:10.1016/j.tics.2013.03.003

Boyke J, Driemeyer J, Gaser C, Büchel C, May A (2008) Training-induced brain structure changes in the elderly. J Neurosci 28:7031–7035. doi:10.1523/JNEUROSCI.0742-08.2008

Carlesimo GA, Caltagirone C, Gainotti G (1996) The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The group for the standardization of the mental deterioration battery. Eur Neurol 36:378–384

Cloninger CR (1986) A unified biosocial theory of personality and its role in the development of anxiety states. Psychiatr Dev 4:167–226

Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, Cipolotti L, Shallice T, Dolan RJ (2003) Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 126:2139–2152

D'Angelo E, Casali S (2012) Seeking a unified framework for cerebellar function and dysfunction: from circuit operations to cognition. Front Neural Circuits 6:116. doi:10.3389/fncir.2012.00116

De Bellis MD, Kuchibhatla M (2006) Cerebellar volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry 60:697–703

de Wit SJ, Alonso P, Schweren L, Mataix-Cols D, Lochner C, Menchón JM, Stein DJ, Fouche JP, Soriano-Mas C, Sato JR, Hoexter MQ, Denys D, Nakamae T, Nishida S, Kwon JS, Jang JH, Busatto GF, Cardoner N, Cath DC, Fukui K, Jung WH, Kim SN, Miguel EC, Narumoto J, Phillips ML, Pujol J, Remijnse PL, Sakai Y, Shin NY, Yamada K, Veltman DJ, van den Heuvel OA (2014) Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive–compulsive disorder. Am J Psychiatry 171:340–349. doi:10.1176/appi.ajp.2013.13040574

Devine H, Stewart SH, Watt MC (1999) Relations between anxiety sensitivity and dimensions of alexithymia in a young adult sample. J Psychosom Res 47:145–158

Di Paola M, Caltagirone C, Petrosini L (2013) Prolonged rock climbing activity induces structural changes in cerebellum and parietal lobe. Hum Brain Mapp 34:2707–2714. doi:10.1002/hbm.22095

Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N (2009) A probabilistic MR atlas of the human cerebellum. Neuroimage 46:39–46. doi:10.1016/j.neuroimage.2009.01.045

Dimitrova A, Kolb FP, Elles HG, Maschke M, Forsting M, Diener HC, Timmann D (2003) Cerebellar responses evoked by nociceptive leg withdrawal reflex as revealed by event-related FMRI. J Neurophysiol 90:1877–1886

Dorard G, Berthoz S, Haviland MG, Phan O, Corcos M, Bungener C (2008) Multimethod alexithymia assessment in adolescents and young adults with a cannabis use disorder. Compr Psychiatry 49:585–592

First MB, Spitzer RL, Gibbon M, Williams JB (1997) Structured clinical interview for DSM-IV axis I disorders (SCID-I), clinician version. American Psychiatric Press, Washington

First MB, Spitzer RL, Gibbon M, Williams JBW (2002) Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition. (SCID-I/NP). Biometrics Research, New York

Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ (2008) A meta-analytic study of changes in brain activation in depression. Hum Brain Mapp 29:683–695. Erratum. Hum Brain Mapp 29:736

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198

Franz M, Schaefer R, Schneider C, Sitte W, Bachor J (2004) Visual event-related potentials in subjects with alexithymia: modified processing of emotional aversive information? Am J Psychiatry 161:728–735

Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P (2009) Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 34:418–432

Gündel H, López-Sala A, Ceballos-Baumann AO, Deus J, Cardoner N, Marten-Mittag B, Soriano Mas C, Pujol J (2004) Alexithymia correlates with the size of the right anterior cingulate. Psychosom Med 66:132–140

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, Greicius MD (2009) Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 29:8586–8594. doi:10.1523/JNEUROSCI.1868-09.2009

Heinzel A, Minnerop M, Schäfer R, Müller HW, Franz M, Hautzel H (2012) Alexithymia in healthy young men: a voxel-based morphometric study. J Affect Disord 136:1252–1256. doi:10.1016/j.jad.2011.06.012

Honkalampi K, Hintikka J, Tanskanen A, Lehtonen J, Viinamäki H (2000) Depression is strongly associated with alexithymia in the general population. J Psychosom Res 48:99–104

Huber M, Herholz K, Habedank B, Thiel A, Müller-Küppers M, Ebel H, Subic-Wrana C, Köhle K, Heiss WD (2002) Different patterns of regional brain activation during emotional stimulation in alexithymics in comparison with normal controls. Psychother Psychosom Med Psychol 52:469–478

Ihme K, Dannlowski U, Lichev V, Stuhrmann A, Grotegerd D, Rosenberg N, Kugel H, Heindel W, Arolt V, Kersting A, Suslow T (2013) Alexithymia is related to differences in gray matter volume: a voxel-based morphometry study. Brain Res 1491:60–67. doi:10.1016/j.brainres.2012.10.044

Ikemi Y, Ikemi A (1986) An oriental point of view in psychosomatic medicine. Psychother Psychosom 45:118–126

Imaizumi S, Mori K, Kiritani S, Kawashima R, Sugiura M, Fukuda H, Itoh K, Kato T, Nakamura A, Hatano K, Kojima S, Nakamura K (1997) Vocal identification of speaker and emotion activates different brain regions. NeuroReport 8:2809–2812

Ito M (2008) Control of mental activities by internal models in the cerebellum. Nat Rev Neurosci 9:304–313. doi:10.1038/nrn2332

Kano M, Fukudo S, Gyoba J, Kamachi M, Tagawa M, Mochizuki H, Itoh M, Hongo M, Yanai K (2003) Specific brain processing of facial expressions in people with alexithymia: an H2 15O-PET study. Brain 126:1474–1484

Kano M, Hamaguchi T, Itoh M, Yanai K, Fukudo S (2007) Correlation between alexithymia and hypersensitivity to visceral stimulation in human. Pain 132:252–263

Karukivi M, Hautala L, Kaleva O, Haapasalo-Pesu KM, Liuksila PR, Joukamaa M, Saarijärvi S (2010) Alexithymia is associated with anxiety among adolescents. J Affect Disord 125:383–387. doi:10.1016/j.jad.2010.02.126

Kh E, Chen SH, Ho MH, Desmond JE (2012) A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. Hum Brain Mapp. doi:10.1002/hbm.22194

Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH (2005) Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? J Psychiatry Neurosci 30:178–186

Kunisato Y, Okamoto Y, Okada G, Aoyama S, Nishiyama Y, Onoda K, Yamawaki S (2011) Personality traits and the amplitude of spontaneous low-frequency oscillations during resting state. Neurosci Lett 492:109–113. doi:10.1016/j.neulet.2011.01.067

Laricchiuta D, Petrosini L, Piras F, Macci E, Cutuli D, Chiapponi C, Cerasa A, Picerni E, Caltagirone C, Girardi P, Tamorri SM, Spalletta G (2012) Linking novelty seeking and harm avoidance personality traits to cerebellar volumes. Hum Brain Mapp. doi:10.1002/hbm.22174

Laricchiuta D, Petrosini L, Piras F, Cutuli D, Macci E, Picerni E, Chiapponi C, Caltagirone C, Spalletta G (2013) Linking novelty seeking and harm avoidance personality traits to basal ganglia: volumetry and mean diffusivity. Brain Struct Funct [Epub ahead of print]

Larsen JK, Brand N, Bermond B, Hijman R (2003) Cognitive and emotional characteristics of alexithymia: a review of neurobiological studies. J Psychosom Res 54:533–541

Le Bihan D (2007) The 'wet mind': water and functional neuroimaging. Phys Med Biol 52:R57–R90

LeDoux JE (2013) Rethinking the emotional brain. Neuron 73:653–676. doi:10.1016/j.neuron.2012.02.004

Lumley MA, Smith JA, Longo DJ (2002) The relationship of alexithymia to pain severity and impairment among patients with chronic myofascial pain: comparisons with self-efficacy, catastrophizing, and depression. J Psychosom Res 53:823–830

Lumley MA, Radcliffe AM, Macklem DJ, Mosley-Williams A, Leisen JC, Huffman JL, D'Souza PJ, Gillis ME, Meyer TM, Kraft CA, Rapport LJ (2005) Alexithymia and pain in three chronic pain samples: comparing Caucasians and African Americans. Pain Med 6:251–261

Marchesi C, Fontò S, Balista C, Cimmino C, Maggini C (2005) Relationship between alexithymia and panic disorder: a longitudinal study to answer an open question. Psychother Psychosom 74:56–60

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 34:939–944

Measso G, Cavarzeran F, Zappalà G, Lebowitz B, Crook T, Pirozzolo F, Amaducci L, Massari D, Grigoletto F (1993) The mini-mental state examination: normative study of an Italian random sample. Dev Neuropsychol 9:77–85

Moriguchi Y, Komaki G (2013) Neuroimaging studies of alexithymia: physical, affective, and social perspectives. Biopsychosoc Med 7:8. doi:10.1186/1751-0759-7-8

Moriguchi Y, Decety J, Ohnishi T, Maeda M, Mori T, Nemoto K, Matsuda H, Komaki G (2007) Empathy and judging other's pain: an fMRI study of alexithymia. Cereb Cortex 17: 2223–2234

Moriguchi Y, Ohnishi T, Decety J, Hirakata M, Maeda M, Matsuda H, Komaki G (2009) The human mirror neuron system in a population with deficient self-awareness: an fMRI study in alexithymia. Hum Brain Mapp 30:2063–2076. doi:10.1002/hbm.20653

Moulton EA, Elman I, Pendse G, Schmahmann J, Becerra L, Borsook D (2011) Aversion-related circuitry in the cerebellum: responses to noxious heat and unpleasant images. J Neurosci 31:3795–3804. doi:10.1523/JNEUROSCI.6709-10.2011

Müller HP, Unrath A, Ludolph AC, Kassubek J (2007) Preservation of diffusion tensor properties during spatial normalization by use of tensor imaging and fibre tracking on a normal brain database. Phys Med Biol 52:N99–N109

Murphy FC, Nimmo-Smith I, Lawrence AD (2003) Functional neuroanatomy of emotions: a meta-analysis. Cogn Affect Behav Neurosci 3:207–233

Nichols T, Hayasaka S (2003) Controlling the familywise error rate in functional neuroimaging: a comparative review. Stat Methods Med Res 12:419–446

Niedenthal PM, Barsalou LW, Winkielman P, Krauth-Gruber S, Ric F (2005) Embodiment in attitudes, social perception, and emotion. Pers Soc Psychol Rev 9:184–211

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113

Pangelinan MM, Zhang G, VanMeter JW, Clark JE, Hatfield BD, Haufler AJ (2011) Beyond age and gender: relationships between cortical and subcortical brain volume and cognitive-motor abilities in school-age children. Neuroimage 54:3093–3100. doi:10.1016/j.neuroimage.2010.11.021

Parker JD, Bagby RM, Taylor GJ (1991) Alexithymia and depression: distinct or overlapping constructs? Compr Psychiatry 32:387–394

Pezzulo G, Castelfranchi C (2007) The symbol detachment problem. Cogn Process 8:115–131

Pezzulo G, Castelfranchi C (2009a) Intentional action: from anticipation to goal-directed behavior. Psychol Res 73:437–440. doi:10.1007/s00426-009-0241-3

Pezzulo G, Castelfranchi C (2009b) Thinking as the control of imagination: a conceptual framework for goal-directed systems. Psychol Res 73:559–577. doi:10.1007/s00426-009-0237-z

Picerni E, Petrosini L, Piras F, Laricchiuta D, Cutuli D, Chiapponi C, Fagioli S, Girardi P, Caltagirone C, Spalletta G (2013) New evidence for the cerebellar involvement in personality traits. Front Behav Neurosci 7:133. doi:10.3389/fnbeh.2013.00133

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR imaging of the human brain. Radiology 201:637–648

Piras F, Caltagirone C, Spalletta G (2010) Working memory performance and thalamus microstructure in healthy subjects. Neurosci 171:496–505

Piras F, Cherubini A, Caltagirone C, Spalletta G (2011) Education mediates microstructural changes in bilateral hippocampus. Hum Brain Mapp 32:282–289

Pouga L, Berthoz S, de Gelder B, Grèzes J (2010) Individual differences in socioaffective skills influence the neural bases of fear processing: the case of alexithymia. Hum Brain Mapp 31:1469–1481. doi:10.1002/hbm.20953

Reker M, Ohrmann P, Rauch AV, Kugel H, Bauer J, Dannlowski U, Arolt V, Heindel W, Suslow T (2010) Individual differences in alexithymia and brain response to masked emotion faces. Cortex 46:658–667. doi:10.1016/j.cortex.2009.05.008

Schmahmann JD (2004) Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci 16:367–378

Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain 121:561–579

Schraa-Tam CK, Rietdijk WJ, Verbeke WJ, Dietvorst RC, van den Berg WE, Bagozzi RP, De Zeeuw CI (2012) fMRI activities in the emotional cerebellum: a preference for negative stimuli and goal-directed behavior. Cerebellum 11:233–245. doi:10.1007/s12311-011-0301-2

Schutter DJ, van Honk J (2009) The cerebellum in emotion regulation: a repetitive transcranial magnetic stimulation study. Cerebellum 8:28–34. doi:10.1007/s12311-008-0056-6

Schutter DJ, Koolschijn PC, Peper JS, Crone EA (2012) The cerebellum link to neuroticism: a volumetric MRI association study in healthy volunteers. PLoS One 7:e37252. doi:10.1371/journal.pone.0037252

Sifneos PE (1972) Short-term psychotherapy and emotional crisis. Harvard University Press, Cambridge

Snider RS, Maiti A (1976) Cerebellar contributions to the Papez circuit. J Neurosci Res 2:133–146

Spalletta G, Pasini A, Costa A, De Angelis D, Ramundo N, Paolucci S, Caltagirone C (2001) Alexithymic features in stroke: effects of laterality and gender. Psychosom Med 63:944–950

Spalletta G, Fagioli S, Caltagirone C, Piras F (2012) Brain microstructure of subclinical apathy phenomenology in healthy individuals. Hum Brain Mapp. doi:10.1002/hbm.22137

Spielberger CD (1989) State-trait anxiety inventory: a comprehensive bibliography, 2nd edn. Consulting Psychologists Press, Palo Alto

Spitzer RL, Williams JB, Gibbon M, First MB (1992) The structured clinical interview for DSM-III-R (SCID). I: history, rationale, and description. Arch Gen Psychiatry 49:624–629

Stoodley CJ, Schmahmann JD (2010) Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 46:831–844. doi:10.1016/j.cortex.2009.11.008

Stoodley CJ, Valera EM, Schmahmann JD (2012) Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. Neuroimage 59:1560–1570. doi:10.1016/j.neuroimage.2011.08.065

Taylor GJ (2000) Recent developments in alexithymia theory and research. Can J Psychiatry 45:134–142

Taylor GJ, Bagby RM (2004) New trends in alexithymia research. Psychother Psychosom 73:68–77

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289

Wei L, Duan X, Yang Y, Liao W, Gao Q, Ding JR, Zhang Z, Zeng W, Li Y, Lu G, Chen H (2011) The synchronization of spontaneous BOLD activity predicts extraversion and neuroticism. Brain Res 1419:68–75. doi:10.1016/j.brainres.2011.08.060

Westlye LT, Bjørnebekk A, Grydeland H, Fjell AM, Walhovd KB (2011) Linking an anxiety-related personality trait to brain white matter microstructure: diffusion tensor imaging and harm avoidance. Arch Gen Psychiatry 68:369–377. doi:10.1001/archgenpsychiatry.2011.24

Wiest-Daesslé N, Prima S, Coupé P, Morrissey SP, Barillot C (2008) Rician noise removal by non-local means filtering for low signal-to-noise ratio MRI: applications to DT-MRI. Med Image Comput Comput Assist Interv 11:171–179

Wildgruber D, Riecker A, Hertrich I, Erb M, Grodd W, Ethofer T, Ackermann H (2005) Identification of emotional intonation evaluated by fMRI. Neuroimage 24:1233–1241

Wolf U, Rapoport MJ, Schweizer TA (2009) Evaluating the affective component of the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci 21:245–253. doi:10.1176/appi.neuropsych.21.3.245

Zhu JN, Yung WH, Kwok-Chong Chow B, Chan YS, Wang JJ (2006) The cerebellar-hypothalamic circuits: potential pathways underlying cerebellar involvement in somatic-visceral integration. Brain Res Rev 52:93–106