Alexithymia and Brain Gray Matter Volumes in a General Population Sample

Hans Jürgen Grabe,^{1,2*} Katharina Wittfeld,² Katrin Hegenscheid,³
Norbert Hosten,³ Martin Lotze,³ Deborah Janowitz,¹ Henry Völzke,^{4,5}
Ulrich John,⁶ Sven Barnow,⁷ and Harald J. Freyberger¹

¹Department of Psychiatry and Psychotherapy, University Medicine Greifswald,
Helios Hospital Stralsund, Germany

²German Center for Neurodegenerative Diseases (DZNE), Rostock/ Greifswald, Germany

³Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald,
Germany

⁴Institute for Community Medicine, University Medicine Greifswald, Germany

⁵German Research Centre of Cardiovascular Disease, Partner Site Greifswald, Germany

⁶Institute of Social Medicine and Prevention, University Medicine Greifswald, Germany

⁷Institute of Psychology, University of Heidelberg, Germany

Abstract: Alexithymia is perceived as a personality construct involving deficits in the cognitive processing of emotion. Brain areas that process emotions might be structurally altered in affected people. Subjects from the Study of Health in Pomerania who underwent whole body magnetic resonance imaging were investigated. After quality control procedures 2,589 subjects with Toronto Alexithymia Scale 20 (TAS-20) data and interview-based information on major depressive disorder (MDD) were available. After exclusion of study participants who were older than 65 years or had MDD in their lifetime, 1,685 subjects were included in the voxel-based morphometric (VBM 8) analyses. In whole-brain analyses, the TAS-20 total score was associated with less gray matter (GM) volumes of the bilateral dorsal anterior cingulate cortex (dACC). The TAS-20 factor scale difficulty identifying feelings (DIF) was associated with less GM volume in three clusters: dACC, left middle and inferior temporal gyrus,

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*Correspondence to: Hans J. Grabe, Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Ellernholzstraße 1–2, 17475 Greifswald, Germany. E-mail: grabeh@uni-greifswald.de
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left fusiform gyrus and cerebellum. The lower GM volume in the left fusiform gyrus was specific for females. Absolute GM volume analyses also revealed associations between the factor scales difficulty describing feelings, external orientated thinking and the dACC. Adjustment for current symptoms of anxiety and depression did not change the effects sizes substantially. In conclusion, lower GM volume in the dACC represents the major structural correlate of alexithymia. Associations with DIF suggest a prominent involvement of left temporal areas. These areas represent language and semantic processing and might be involved in the cognitive processing of emotions and the conscious identification of feelings. *Hum Brain Mapp* 35:5932–5945, 2014. © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Subjects with alexithymia (no words for emotions) have difficulties identifying subjective feelings and distinguishing between feelings and the bodily sensations that accompany states of emotional arousal. Additionally they have an externally oriented style of thinking and an impoverished fantasy life [Bagby et al., 1994]. They often avoid social situations, seem cold, show a lack of intimacy and warmth and are insecurely attached to others [Grabe et al., 2001]. Research on the alexithymia construct has advanced rapidly over the past decade due to the development of the self-report 20-item Toronto Alexithymia Scale (TAS-20) that provided investigators a reliable and valid assessment tool [Grabe et al., 2004; Taylor and Bagby, 2004]. The high stability of the TAS-20 over a 5-year period underscores the trait characteristic of alexithymia [Saarijarvi et al., 2006]. In a general population sample >10% [Franz et al., 2008] and in a patient sample with mental and psychosomatic disorders >25% scored in the high range of the TAS-20 (>60) [Grabe et al., 2008].

It was hypothesized that the alexithymic deficit in the cognitive processing of emotions would be associated with altered functions of an emotion-processing cortical and sub-cortical network. The ventral part of the anterior cingulate cortex (ACC) plays an important role within this network. The ventral ACC is connected with further brain regions processing emotional, motivational, and interoceptive information (amygdala, nucleus accumbens, anterior insula). Furthermore, it impacts on physiological processes through connections to the hypothalamus [Allman et al., 2001]. The dorsal ACC (dACC) has been implicated in cognitive processing rather than emotion processing [Mohanty et al., 2007]. The gray matter (GM) volume of the dACC has been associated with attention to emotions and the ability to regulate negative feeling states [Koven et al., 2011].

Likewise, a number of functional brain imaging studies on alexithymia or emotional awareness revealed hypoactivation but also hyperactivation of those emotion-processing brain areas, like of the dACC, amygdala, and fusiform gyrus in response to a variety of affect-provoking paradigms [Deng et al., 2013; Kano et al., 2003; Karlsson

et al., 2008; Kugel et al., 2008; Lane et al., 1998; Meriau et al., 2006; Miyake et al., 2012; Moriguchi and Komaki, 2013; van der Velde et al., 2013].

Volumetric studies so far used different morphometric approaches or comprised small sample sizes. In an earlier structural magnetic resonance imaging (MRI)-based analysis of 100 students using manual segmentation of the ACC, a positive correlation between the size of the right ACC and TAS-20 scores was observed [Gündel et al., 2004]. Subsequent studies did not replicate this finding. Borsci et al. [2009] investigated 14 healthy women with high alexithymia scores compared with 30 matched controls in a whole-brain voxel-based morphometric (VBM) approach. Without correcting for multiple comparisons (P -values < 0.005) they found a smaller GM volume for the left ACC and the left middle temporal gyrus for the alexithymic group.

Heinzel et al. [2012] investigated 33 high versus 31 low alexithymic young males. They neither found a group or regression effect of TAS-20 over whole brain nor did they observe relevant effects for the ACC by applying a region of interest (ROI) analysis.

Recently, Ihme et al. [2013] compared 17 individuals with high versus 17 subjects with low TAS-20 scores and used ROI-based approaches for the GM volumes of the ACC, insula, and amygdala and an exploratory whole-brain approach. Their data revealed that high alexithymic individuals had less GM volumes in all ROIs preselected than low alexithymic individuals. In the whole-brain analysis, a cluster in the left middle temporal gyrus survived correction for multiple comparisons but none of the clusters within the ROI areas.

Although some of the results were not consistent in these small sample studies, two studies revealed volume reductions in emotion processing regions and in the left middle temporal gyrus [Borsci et al., 2009; Ihme et al., 2013]. Moreover, putative gender differences have not been addressed so far which might account for the inconsistent results of Heinzel et al. [2012] and Borsci et al. [2009] who investigated either males or females. Brain areas such as the bilateral superior temporal sulcus (STS) which has been implicated in the processing of social emotional stimuli have not been analyzed

specifically in volumetric studies in alexithymia [Allison et al., 2000].

Based on the evidence so far, we assumed that alexithymia is associated with GM volumes in emotion-processing areas in general population adults. We hypothesized that a brain network involved in emotion processing like ACC, hippocampus, amygdala, insula, and areas involved in processing of social emotional stimuli like the STS reveal GM volumes to be inversely associated with the TAS total score.

Furthermore, we hypothesize that the different factor scales of the TAS-20 that assess different facets of the alexithymia construct differ in their brain structure correlates. Especially, external orientated thinking (EOT) reflects concrete externally oriented thinking or a preoccupation with the details of external events and might be less directly associated with the emotion-processing brain areas. Given the contradictory findings in males and females among different studies, we also performed gender-stratified analyses.

MATERIALS AND METHODS

General Population Sample

We analyzed data from the Study of Health in Pomerania (SHIP) [Grabe et al., 2005; John et al., 2001; Völzke et al., 2011]. The target population was comprised of adult German residents in northeastern Germany living in three cities and 29 communities, with a total population of 212,157. A two-stage stratified cluster sample of adults aged 20–79 years (baseline) was randomly drawn from local registries. The net sample (without migrated or deceased persons) comprised 6,267 eligible subjects, of which 4,308 Caucasian subjects participated at baseline SHIP-0 between 1997 and 2001. Follow-up examination (SHIP-1) was conducted 5 years after baseline and included 3,300 subjects. From 2008 to 2012, the third phase of data collection (SHIP-2, $N = 2,333$) was carried out. Concurrent with SHIP-2, a new sample called SHIP-Trend-0 ($N = 4,420$) in the same area was drawn in 2008 and similar examinations were undertaken.

Subjects from SHIP-2 and SHIP-TREND-0 were asked to participate in a whole-body MRI assessment [Hegenscheid et al., 2009; Stein et al., 2012]. After exclusion of subjects who refused participation or who fulfilled exclusion criteria for MRI (e.g., cardiac pacemaker) 1,163 subjects from SHIP-2 and 2,154 subjects from SHIP-Trend-0 underwent the MRI scanning (total number $n = 3,317$). SHIP and SHIP TREND were approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

Complete datasets including TAS-20 and the diagnosis of lifetime major depressive disorder (MDD) were available for 2,911 subjects. After exclusion of medical conditions (e.g., a history of cerebral tumor, stroke, Parkinson's diseases, multiple sclerosis, epilepsy, hydrocephalus, enlarged ventricles, pathological lesions) or technical rea-

sons (e.g., severe movement artifacts or inhomogeneity of the magnetic field) 2,589 subjects were available. Applying the age cut-off ≤ 65 years, 2,090 subjects remained. After exclusion of subjects with a lifetime diagnosis of MDD, data from $n = 1,685$ were available for analyses.

Interview and Psychometric Data

Sociodemographic factors and medical history were assessed by a computer-assisted face-to-face interview. The diagnosis of depressive disorders was assessed using the Munich-Composite International Diagnostic Interview (M-CIDI; [Wittchen et al., 1998]) in SHIP-2-LEGEND and SHIP-Trend-0 [Völzke et al., 2011]. The M-CIDI is a standardized fully structured instrument for assessing psychiatric disorders over the lifespan according to DSM-IV criteria. Alexithymia was assessed with the German version of the TAS-20 [Bach et al., 1996; Bagby et al., 1994]. This self-report measure uses a five-point Likert scale for 20 items, resulting in a maximum score of 100 points. The TAS-20 comprises three factor scales (1) difficulties identifying feelings (DIF), (2) difficulties describing and communicating feelings (DDF), and (3) EOT. DIF assesses difficulties in identifying feelings (seven items), DDF is concerned with difficulties in describing feelings (five items), and EOT reflects concrete externally oriented thinking or a preoccupation with the details of external events (eight items). To adjust for symptoms of negative affect, we used the subscale "anxiety/depression" of a validated German Subjective Health Complaints (SHC) scale [Konerding et al., 2006]. The following items (coded on a four-point Likert scale) were summarized to a dimensional score: Inner restlessness, depression, feelings of anxiety, brooding, inner tension, irritability, and insomnia.

Image Acquisition

All images were obtained using a 1.5 T Siemens MRI scanner (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) with a T1-weighted magnetization prepared rapid acquisition gradient echo sequence and following parameters: axial plane, TR = 1900 ms, TE = 3.4 ms, and Flip angle = 15° and an original resolution of $1.0 \times 1.0 \times 1.0 \text{ mm}^3$ image processing.

Preprocessing

We preprocessed the images with SPM 8 (Wellcome Trust Centre for Neuroimaging, University College London) and the VBM 8 toolbox. The images were bias corrected, spatially normalized using the high-dimensional DARTEL normalization, segmented into the different tissue classes, modulated for nonlinear warping only, and smoothed by a Gaussian kernel of 8 mm full width at half maximum. Different brain sizes were already taken into account in the modulation step. Therefore, no further

correction for total brain volume (TBV) was required. Homogeneity of GM images was checked using the covariance structure of each image with all other images, as implemented in the check data quality function.

Additionally, we prepared a set of modulated (affine + nonlinear) and warped GM images to be able to access the absolute local GM volume within a mask.

Statistical Analyses

We used SPM8 to analyze the preprocessed GM segments by applying regression analyses between GM volume and the TAS-20 total score and its factor scores using age and gender (in combined analyses) as covariates in all models (also in ROI analyses). The uncorrected statistical threshold for voxels in the whole-brain analysis was set at $P < 0.001$ with subsequent family wise error (FWE) correction with $P < 0.05$ for peak level and cluster level significance using VBM8. VBM analyses were repeated with adjustment for anxiety/depression symptoms. Additionally, ROI analyses with adjustment for anxiety/depression symptoms were performed for the prominent VBM findings (e.g., ACC and the left fusiform, cerebellum, temporal inferior area).

Furthermore, ROI analyses focusing on previously published affect processing regions like the bilateral STS (5-mm thick mask around the STS), hippocampus (including the parahippocampal gyrus), amygdale, and insula as defined by the AAL-atlas [Tzourio-Mazoyer et al., 2002] implemented in the WFU-PickAtlas (<http://fmri.wfubmc.edu/software/PickAtlas>) were performed.

To determine statistical significance of putative clusters in each of the four bilateral ROIs, we used Monte Carlo simulation. Based on the uncorrected voxel-wise P -value threshold, the inherent smoothness of the data within the ROI, and the predefined α -level significance, this simulation provides a minimum cluster size threshold (k). All clusters within the ROI exceeding k in size are significant on this α -level. We used AlphaSim (implemented in the Resting State fMRI Data Analysis Toolkit REST 1.8; <http://restfmri.net>) to estimate the smoothness and to perform the simulation. We chose the uncorrected voxel-wise $P = 0.01$, $\alpha = 0.05$ and ran 1,000 iterations to estimate the cluster size threshold in every ROI.

To study the differential effect sizes of the association between alexithymia and local GM volume reduction, we extracted the volumes of significant clusters derived by the VBM analyses. We applied masks based on the significant clusters on the modulated (affine + nonlinear) and warped GM images and summed up the GM content of each voxel within the mask. Our main goals were the following: (1) estimation of the local effects sizes of the most prominent VBM findings, (2) estimation of effects sizes under adjustment for the depression/anxiety subscale of the SHC scale, and (3) estimation of effects sizes for the gender-stratified approach for all TAS-20 factor scales. The clusters were chosen based on the following principles: selection of the most

comprehensive results from our analyses (TAS-20 total score results, males and females) and putatively significant VBM results of the factor scales (preferentially of combined [males and females] VBM analyses).

We used linear regression analyses with the respective cluster volumes as dependent variable, TAS-20 (total score or one of the three factor scales, each single one in a separate regression analysis) as predictors and TBV, age, and sex (only in gender combined analyses) as covariates. In a second set of models, we additionally adjusted for the depression/anxiety subscale of the SHC scale to check for the stability of the results.

RESULTS

TAS-20 Scores

The distribution of the TAS-20 data is given in Table I. In our sample ($n = 1,685$), 43 subjects (2.6%) scored higher than 60 in the TAS-20 total score (30 males [3.6%], 13 females [1.6%]). No association was observed between smoking status (never smoker, former smoker, current smoker) and the TAS-20 scores in males ($F = 1.86$, $df = 2$, 817, $P = 0.16$) and females ($F = 0.24$, $df = 2$, 835, $P = 0.79$) and between alcohol intake (gram per day) and TAS-20 scores males: $r = 0.06$, $P = 0.1$; females: $r = -0.02$, $P = 0.49$.

VBM Whole-Brain Results for the TAS-20 Total Score

In VBM analysis, the TAS-20 total score was associated with a large cluster of GM volume reduction in the bilateral ACC and in the right middle cingulate cortex (FWE-corrected $P = 0.002$) in the combined males and females sample (Fig. 1A, Table II).

In the gender-stratified VBM analyses, no cluster reached the FWE-corrected significance level ($P < 0.05$) for the TAS-20 total score. The descriptive data are given in Table II.

VBM Whole-Brain Results for DIF

DIF was associated with a complex pattern of lower GM volume in three large clusters in the combined sample (females and males; Table III, Fig. 1B): The largest cluster (1,811 voxels) comprised the bilateral ACC (81%), the right middle cingulate cortex (15%), and the bilateral medial superior frontal cortex (3%) (FWE corrected cluster-level P -value = 0.001). Another cluster (714 voxels) comprised the left fusiform gyrus (50%), the cerebellum (38%), and the left inferior temporal gyrus (9%) (FWE corrected P -value = 0.046). The third largest cluster (680 voxels) comprised the left middle temporal gyrus (91%) and parts of the inferior temporal gyrus (9%) (FWE corrected P -value = 0.053).

TABLE I. Descriptive characteristics of age and TAS-20 scores

	Total sample N = 1685			Males N = 844			Females N = 841		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age	47.38	11.15	21–65	47.06	11.43	21–65	47.7	10.86	21–65
TAS-20 ^a	41.21	8.96	20–74	42.2	9.30	20–74	40.21	8.49	20–70
DIF	10.69	3.69	7–29	10.55	3.71	7–29	10.82	3.66	7–25
DDF ^a	10.76	3.43	5–24	11.33	3.60	5–24	10.19	3.14	5–22
EOT ^a	19.76	4.33	8–39	20.32	4.45	8–34	19.2	4.14	8–39
Depression/Anxiety ^a	11.22	3.56	7–27	10.60	3.29	7–25	11.84	3.70	7–27

^aSignificant gender difference, $P < 0.001$

TAS-20 Toronto Alexithymia Scale total score

DIF= Toronto Alexithymia subscale difficulty identifying feelings

DDF= Toronto Alexithymia subscale difficulty describing feelings

EOT= Toronto Alexithymia subscale externally orientated thinking

Depression/Anxiety= subscale of the German Subjective Health Complaints (SHC), available for $N = 1661$ subjects (831 men, 830 women).

In the gender-stratified VBM analyses, the following results emerged: In males, DIF was associated with a cluster (2,129 voxels) within the bilateral ACC, middle cingulate cortex, and medial superior frontal cortex (FWE-corrected cluster level P -value = 4.3×10^{-4}). In females, no significant cluster emerged (Table III, for brain maps see Figure 3, Supporting Information).

In the gender-stratified VBM analyses, DDF was associated with a cluster (1,123 voxels) in the left temporal region (fusiform gyrus, cerebellum, inferior temporal gyrus) in females (FWE-corrected cluster level P -value = 0.01). In males, no significant cluster emerged (Table IV, for brain maps see Figure 3, Supporting Information).

VBM whole-Brain Results for DDF

Two nonsignificant clusters (FWE) emerged in the right ACC and right middle cingulate gyrus and in the left ACC (Table IV).

VBM Whole-Brain Results for EOT

Only small nonsignificant clusters (<100 voxels) emerged in the combined sample. In the gender-stratified VBM analyses, two nonsignificant clusters (≥ 100 voxels) in

Figure 1.

A: Decreased gray matter volumes associated with TAS-20 sum scores in 1685 subjects from the general population (cluster-level FWE-corrected $P = 0.002$). **B:** Decreased gray matter volumes associated with the TAS-20 factor scale “difficulty identifying feelings” (FWE-corrected clusters: ACC, $P = 0.001$; left temporal cortex, $P = 0.046$). Color scale indicates t -values.

TABLE II. Brain regions with negative correlation between gray matter volumes and TAS-20 total score in whole-brain analysis

			Stereotaxic coordinates (mm)			
k	Regions	Brodman areas	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> score
Males + females						
1553 ^a	L anterior cingulate cortex	32, 24, 9, 10	−12	30	25	4.24
	R anterior cingulate cortex		14	23	33	4.20
	R middle cingulate cortex		−2	39	12	3.85
	L medial superior frontal cortex					
Males						
466	L anterior cingulate cortex	32, 24	−12	30	25	4.23
	L middle cingulate cortex		−3	41	12	3.46
	R anterior cingulate cortex					
	L medial superior frontal cortex					
Females						
130	L inferior temporal gyrus L cerebellum	37, 20, 36	−51	−43	−27	3.89
274	R middle occipital gyrus R angular gyrus	39, 19	45	−69	28	3.69
112	R inferior temporal gyrus R fusiform gyrus	37, 20	50	−49	−18	3.40

k denotes the cluster size in voxels, all clusters with $k \geq 100$ are listed in the table, $P < 0.001$ (uncorrected)

^aClusters that reach cluster-level significance ($P < 0.05$, FWE corrected).

females emerged (Table V, for brain maps see Figure 3, Supporting Information).

VBMs Adjusted for Depression and Anxiety

To evaluate the possible impact of depression and anxiety on our findings, we reanalyzed those VBM analyses which yielded significant clusters by additional adjustment for the depression/anxiety subscale of the SHC scale.

Adjusted VBM Whole-Brain Results for TAS-20 Total Score

Adjusting the VBM analysis for the depression/anxiety subscale of the SHC scale, the cluster sizes of the GM volume reduction in the ACC and right middle cingulate cortex became smaller (475 voxel in the left and right ACC and the frontal superior medial gyrus left; 328 voxel right ACC and medial cingulate cortex). At the whole brain level, those adjusted clusters failed to reach FWE-corrected statistical significance for cluster and peak level. Using a ROI-based approach, a cluster (adjusted for depression/anxiety) within the ACC of 2,169 voxels (uncorrected $P < 0.01$) emerged that clearly exceeded the cluster size threshold (corresponding to a P -value < 0.05) for the ACC of 128 voxel (AlphaSim).

Adjusted VBM Whole-Brain Results for DIF

Adjusting the VBM analysis for the depression/anxiety subscale of the SHC scale, the cluster sizes of the GM volume reduction in the ACC and right middle cingulate cor-

tex became smaller: the first cluster (ACC) decreased to 357 voxels in the left and right ACC and to 129 voxels in the right ACC and medial cingulate cortex. Applying a ROI approach to the ACC, a cluster (adjusted for depression/anxiety) of 2,494 voxels (uncorrected, $P < 0.01$) emerged in the adjusted analysis exceeding the $P < 0.05$ threshold of 119 voxels (AlphaSim). The second cluster (left fusiform gyrus, cerebellum, left inferior temporal gyrus) decreased to 321 voxels (FWE corrected P -value = 0.25). Applying a ROI approach to the combined region of cerebellum, fusiform gyrus, and inferior temporal gyrus in the left hemisphere, we obtained a cluster (adjusted for depression/anxiety) of 2,123 voxels (uncorrected, $P < 0.01$) that exceeds the $P < 0.05$ threshold of 339 voxels (AlphaSim). The third cluster (left middle temporal gyrus and parts of the inferior temporal gyrus) even increased to 694 voxels under the adjustment (FWE corrected P -value = 0.049).

Adjusted VBM Whole-Brain Results for DDF

In females, the VBM of DDF with additional adjustment for the depression/anxiety subscale of the SHC scale split up the cluster in the cerebellum, fusiform gyrus, and inferior temporal gyrus into three clusters with sizes of 108, 134, and 423 voxels. None separate cluster reached whole-brain significance on a level of FWE correction. In the ROI-based approach, however, the combined region of the left cerebellum, fusiform gyrus, and inferior temporal gyrus obtained a cluster (adjusted for depression/anxiety) of 3,294 voxels (uncorrected, $P < 0.01$) that exceeded the $P < 0.05$ threshold of 378 voxels (AlphaSim).

TABLE III. Regions with negative correlation between gray matter volumes and the TAS-20 factor scale “difficulty identifying feelings” (DIF) in the whole-brain analysis

k	Regions	Brodmann areas	Stereotaxic coordinates (mm)			t score
			x	y	z	
Males + females						
680 ^b	L middle temporal gyrus	21, 22, 20	−56	−49	0	4.40
	L inferior temporal gyrus		−63	−34	−14	4.17
1811 ^a	R anterior cingulate cortex	32, 24, 10, 9	12	30	28	4.23
	L anterior cingulate cortex		14	20	36	4.20
	R middle cingulate cortex		−6	41	13	3.76
	R medial superior frontal cortex					
	L medial superior frontal cortex					
	L middle cingulate cortex					
714 ^a	L fusiform gyrus	37, 20	−38	−51	−23	4.00
	L cerebellum		−47	−49	−29	3.39
	L inferior temporal gyrus		−50	−46	−17	3.31
274	R inferior temporal gyrus	37, 20, 36	56	−39	−24	3.99
	R fusiform gyrus		41	−46	−18	3.36
112	L postcentral gyrus	3, 43, 4, 1, 40	−63	−18	22	3.85
221	R temporal pole, superior gyrus R superior temporal gyrus R temporal pole, middle gyrus	38, 21	53	11	−11	3.82
Males						
434	R temporal pole, superior gyrus	38, 13, 28	36	8	−21	4.70
	R amygdala		45	3	−14	3.18
	R superior temporal gyrus					
	R insula					
500	L temporal pole, superior gyrus L insula L superior temporal gyrus L amygdala	38, 13, 34	−38	3	−18	4.26
2129 ^a	L anterior cingulate cortex	32, 24, 10, 9, 33	0	38	18	4.12
	R anterior cingulate cortex		12	30	28	4.03
	R middle cingulate cortex		−9	32	25	4.00
	L middle cingulate cortex					
	R medial superior frontal cortex					
	L medial superior frontal cortex					
120	L middle temporal gyrus L inferior temporal gyrus	21	−66	−37	−15	3.59
204	L medial orbital frontal gyrus L gyrus rectus L anterior cingulate cortex	10, 32, 11	−8	38	−12	3.54
Females						
236	R inferior temporal gyrus	20, 37, 36	56	−36	−23	3.62
			51	−28	−20	3.51
113	L fusiform gyrus L cerebellum	37, 20	−35	−45	−21	3.61

k denotes the cluster size in voxels, all clusters with $k \geq 100$ are listed in the table, $P < 0.001$ (uncorrected)

^aClusters that reach cluster-level significance ($P < 0.05$, FWE corrected).

^bCluster reached cluster-level $P = 0.053$ (FWE corrected).

Effect Sizes of the Association Between TAS-20 and GM Cluster Volumes

To study the effect sizes of TAS-20 scores on the GM volume within regions that showed up in the VBM analyses, we extracted the GM volume from three different parts of the brain: (1) the ACC-cluster of the gender-mixed TAS-20 total score VBM analysis (cluster size = 1,553 voxels), (2) the cluster in the left middle and inferior temporal gyrus (temporal cluster) of the gender-mixed DIF VBM analysis (cluster size = 680 voxels), and (3) the cluster in

the left cerebellum, fusiform gyrus, and inferior temporal gyrus (fusiform cluster) for the same DIF VBM analysis (cluster size = 714 voxels). The detailed results for TAS-20 and its factor scales with and without adjustment for depression/anxiety are depicted in Table VI. To further explore the indicated gender differences in the fusiform cluster, we performed interaction analyses for gender and DDF by adding an interaction term (gender*DDF). In the fully adjusted regression model, the interaction term was statistically significant ($\beta = -5.29$; $P = 0.025$) as well under additional adjustment for depression/anxiety ($\beta = -5.03$;

TABLE IV. Regions with negative correlation between gray matter volumes and the TAS-20 factor scale “difficulty describing feelings” (DDF) in the whole-brain analysis

k	Regions	Brodmann areas	Stereotaxic coordinates (mm)			t score
			x	y	z	
Males + females						
574	L anterior cingulate cortex	32, 24, 9	−5	38	13	4.05
	R anterior cingulate cortex		−9	30	16	3.80
	L medial superior frontal cortex		−12	32	24	3.69
190	R middle cingulate cortex	32, 24, 9	14	23	33	4.05
	R anterior cingulate cortex		14	35	27	3.73
Males						
116	R middle cingulate cortex	32, 9	14	27	31	3.97
	R anterior cingulate cortex		14	36	25	3.52
178	L anterior cingulate cortex	32	−3	41	10	3.61
			−12	30	24	3.54
			−9	33	13	3.21
Females						
1123 ^a	L cerebellum	37, 20, 36	−33	−49	−23	4.10
	L fusiform gyrus		−36	−58	−23	4.08
	L inferior temporal gyrus		−53	−42	−27	3.84

k denotes the cluster size in voxels, all clusters with $k \geq 100$ are listed in the table, $P < 0.001$ (uncorrected)

^aClusters that reach cluster-level significance ($P < 0.05$, FWE corrected)

$P = 0.03$) indicating a robust difference between males and females. Corresponding interaction analyses for the ACC and the temporal cluster did not reveal any significant impact of gender on those GM volumes.

The associations between the ACC GM volume and TAS-20 total score, the left middle temporal gyrus volume and DIF, and the fusiform GM volume and DDF in males and females are depicted in Figure 1–3 of the Supporting Information.

ROI-Based Results for the TAS-20

We did not find any associations of GM volume in the bilateral amygdala, insula, and hippocampus with the TAS-20 total or the TAS factor scales in the combined (males and females) analyses. However, for STS relevant decreases of GM volume emerged: in association with DIF, a cluster comprising 76 voxels in the right STS and 116 voxels in the

left STS clearly exceeded the AlphaSim of 55 voxels for statistical significance ($P < 0.05$). Also in the right STS, a significant cluster emerged with 85 voxels for DDF.

The gender-stratified analyses yielded significant ($P < 0.05$) GM volume reductions in males: in association with DIF clusters emerged in the right STS (404 voxels), in the right amygdala (175 voxels; AlphaSim threshold for $P < 0.05 = 45$ voxels), in the left insula (233 and 114 voxels; AlphaSim threshold for $P < 0.05 = 97$ voxels), whereas a cluster in the right hippocampus (106 voxels; AlphaSim threshold for $P < 0.05 = 112$ voxels) missed statistical significance. In females, only the right STS showed reduced GM volumes in association with DDF (102 voxels) but none of the other regions.

Positive Correlations of Alexithymia and GM

In all VBM analyses using the TAS-20 total score, DIF and DDF no voxels with positive associations (volume

TABLE V. Regions with negative correlation between gray matter volumes and the TAS-20 factor scale “external orientated thinking” (EOT) in the whole-brain analysis

			Stereotaxic coordinates (mm)			
k	Regions	Brodman areas	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> score
Females						
250	R middle occipital gyrus R angular gyrus	39, 19	44	−75	31	4.08
173	R inferior temporal gyrus R fusiform gyrus	37, 20	48	−52	−12	3.66

k denotes the cluster size in voxels, all clusters with $k \geq 100$ are listed in the table, $P < 0.001$ (uncorrected)

*clusters that reach cluster-level significance ($P < 0.05$, FWE corrected)

TABLE VI. Association of the TAS-20 total score and its factors scales with the volumes of the significant clusters in the ACC, temporal, and fusiform gyrus (Linear regression analyses)

	Males and females				Males				Females			
	Lin. model 1		Lin. model 2		Lin. model 1		Lin. model 2		Lin. model 1		Lin. model 2	
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
ACC cluster												
TAS-20	-3.49	2.91×10^{-6}	-3.44	1.25×10^{-5}	-3.98	1.9×10^{-4}	-3.87	5.7×10^{-4}	-2.91	0.005	-2.88	0.009
DIF	-7.29	5.33×10^{-5}	-7.38	2.37×10^{-4}	-9.64	3.3×10^{-4}	-9.84	0.001	-4.80	0.047	-4.61	0.086
DDF	-8.71	9.60×10^{-6}	-8.40	3.51×10^{-5}	-9.78	3.9×10^{-4}	-9.33	9.8×10^{-4}	-7.45	0.008	-7.22	0.014
EOT	-4.27	0.006	-4.06	0.009	-4.36	0.050	-4.05	0.071	-4.27	0.048	-4.13	0.056
Temporal cluster												
TAS-20	-0.93	0.010	-0.79	0.037	-0.89	0.088	-0.78	0.155	-0.99	0.044	-0.79	0.128
DIF	-4.82	2.96×10^{-8}	-5.04	1.81×10^{-7}	-4.99	1.4×10^{-4}	-5.41	2.3×10^{-4}	-4.60	5.5×10^{-5}	-4.58	2.9×10^{-4}
DDF	-1.96	0.040	-1.59	0.104	-2.49	0.066	-2.26	0.104	-1.36	0.307	-0.76	0.582
EOT	0.74	0.327	0.88	0.243	1.16	0.289	1.31	0.233	0.21	0.839	0.34	0.739
Fusiform cluster												
TAS-20	-1.00	0.025	-0.71	0.128	-0.35	0.592	-0.11	0.867	-1.84	0.002	-1.45	0.022
DIF	-4.12	1.24×10^{-4}	-3.63	0.002	-2.89	0.075	-2.53	0.164	-5.15	2.0×10^{-4}	-4.28	0.005
DDF	-2.99	0.011	-2.40	0.047	-0.84	0.615	-0.42	0.808	-6.09	1.6×10^{-4}	-5.24	0.002
EOT	0.59	0.522	0.81	0.381	1.02	0.447	1.22	0.370	-0.19	0.878	0.06	0.962

DIF: difficulty identifying feelings; DDF: difficulty describing feelings, EOT: external orientated thinking.

Model 1: total brain volume (TBV), age, and (sex) as covariates.

Model 2: with additional adjustment for the depression/anxiety subscale.

increase) emerged. In EOT, a nonsignificant positive correlation with a cluster of 62 voxels in the inferior temporal gyrus (coordinates: 48 -72 -9; FWE corrected P -value: 0.808) emerged. In the ROI analyses of ACC, no single positive voxel emerged (uncorrected P -value 0.01). In the ROI analyses of the hippocampus/parahippocampus and the STS, a few nonsignificant small clusters emerged (2–34 voxels).

DISCUSSION

We hypothesized low GM volumes in brain areas that contribute to emotion processing in association with alexithymia. Our whole-brain VBM results suggest an involvement of the ACC in the neurobiology of alexithymia. The most prominent associations were identified with the dorsal part of the ACC which has been implicated in cognitive and attentional processes [Koven et al., 2011]. We identified an inverse association between TAS-20 scores and dACC volumes which is in line with some of the previous studies which were based on much smaller sample sizes [Borsci et al., 2009; Ihme et al., 2013]. Since Heinz et al. [Heinz et al., 2012] investigated 33 high versus 31 low alexithymic males and did not find any group or regression effects of TAS-20 on whole brain or specifically on the ACC by applying a ROI analysis we performed gender-stratified analyses too. In contrast to Heinz et al. in whole-brain VBM analyses, we demonstrated an association of alexithymia on the ACC in males. In females, however, the ACC cluster was much smaller than in males but still statistically significant in the ROI analysis (123 voxels, AlphaSim threshold $P < 0.05$: 119 voxels). In the absolute GM volumes regression analyses, the effect sizes in males were higher than in females ($\beta = -3.98$ vs. -2.91) but statistically significant in both gender. Those associations were maintained while adjusting for the anxiety/depression subscale. The absolute GM volume of the left middle temporal gyrus was equally associated with alexithymia in males and females. However, the cluster in the left cerebellum, fusiform gyrus, and inferior temporal gyrus (fusiform cluster) was highly associated with DDF in females only. This gender difference was further supported by interaction analysis. Thus, our study revealed a stronger association of alexithymia with the ACC in males but an exclusive association of the fusiform cluster in females.

Gündel et al. identified a positive correlation between the size of the right ACC and TAS-20 scores [Gündel et al., 2004]. This result has not been replicated so far. Two explanations might apply: (1) Gündel et al. used a manual tracing method that measured the surface area of the ACC but not the GM volume. Furthermore, the manual differentiation between the anterior and posterior part of the cingulate cortex had a huge impact on the resulting surface area of the ACC. Thus, the structural markers of the ACC used by Gündel et al. and the more recent studies using

VBM methods have been highly different. (2) Gündel et al. studied a relative homogenous group of university students with relatively low TAS-20 scores. It is conceivable that intelligence interferes with the neurobiological representation of alexithymia in a yet unknown way.

The strongest effect on brain GM volume decrease was observed for the first factor scale DIF. Besides the ACC, volume reductions in the left temporal areas emerged which are in line with whole-brain VBM findings from Ihme et al. [2013] and Borsci et al. [2009] who both described GM volume reductions in the left middle temporal gyrus.

The middle and the inferior temporal gyrus are involved in semantic processing, visual perception, and multimodal sensory integration. Thus, a functional role in the cognitive processing of emotions and mental representation of feelings seems conceivable [Onitsuka et al., 2004].

Interestingly, the GM volume of the left fusiform gyrus was reduced in DIF (males and females combined) but predominantly in DDF in females. The so-called fusiform face area is involved in face perception [McCarthy et al., 1997] and in the perception of emotions in facial stimuli [Radua et al., 2010]. Recent research identified different cytoarchitectonic areas within the fusiform gyrus and confirmed an important role of the fusiform gyrus in a core network subserving different cognitive tasks like object recognition, visual language perception, or visual attention [Caspers et al., 2013]. From this, we hypothesize that difficulties in the perception and interpretation of emotional facial expressions represent an important characteristic of alexithymia, especially in females. This has been demonstrated by a number of studies also including a recent fMRI study which related the neuropsychological dysfunction to altered, mostly decreased patterns of activation [Jongen et al., 2014]. However, to our best knowledge only Dittrich et al. [2013] so far have addressed putative gender differences in facial emotion perception in alexithymia. In this study, TAS-20 total scores were significantly correlated to perception errors of emotional facial expressions in females ($r = 0.37$, $P = 0.012$) but not in males ($r = 0.02$, $P = 0.929$) from a psychiatric inpatient and outpatient sample [Dittrich et al., 2013].

A significant loss of GM volume in areas of the cerebellum was associated with DIF. During the last years, evidence has accumulated that the posterior cerebellar hemispheres do also have functional relevance for cognitive and emotional processing [de Greck et al., 2012; Schienle and Scharnüller, 2013].

As we did not detect any association between the TAS-20 score or its three factor scales with the bilateral hippocampus, amygdale, and insula in whole-brain VBM analyses, we performed ROI analyses. Those regions have been identified as being involved in emotion processing and fMRI studies in alexithymia have discovered task dependent differences in activation of those regions in subjects with high versus low alexithymia [Kano et al., 2003; Kugel et al., 2008; Meriau et al., 2006; Moriguchi and Komaki,

2013]. Interestingly, the bilateral STS emerged in the ROI analyses with structural changes in DIF indicating that especially the processing of social emotional situations may be impaired in individuals with increasing scores of DIF [Lotze et al., 2006]. Subsequently, misperception and misinterpretation of social situations might occur in subjects with alexithymia [Grabe et al., 2001, 2004].

Furthermore, GM volume reductions in the right amygdala and the left insula were only found in males which might be related to a dysfunctional network also including the prominent GM volume reductions of the dACC in males. Those findings are partially in line with the study of Ihme et al. [Ihme et al., 2013] who found a reduction of GM volumes in ACC, left amygdala, and left anterior insula in subjects with alexithymia.

There has been a debate on the association of alexithymia and negative affect like anxiety and depression. The TAS-20 scale is clearly associated with symptoms of general psychopathology and harm avoidance [Grabe et al., 2001, 2004]. The direction of this association is not fully understood. However, developmental models (see below) point to early developmental deficits in emotional maturation that may lead to reduced capacity of emotion regulation. Thus, increased levels of psychopathological distress may be present in subjects with alexithymia which is also reflected by the statistically significant correlation ($r = 0.3$) between the TAS total score and the anxiety/depression subscale of the SHC scale in our sample. To explore the possible impact of negative affect on the association between TAS-20 and GM volumes, we applied two methods: (1) adjustment of the VBM analyses for the anxiety/depression subscale of the SHC scale; (2) analysis of absolute GM volume with subsequent adjustment of the anxiety/depression subscale (see Table VI). In VBM, the association between TAS-20, DIF, and the GM volume of the ACC was reduced by the adjustment, still maintaining ROI-level significance. The absolute GM volume analyses revealed highly significant associations between the TAS-20, its subscales and the ACC GM absolute volume that were largely unaffected by additional adjustment for the anxiety/depression subscale. Interestingly, the association between DIF and the left middle temporal gyrus even became slightly stronger in VBM and absolute GM volume analyses on adjustment for the anxiety/depression subscale. This leads to the interpretation that the latter association between DIF and the middle temporal is fully independent from negative affect and psychopathology and may constitute a core deficit in semantic processing, visual perception, and multimodal sensory integration associated with alexithymia. However, the associations between DDF, EOT, and the middle temporal gyrus were weaker to absent contributing to a modest overall association of the TAS-20 total score and the middle temporal gyrus. In terms of the VBM-ACC analyses, the results point to some mediating effects of negative affect leading to smaller cluster sizes in the adjusted analyses. Such effects were largely absent in absolute GM volume analyses

as the β -coefficients for TAS-20, DIF, DDF, and EOT did not change substantially ($>10\%$) on adjustment for anxiety/depression. However, the P -values increased by adjustment for anxiety/depression roughly by $\times 10$ in the absolute GM volume analyses (Table VI). This effect also explains the obviously larger effects of the adjustment in VBM analyses as those results are completely dependent on the P -value thresholds but not on effects sizes.

There are at least two different models how structural changes might be associated with alexithymia: (1) Alexithymia has a genetic component. A study with 8,785 twin pairs from the general population in Denmark found an overall heritability of alexithymia of 30–33% [Jørgensen et al., 2007]. Thus, a genetic component could lead to changes in brain structure and function and thereby contribute to alexithymia. (2) Developmental models of alexithymia point to dysfunctional mother–child interactions. In accordance with this model, empirical studies reported evidence that childhood family factors such as parent–child relationships, a lack of general sense of warmth or hostility, and low levels of perceived openness, closeness, and safety among family members may contribute to alexithymia [Berenbaum, 1996; Joukamaa et al., 2003]. Dysfunctional mother–child interactions are hypothesized to disable the complex process of mentalization. During mentalization, the child progressively develops symbolic representations of emotional states that distinguishes them from purely somatic states and connects emotional states to conscious and verbal processing [Fonagy et al., 2002]. As brain areas develop in interaction with genetic factors, brain activity and related neuroplastic learning processes, impaired mentalization might inhibit the proper maturation of brain structures that usually represent the cognitive processing of emotions.

Our findings support the model that the primary dysfunction of alexithymia converges in the ACC. In line with our results, van der Velde et al. [2013] found in their meta-analysis of fMRI studies on alexithymia that during presentation of stimuli with positive and negative valence, higher activation was found in the dorsal anterior cingulate. The authors interpreted this activation as a correlate of an increased, presumably compensatory, cognitive demand. However, based on the structural alteration of the ACC, we would argue that the ACC is a primary source of dysfunctional cognitive processing of emotion. This dysfunction of the ACC might impact subsequently on brain networks of emotion processing. Thus, interconnected areas like the amygdala, the insula, the precuneus and supplementary motor, and premotor brain areas might react differently to emotional processing tasks in alexithymic individuals as shown by the meta-analysis of van der Velde [2013] but do not represent the primary neuroanatomical correlate of alexithymia. The loss of GM volume in the left temporal area, the left fusiform gyrus and the bilateral STS points to broad range of subtle dysfunctions in semantic processing, visual perception, and multimodal sensory integration as for instance of socially

relevant signals. Interestingly, robust meta-analytic evidence for decreased activation in response to negative stimuli in a large cluster comprising the left fusiform gyrus, the middle temporal gyrus, and the left cerebellum was reported [van der Velde et al., 2013] which supports the functional relevance of the structural correlates of alexithymia found in our study.

Dysfunctions in the ACC and the left temporal region contribute to deficits in the symbolization of emotions and identification of feelings which fits well into Bucci's multiple code theory [Bucci, 1997]. The multiple code theory postulates three modes of representing and processing emotional information: (1) the nonverbal subsymbolic mode (patterns of sensory, visceral, or kinesthetic sensations and motor activity experienced during states of emotional arousal), (2) the nonverbal symbolic mode (images), and (3) the verbal symbolic mode (words). During maturation and language acquisition, the subsymbolic information and nonverbal symbolic representations are connected to verbal symbols [Taylor and Bagby, 2013].

As our results show distinct structural patterns in the VBM analyses between the three factor scales, one might question the biological homogeneity of the TAS-20. However, in the absolute volume analyses, the dACC was associated with all three subscales although the effect size for EOT was smaller.

A potential limitation of our study is the reliance on the self-report measure TAS-20. It has been argued that especially subjects with severe degrees of alexithymia might not be able to properly answer the questions of the TAS-20. However, interview measures of alexithymia like the Toronto Structured Interview for Alexithymia [Grabe et al., 2009] are difficult to perform in large samples. The use of a 1.5 T scanner in our study might have limited in the resolution of subtle differences of brain structure between subjects. The strengths of our study are the large, community-based sample and the use of one single MRI scanner and the identical scanning protocol. As we aimed to reduce the heterogeneity that would have been introduced by higher age (atrophy) and MDD as potential modifiers of alexithymia and regional brain volumes [Frodl et al., 2008; Grabe et al., 2008, 2004], we excluded subjects older than 65 years and subjects with lifetime diagnosis of MDD. As no association was observed between smoking status, alcohol intake, and TAS-20 scores smoking and alcohol consumption should not act as mediators of the association between alexithymia and GM volume reduction.

In all, we describe structural correlates of the alexithymia construct that correspond much closer to its core feature "deficits of cognitive processing of emotions" than in previous studies. Apart from the ACC, the STS, left temporal and fusiform areas as well as the amygdala and insula (in males only) were associated with alexithymia in this general population sample. The TAS-20 factor scale DIF was most prominently associated with GM volume reductions largely independent from current anxiety and depression scores.

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