

# Alexithymia Is Associated with Altered Cortical Thickness Networks in the General Population

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## Keywords

Alexithymia · Correlation networks · Connectivity · Centrality · Cortex · General population

## Abstract

**Background:** Alexithymia is a personality trait characterized by difficulties in identifying and describing emotions and associated with various psychiatric disorders. Neuroimaging studies found evidence for morphological and functional brain alterations in alexithymic subjects. However, the neurobiological mechanisms underlying alexithymia remain incompletely understood. **Methods:** We study the association of alexithymia with cortical correlation networks in a large community-dwelling sample of the Study of Health in Pomerania. Our analysis includes data of  $n = 2,199$  individuals (49.4% females, age =  $52.1 \pm 13.6$  years) which were divided into a low and high alexithymic group by a median split of the Toronto Alexithymia Scale. Cortical correlation networks were constructed based on the mean thicknesses of 68 regions, and differences in centralities were investigated. **Results:** We found a significantly increased centrality of

the right paracentral lobule in the high alexithymia network after correction for multiple testing. Several other regions with motoric and sensory functions showed altered centrality on a nominally significant level. **Conclusions:** Finding increased centrality of the paracentral lobule, a brain area with sensory as well as motoric features and involvement in bowel and bladder voiding, may contribute to explain the association of alexithymia with functional somatic disorders and chronic pain syndromes.

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## Introduction

Alexithymia is a personality trait characterized by difficulties in identifying and expressing emotions, impoverished fantasy life and an externally oriented thinking style [1]. It has been linked with alterations in cognitive processing and regulation of emotions [2]. The Toronto Alexithymia Scale-20 (TAS-20) has been the most widely used self-report instrument for the assessment of alexithymia in the past two decades. It is comprised of the

three factors difficulties identifying feelings (DIF), difficulties describing feelings (DDF), and externally oriented thinking (EOT) [3]. Studies found associations of the TAS-20 and particularly of the DIF factor with different physical and mental health problems, particularly affective and anxiety disorders [4–6]. Moreover, studies found between one quarter and one third of patients being alexithymic in samples with mixed psychiatric diagnoses [7, 8] while in general population studies proportions between 10 and 13% were observed. Considering the high prevalence and the clinical relevance of alexithymia, it is important to improve our understanding of the neurobiological bases of emotion-processing difficulties in alexithymic subjects.

Evidence from neuroimaging studies suggested that structural and functional alterations in emotion-relevant brain regions are associated with alexithymia: for example, a recent coordinate-based meta-analysis evaluated results of 17 structural magnetic resonance imaging (MRI) studies investigating gray matter volumes in alexithymic subjects [9]. While observing a large heterogeneity among existing studies, the authors were able to find consistent evidence for reduced volumes of regions implicated in emotion identification and expression including the left insula, left amygdala, orbital frontal cortex, and striatum in persons high in alexithymia. However, results on morphological alterations of other brain regions which are involved in emotion processing like the anterior cingulate cortex (ACC), the hippocampus and parahippocampal areas remained inconclusive.

Functional neuroimaging studies investigated activation of brain areas in response to positive or negative emotional stimuli and identified altered brain activation in alexithymic subjects in various brain regions involved in emotion processing: in their review and meta-analysis, Van der Velde et al. [10] found evidence for increased activation in the dorsal ACC and middle cingulate gyrus in alexithymic subjects independently from the valence of the task, indicating higher demand in cognitive processing of emotions. For negative stimuli, their results revealed lower activation in the amygdala, fusiform gyrus, premotor areas as well as the dorsomedial prefrontal cortex while for positive stimuli lower activation of the right insula and precuneus were found.

Results from behavioral and neuroimaging studies demonstrated that alexithymia is associated with deficits in automatic emotion processing (for a review, see Donges and Suslow [11]) and supported previous findings of altered structure and function of emotion-relevant brain regions. More specifically, reduced automatic activity in

response to positive and negative facial emotions was detected in brain regions involved in the initial assessment and encoding of emotional stimuli including the amygdala, parahippocampal areas and the insula in alexithymic subjects [12, 13]. Liemburg et al. [14] investigated the default mode network of subjects high versus low in alexithymia. For alexithymic subjects, the authors found diminished connectivity within the default mode network, while connectivity of the sensorimotor cortex, occipital areas as well as the right lateral occipital cortex were enhanced, suggesting that the default mode network has a stronger connectivity with brain areas involved in the sensory perception and control of emotions.

In all, existing evidence suggests structural and functional alterations of different brain regions, while results revealed a large heterogeneity and also include brain regions which are not primarily implicated in emotion perception and processing like the cerebellum [15] or the occipital lobe [13]. Given that alexithymia is better understood as a dimensional and multifaceted construct, the role of the different factors of alexithymia may contribute to the heterogeneity of findings. In fact, there is increasing evidence that the different facets of alexithymia are associated with specific neural correlates. For example, in the voxel-based morphometric study, Grabe et al. [16] reported that reduced volumes of three clusters comprising the dorsal ACC, the left middle and inferior temporal gyrus as well as the left fusiform gyrus were specifically associated with the DIF factor. Results from fMRI studies showed that DIF was linked to reduced activation brain regions including the amygdala [12] and the fusiform gyrus [17] in response to facial emotion. Regarding the EOT factor, Li et al. [18] demonstrated positive correlations with volumes of the ventromedial prefrontal cortex in females and with volumes of supplementary motor areas in males. Therefore, improving our understanding of neural networks underlying alexithymia and its subfactors could contribute to integrate existing findings.

Structural correlation network analyses are based on interregional (partial) correlations of structural measures, e.g. volumes of distinct brain regions. The main rationale of this approach is based on the observation that positive correlations of volumetric measures between distinct brain regions partly reflect structural and functional connections [19]. Networks derived from correlations of structural measures contribute to our understanding of the brain connectome and have been found useful in characterizing the general structure of the brain [20] as well as common psychiatric disorders [21–26]. Investigating alterations in structural correlation networks as-

**Table 1.** Demographic characteristics of the combined SHIP-2 and SHIP-Trend samples

Covariate	Low alexithymic group	High alexithymic group	Overall	Group comparison
<i>N</i>	1,100	1,099	2,199	
Age, years	51.5	52.7	52.1	$t = -2.0; p = 0.04$ *
Sex ratio = F/(M + F)	0.52	0.46	0.49	$\chi^2 = 9.0; p = 2.6e-3$ *
Handedness = R/(R+L)	0.91	0.91	0.91	$\chi^2 = 4.5e-5; p = 0.99$
Intracranial volume, liters	1.59	1.59	1.59	$t = -0.99; p = 0.32$
Smoking				$\chi^2 = 3.7; p = 0.16$
Never	454	431	885	
Former	420	405	825	
Current	226	263	489	
Educational attainment				$\chi^2 = 39.2; p = 3.1e-9$ *
$\geq 8$ years	135	223	358	
$\geq 10$ years	602	617	1,219	
$\geq 12$ years	363	259	622	
Alcohol consumption				$\chi^2 = 5.4; p = 0.02$ *
Low	1,024	992	2,016	
High	76	107	183	
Cohort				$\chi^2 = 34.5; p = 4.1e-9$ *
SHIP-2	284	413	697	
SHIP-Trend	816	686	1,502	
Prevalence of clinical alexithymia	0	0.06	0.03	

sociated with alexithymia could improve our understanding of the psychopathology of alexithymia and its relationship with other mental disorders. Also, given that alexithymia reflects the reduced ability to identify and describe emotions, it could contribute to elucidate the neural bases of cognitive emotion processing.

While there are numerous metrics for comparison of networks, each of them requires great care with respect to calculation, interpretation, and statistical analyses. The present paper focuses on centralities of single network nodes which are being assessed by two common measures, namely degree centrality and eigenvector centrality (e.g. [27]). The degree of a single network node is certainly the most basic measurement of its centrality. In addition, we have chosen eigenvector centrality because it is the basis of a variety of very popular and established centrality measures like Google's PageRank algorithm [28].

Previous studies showed strong associations between alexithymia and depression in general population and clinical samples [5, 6]. Structural connectivity analyses revealed altered centrality of different regions including the amygdala and the ventral medial prefrontal cortex in depressed subjects [29, for a review 30]. Therefore, subjects with the lifetime diagnosis of major depressive disorder were excluded from our analyses.

To our best knowledge, structural MRI studies investigating putative alterations of correlation networks in alexithymia are still lacking. In our study we investigated correlations of 68 cortical regions in participants with high alexithymia compared to participants low in alexithymia. We hypothesized that we would identify cortical regions with increased or reduced centrality and thereby influence in the high alexithymia network. In particular, we expected to find decreased centrality of cortical regions involved in emotion processing including the orbital frontal cortex, the ACC and the middle cingulate gyrus. Moreover, we predicted that these findings would be mainly carried by the factors DIF and DDF. In contrast, we expected that subjects high in EOT would show increased centrality of the ventromedial prefrontal cortex and supplementary motor areas.

## Methods

### General Population Sample

The Study of Health in Pomerania (SHIP) was designed to assess the prevalence of common risk factors and diseases and to investigate their complex associations in a population of northeast Germany randomly drawn from local registers [31]. 4,308 subjects participated at baseline between 1997 and 2001. From 2008 to 2012

the second follow-up (SHIP-2), which included whole-body MRI, was carried out. In parallel an independent new sample was drawn, and examinations of similar extent were undertaken (SHIP-Trend). All participants gave informed consent to the study and scientific use of the data. In total, data from  $n = 3,013$  participants were evaluated. After quality control of magnetic resonance images, removal of subjects with lifetime diagnosis of major depressive disorder (MDD), and removal of outliers as explained below, the combined samples of SHIP-2 and SHIP-Trend contained  $n = 2,199$  cases.

Sociodemographic and health-related characteristics are given in Table 1. Besides age and sex, we included handedness (left, right), smoking (never, ever, currently), educational attainment (8, 10, 12 years), cohort (SHIP-2, SHIP-Trend), and alcohol consumption (low, high) as covariates in our study. Low alcohol consumption was defined by  $<20$  g/day for women and  $<30$  g/day for men (procedure described in detail in Baumeister et al. [32]).

#### Assessment of Alexithymia

Alexithymia was assessed with the German version of the widely used 20-item version of the Toronto Alexithymia Scale (TAS-20) [33, 34]. All items are rated on a 5-point scale (1 = never applies; 5 = applies always). The German version of this self-report questionnaire has good psychometric properties (internal consistency  $\alpha = 0.70$ ; test-retest reliability  $r = 0.71$ ) [35]. The 3-factor structure has also been confirmed in the German version: (1) difficulty identifying feelings; (2) difficulty describing feelings; (3) externally oriented thinking.

Due to the strong correlation of alexithymia with negative affectivity and depression [5], subjects with lifetime diagnoses of MDD were excluded from the analysis ( $n = 518$ ; 17%). The diagnosis of MDD was determined based on the standardized and computerized Munich-Composite International Diagnostic Interview (M-CIDI) [36], for which satisfactory psychometric properties have been shown [37]. Clinically experienced psychologists conducted the interviews in face-to-face situations. We used the lifetime diagnosis of MDD as a dichotomous outcome measure.

As our data come from a general population study, the percentage of individuals with clinical alexithymia (TAS-20 score  $>60$ ) is very small ( $n = 74$ , 3%), and males are highly overrepresented in this group (61 vs. 50% overall). Since the connectome of the brain has been found to be widely different between males and females (e.g. [38]) the results of such a group comparison would be very difficult to interpret. More seriously, the large difference in sample size between both groups would lead to large differences in estimation biases of the partial correlation matrix and derived network measures and therefore to spurious group differences. Because of this we decided to use a median split of the TAS-20 overall score. This leads to nearly balanced groups with respect to the major covariates sex and age (Table 1) and reduces their confounding impact. At the same time differences in random and systematic estimation errors between both groups can be neglected.

In supplementary analyses, we also tested whether the top 25% versus bottom 25% of the sample in terms of TAS-20 scores differed regarding the centrality measures. However, this additional approach was as a matter of course associated with a substantial reduction of statistical power.

#### MRI and Cortical Parcellation

All subjects underwent whole-body MRI on a 1.5-T scanner as part of the standard protocol of both SHIP-2 and SHIP-Trend [39].

T1-weighted images of the head were taken with the following parameters: axial plane, repetition time = 1,900 ms, echo time = 3.4–37 ms, flip angle  $15^\circ$ , and resolution  $1 \times 1 \times 1 \text{ mm}^3$ , matrix  $256 \times 176$ , bandwidth 130 Hz/pixel. Images showing structural abnormalities (e.g., tumors, cysts, or hydrocephalus) and images with strong inhomogeneities in intensity, which typically leads to failure of automated image processing, were excluded after visual inspection ( $n = 163$ ; 5%).

MR images were processed with FreeSurfer 5.3 [40], a software suite for processing and analyzing of human brain MR images. As part of the standard pipeline of FreeSurfer the cortex was parcellated into 68 regions according to the Desikan-Killiany atlas [41], and mean cortical thickness was calculated for each region. We performed quality control of the FreeSurfer output by visual inspection of each region. Cases with more than 3 badly segmented regions were rejected ( $n = 156$ ; 5%). In all other cases thicknesses of badly segmented regions were replaced by the whole sample mean value ( $n = 454$ , 20%).

#### Construction of Correlation Networks and Centrality Measures

We used the positive part of the partial correlation matrix of the cortical thicknesses in order to define weighted networks with nodes representing cortical regions and edges representing partial correlations between them. This was done for both the low and high alexithymic group separately. Figure 1 shows the corresponding network for the high alexithymic group with the width of edges being drawn in proportion to the positive part of the partial correlations. Interhemispheric symmetry is clearly reflected in the strong edges between nodes of opposite hemispheres.

Partial correlation between two regions  $i$  and  $j$  was estimated based on the adjusted cortical thicknesses using the formula

$$R_{ij} = -\frac{P_{ij}}{\sqrt{P_{ii}P_{jj}}},$$

where  $P = S^{-1}$  is the inverse sample correlation matrix. Two nodes of the network were defined as being connected if there was a partial correlation greater than zero between them and the weight of the connection was defined as the partial correlation coefficient. Entries of the adjacency matrix  $A$  of the network are therefore given by

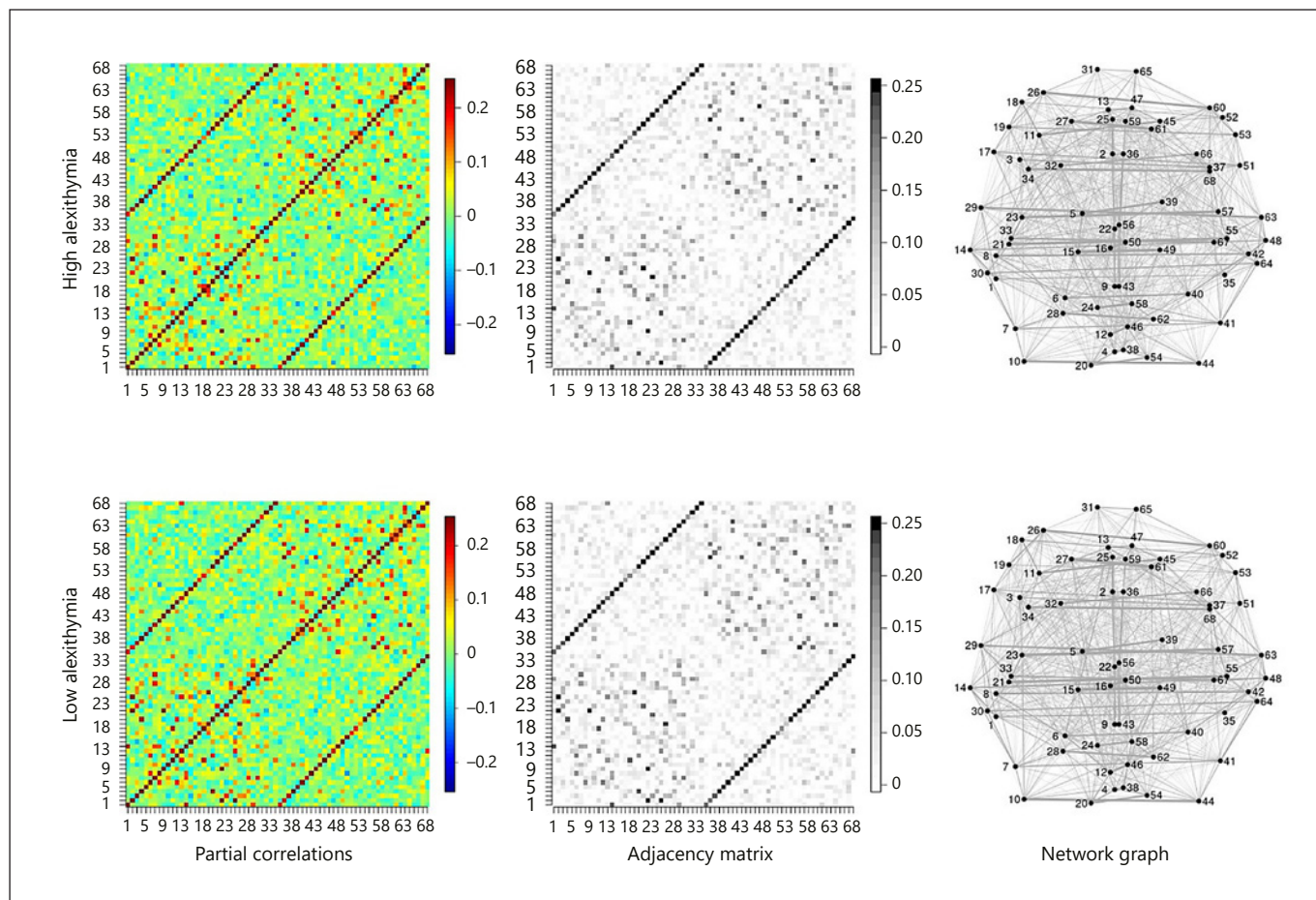
$$A_{ij} = \max(R_{ij}, 0).$$

In the present study we investigate the centrality of single nodes, i.e. how strong single nodes were connected to other nodes of the network. Differences in centrality between nodes is a key prerequisite for efficient information transfer within networks. Nodes which are high in centrality may serve as hubs which connect different modules of the network [42].

Here we considered two measures of node centrality. *Weighted degree* (or nodal strength)

$$s_i = \sum_{j=1} A_{ij}$$

measures how strong a single node is connected to all of its neighbors by summing up all weights of the corresponding edges irrespective of whether these nodes are themselves strongly connected to other nodes. In case of a simple binary graph with weights either being zero or one, this would be the number of nodes a single node is connected to.



**Fig. 1.** Construction of cortical thickness correlation networks of both the low alexithymic and high alexithymic group. Nodes represent cortical regions according to the Desikan-Killany atlas, and edges were defined as positive partial correlations between their mean thicknesses.

In order to take the importance of nodes into account, we also considered the *eigenvector centrality* which is implicitly defined by the matrix equation

$$Ac = \lambda c,$$

with  $\lambda$  denoting the largest eigenvalue of  $A$  and  $c$  being the corresponding eigenvector. The entries of vector  $c$  are the eigenvector centralities of all nodes of the network. Eigenvector centrality measures how strong a single node is connected to important nodes of the network. A single node which has many connections to unimportant ones may have lower eigenvector centrality than one with few connections to important ones. The above equation may have multiple solutions. However, it is guaranteed to have a unique solution for the largest eigenvalue if  $A$  has positive entries only, which is the case in our study.

Here we are not interested in the exact values of the centrality measures but rather in comparing values of single nodes with the remaining ones of the network [22]. Therefore, centrality measures were ranked ordinarily in increasing order with a rank number equal to one indicating a node having a smaller value than all

other ones. This makes the analyses more robust against spurious group differences, e.g. due to differences in estimation biases between both groups.

#### Statistical Analysis

Before constructing the cortical networks, the data were adjusted for possible confounders. For each cortical region we fitted a generalized linear model including age, age<sup>2</sup>, sex, and age-sex interactions. Moreover, we included total intracranial volume (eTIV from FreeSurfer), handedness (left, right), smoking (never, ever, currently), educational attainment (8, 10, 12 years), alcohol consumption (low, high), and cohort (SHIP-2, SHIP-Trend), with nonmetric covariates being included as factors. After fitting the generalized linear model for each region, we computed the corresponding residuals which were then used for the subsequent network analyses.

Given the correlation of alexithymia with different anxiety syndromes, we performed additional analyses with adjustment for anxiety as measured in the subjective health complaints questionnaire [43]. However, entering anxiety as covariate only slightly

**Table 2.** TAS-20: group comparison of centrality measures

Nodal measure	Cortical region	Low alexithymic group	High alexithymic group	<i>p</i>	<i>P<sub>FDR</sub></i>	
Weighted degree	R paracentral	11	61	0.00039	0.026	*
	L pars triangularis	38	5	0.0051	0.174	
	R caudal middle frontal	47	15	0.0249	0.509	
	R medial orbitofrontal	57	22	0.0250	0.509	
Eigenvector centrality	R paracentral	10	64	0.00002	0.001	*
	L pars triangularis	34	7	0.0094	0.319	
	R transverse temporal	4	25	0.0230	0.520	
	L superior temporal	33	61	0.0356	0.520	
	R superior temporal	41	63	0.0361	0.520	

Only cortical regions with uncorrected  $p < 0.05$  are shown (asterisks indicate significance after FDR correction for multiple comparisons). TAS-20, 20-item Toronto Alexithymia Scale;  $P_{FDR}$ , false discovery rate correction.

changed the results. As anxiety is a distinctive syndrome which is independent from alexithymia, we did not include anxiety in the final analyses presented in this study.

After networks of both groups had been constructed, we computed two centrality measures, i.e. weighted degree and eigenvector centrality, for each node (see above). To assess the significance of the observed differences between the low and high alexithymic groups we used random permutation testing with  $10^5$  repetitions for each centrality measure separately. During each repetition group labels were randomly shuffled, and centrality measures were calculated again for each node of the network. Afterwards significance was assessed by counting the number of repetitions where the absolute difference between the ranked centrality measures of both groups was larger than the one in the observed (nonshuffled) data.  $p$  values were estimated by the relative number of those cases. Finally,  $p$  values were corrected for multiple testing of 68 regions using the false discovery rate (FDR) method. All statistical analyses were performed using R version 3.4.3 [44] and the igraph package [45].

## Results

Table 1 shows demographic characteristics of the high and low alexithymic participants. Significant differences were found for sex ratio, educational attainment, and cohort membership. Moreover, there were small but significant differences in age and alcohol consumption between both groups. No significant differences were found with respect to handedness, intracranial volume, and smoking. After constructing the correlation networks, we also checked for potential differences in graph density between both groups. Edge densities were very close with 55.4 and 55.1% for the low and high alexithymic network.

We found both regions with increased and decreased centrality in the high alexithymic network compared to the low alexithymic network (Table 2). In detail, our results showed a significantly higher degree of connectivity of the right paracentral lobule. Both weighted degree and eigenvector centrality were significantly larger in the high alexithymic network after FDR correction for multiple comparisons of 68 regions ( $P_{FDR} = 0.026$  and  $P_{FDR} = 0.001$ ). Larger eigenvector centrality was also found in the right transverse temporal gyrus and the superior temporal gyrus in both hemispheres with significance at the nominal level.

Moreover, we also found regions with reduced centrality, albeit these differences did not remain significant after FDR correction for multiple testing. More specifically, both eigenvector centrality and weighted degree of the left pars triangularis were smaller in the high alexithymic network. Reduced weighted degree was present in the right medial orbitofrontal cortex and the right caudal middle frontal gyrus.

We also investigated the subscales of the TAS-20 (online suppl. Tables 3–5; for all online suppl. material, see [www.karger.com/doi/10.1159/000504983](http://www.karger.com/doi/10.1159/000504983)). The results of subscale 3 (EOT) were similar to those of the TAS-20 overall score, with increased centrality of the right paracentral cortex and decreased centrality in the right medial orbitofrontal cortex. However, these findings did not remain significant after correction for multiple comparisons.

To investigate whether altered cortical networks were sex-specific, all statistical analyses were repeated after di-

viding the analytic sample into female and male participants. In general, the sex-specific analyses pointed in the same direction with the paracentral lobule showing increased weighted degree and eigenvector centrality in the high alexithymic group. Differences were larger in female subjects than in males but missed statistical significance, probably because of reduced statistical power.

Results of supplementary analyses comparing the top 25% versus the bottom 25% of the sample did not reveal any significant differences after adjusting for multiple testing (online suppl. Table 7). However, similar brain regions including the right paracentral lobe emerged as top results and showed significance at the nominal level.

## Discussion

In our study, we aimed at investigating differences in cortical correlation networks between low and high alexithymic subjects in the general population. The most compelling evidence was found for a higher centrality of the right paracentral lobule, which emerged in both weighted degree and eigenvector centrality and remained significant after FDR correction for multiple comparisons. Moreover, the paracentral lobule emerged in all subscale analyses as a structure with increased centrality. It is a U-shaped structure on the medial surface stretching underneath the central sulcus, thereby forming the connection between the frontal and parietal cortices. It represents the primary motor cortex for the contralateral lower limb as well as the sensory area for the lower limb and the genitalia. Moreover, the paracentral lobule facilitates the cortical inhibition of bladder and bowel voiding.

To date, there is only little neurobiological evidence for an involvement of the paracentral lobule in alexithymia. In their MRI study, Bøen et al. [46] investigated cortical thickness in relation to borderline personality disorder and facets of alexithymia. The authors found a cluster of reduced cortical thickness including the bilateral paracentral lobules being associated with both, borderline personality disorder and the DDF factor of the TAS-20. However, the results are based on a relatively small sample, and no significant association of the paracentral lobule thickness was found with the TAS-20 total score. More recent evidence related increased cortical thickness of the paracentral lobule to greater thermal and pain sensitivity [47]. Kano et al. [48] showed increased sensitivity to visceral stimulation induced by colonic distension in alexithymic subjects. In this context, our finding of a significantly higher centrality of the paracentral

lobule in the alexithymia network may represent a morphological correlate of the association of alexithymia with chronic pain syndromes [49, 50]. Given its role as sensory cortex for the genitalia and its function in the regulation of bowel and bladder voiding, our findings may contribute to explain the association of alexithymia with different functional disorders and particularly irritable bowel syndrome [51, 52] and bladder pain syndrome [53]. In support of this concept, Bagarinao et al. [54] reported higher gray matter density of different brain regions including the paracentral lobule in an MRI-based brain classification study of chronic pelvic pain patients.

Different other brain regions showed altered centrality in the high alexithymia network at a nominally significant level. However, significance was lost after correction for multiple testing. For instance, two areas which are directly or indirectly involved in the processing of emotions showed a lower connectedness in the high alexithymia network: the left pars triangularis and the right medial orbitofrontal cortex (mOFC). The pars triangularis of the dominant, mostly left hemisphere is a portion of Broca's area which is a key region for language processing and particularly speech production. More recent findings also suggest an involvement in language comprehension [55]. There is increasing evidence indicating that language comprehension and production and Broca's area are relevant factors for the identification, processing, and regulation of emotions [56, 57].

The OFC, located at the ventral surface of the prefrontal cortex, has been proposed to be an important part of networks implicated in emotion processing with direct connections to the amygdalae and parts of the ACC [58]. The mOFC has commonly been associated with reward processing, thereby enabling value-guided decision making and guiding of adaptive behavior [59, 60]. Existing studies showed that greater volumes of the mOFC were linked to increased expression of positive affectivity [61], while reduced mOFC volumes were repeatedly found in subjects suffering from MDD [62, 63]. Our nominally significant result of a reduced centrality of the right mOFC in the high alexithymia network may reflect the association of alexithymia with negative affectivity and dysfunctional emotion regulation strategies.

The uncorrected results also revealed enhanced eigenvector centrality of two cortical areas involved in the processing of auditory information: the right transverse temporal gyrus, also known as Heschl's gyrus, as well as the bilateral superior temporal gyri. The transverse temporal gyrus receives projections from the medial geniculate body and represents a part of the primary auditory cortex.

Its main function is the processing of incoming auditory information. The superior temporal gyri are primarily part of an auditory processing network and receptive language function [64]. However, more recent models described its role in social cognition and interaction, for instance by integrating emotional, auditory, and visual stimuli [65]. Interestingly, results from diffusion tensor imaging (DTI) analyses showed abnormal connectivity of the superior temporal lobe in association with autism [66], a disorder which shares some features with alexithymia [67, 68].

Also, the caudal division of the right middle frontal gyrus showed nominally reduced weighted degree centrality in the high alexithymia network. Previous studies suggested the middle frontal gyrus to play a central role in social cognition [69] with the caudal part of this gyrus being related to behavioral response rates [70]. The caudal part of the middle frontal gyrus shows strong connections with the premotor cortex, but also with the dorsal parts of the ACC, which have been found to be negatively associated with alexithymia [16].

Additional analyses comparing the top 25% versus bottom 25% subjects in terms of TAS-20 scores did not reveal any significant differences after correction for multiple testing (online suppl. Table 7). However, we again found a strong increase in centrality of the right paracentral lobule and the left superior temporal cortex, reaching significance at the nominal level. Moreover, the right mOFC and the right caudal middle frontal cortex showed decreased centrality. In sum, these supplementary results reflect the pattern found in the whole-sample analysis and thus provide further support for our findings.

While our results are in line with findings from different authors demonstrating a role of sensorimotor areas including the paracentral gyrus in alexithymia [14, 46], the corrected results failed to show an altered connectivity of brain regions which are typically associated with emotion regulation like the dorsal ACC, the cingulate gyrus, or the amygdala. However, as noted above, existing studies on brain structural and functional alterations in association with alexithymia yielded heterogeneous results with a substantial proportion of studies pointing at a role of cognitive, motoric or sensory brain regions rather than parts of the limbic system [13, 15]. Moreover, the focus of this study was to investigate network centrality as reflected by cortical thickness correlations. Network centrality is based on a very different concept compared to classical structural and functional studies and therefore are not necessarily in conflict with previous findings on an implication of emotion areas. In fact, it could be spec-

ulated that the paracentral gyrus serves as a central node for emotional or cognitive brain areas associated with alexithymia. Also, we did not calculate negative thickness correlations in this study as the positive correlations are considered to better reflect fiber connections. Still, it is conceivable that analyzing negative thickness correlations could reveal additional regions with altered centrality. Finally, although significance was lost after correction for multiple testing, some findings pointed at an involvement of emotional brain regions, i.e. the mOFC and the pars triangularis.

In summary, our results identified altered centrality in the alexithymia network of emotion relevant brain regions as well as of cortical structures which have not typically been linked to emotion processing. These findings support the concept of neurobiological alterations underlying alexithymic personality traits.

In our study cortical thicknesses were calculated for a predefined set of regions as defined by the Desikan-Killany atlas which largely reflects the gyrification patterns of the cortex [41]. Several more refined cortical atlases have been proposed, e.g. the multimodal atlas proposed by Glasser et al. [71]. Using a finer atlas more accurately reflects anatomically and functionally consistent cortical regions but at the same time it also increases the size of the networks. This leads to larger estimation errors and requires correcting for larger numbers of statistical tests. Moreover, direct application may be impossible because of these atlases requiring additional imaging modalities. The Desikan-Killany atlas used here is reasonable for nontargeted network analyses. However, more refined atlases should be considered in future studies especially when investigating specific parts of the brain.

Our approach of analyzing cortical thickness correlations includes some differences to other techniques of connectivity analysis like resting-state fMRI and DTI. For example, thickness connections allow to identify long-range connections between regions with enhanced centrality while in contrast results from DTI connectivity studies are limited in their ability to reveal long-range as well as crossed connections. Also, resting-state-based functional connectivity is specifically sensitive to artifacts from brain and non-brain sources. However, thickness correlation analysis goes along with some limitations which need to be acknowledged: first, our approach only allows investigation of cortical networks, while connectivity of subcortical structures remains unresolved. Therefore, additional connectivity analyses using techniques like fMRI or DTI are needed in order to improve our understanding of alexithymic network architecture.

Also, previous studies found that thickness correlations only partly converge with underlying fiber connections. For example, Gong et al. [19] reported that thickness correlations converged with fiber connections as measures with DTI by approximately 35–40%. However, the results reported by Gong et al. related to overall correlations including positive as well as negative correlations. In this study we focused on positive correlations which are supposed to show a significantly greater convergence with fiber connections. Moreover, the authors pointed out that with respect to a significant correlation of nodal characteristics between the two networks, thickness correlations contain important data above information on fiber connections. Finally, using the median TAS-20 score as a cut-off may be regarded as a limitation as the clinical cutoff for alexithymia is typically defined as TAS-20 >60. However, since we used data from the general population, only very few subjects showed scores above the clinical threshold.

The use of a 1.5-T scanner is another limitation to this study. Image resolution and signal-to-noise ratio are significantly better when using 3-T scanners. Performing a similar cortical thickness connectivity analysis using a 3-T scanner is wanted.

Moreover, the use of a self-rating questionnaire like the TAS-20 for measuring alexithymia has been called into question, since alexithymic subjects showing problems in identifying and describing feelings may be particularly challenged in reporting about their own alexithymic characteristics. However, the TAS-20 is the most commonly used instrument for the assessment of alexithymia in the clinic and research, and its satisfactory psychometric properties have repeatedly been shown [33, 35].

In sum, our study using data from two large, general population samples provides evidence for altered struc-

tural connectivity in subjects with high alexithymia scores, thereby contributing to clarify the neurobiological bases of alexithymia and of emotion processing in general. Brain areas with altered connectivity included regions involved in emotion regulation as well as areas relevant to motoric and sensory processing, indicating that various networks are involved in the development of alexithymia.

## Statement of Ethics

The investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. The survey and study methods of both the studies were approved by the institutional review boards of the University of Greifswald.

## Disclosure Statement

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