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Review article

Structure of the alexithymic brain: A parametric coordinate-based meta-analysis

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ABSTRACT

Alexithymia refers to deficiencies in identifying and expressing emotions. This might be related to changes in structural brain volumes, but its neuroanatomical basis remains uncertain as studies have shown heterogeneous findings. Therefore, we conducted a parametric coordinate-based meta-analysis. We identified seventeen structural neuroimaging studies (including a total of 2586 individuals with different levels of alexithymia) investigating the association between gray matter volume and alexithymia. Volumes of the left insula, left amygdala, orbital frontal cortex and striatum were consistently smaller in people with high levels of alexithymia. These areas are important for emotion perception and emotional experience. Smaller volumes in these areas might lead to deficiencies in appropriately identifying and expressing emotions. These findings provide the first quantitative integration of results pertaining to the structural neuroanatomical basis of alexithymia.

1. Introduction

Recognizing, distinguishing and describing emotions are important capacities in our daily lives. However, individuals with high levels of alexithymia have difficulties identifying and communicating emotions, which is a risk factor for various psychiatric and psychosomatic disorders (Aleman, 2005; Lane et al., 1997). Therefore, unraveling the neural basis of alexithymia is important for understanding the pathogenesis and risk factors for emotional disorders. However, reported findings regarding structural neural abnormalities of alexithymia have been heterogeneous up until now.

A body of neuroimaging studies has identified differences in the brain that may be associated with alexithymia. For instance, alexithymia has consistently been associated with functional brain alterations during emotional experience and recognition and regulation, in the amygdala, insula and medial prefrontal cortex (for a meta-analysis, see van der Velde et al., 2013). On the other hand, structural neuroimaging studies using voxel-based morphometry (VBM) have shown brain volumetric changes in alexithymia. For example, volumes of the insula and amygdala, which are relevant areas for computing affective value and generating emotional experience (for a review, see Donges and Suslow, 2017), have been found to be decreased in alexithymic individuals (Goerlich-Dobre et al., 2014; Goerlich-Dobre et al., 2015b; Ihme et al., 2013; Laricchiuta et al., 2015). Smaller striatal and orbital frontal regions have also been associated with alexithymia, which might be related to deficient reward and emotion valuation (Borsci et al., 2009; Goerlich-Dobre et al., 2015b; Kubota et al., 2011). However, there are also inconsistent findings on brain structural abnormalities in alexithymia. Some studies have found that gray matter volume of the anterior cingulate cortex (ACC) is smaller in alexithymic individuals (Borsci et al., 2009; Grabe et al., 2014; Ihme et al., 2013; van der Velde et al., 2014), but others have shown positive correlations between levels of alexithymia and ACC volume (Gündel et al., 2004; Goerlich-Dobre et al., 2015b) or no differences in ACC volume related to alexithymia (Goerlich-Dobre et al., 2015a; Heinzel et al., 2012). Therefore, a quantitative integration of brain structural findings of alexithymia is necessary.

Here, we conducted a parametric coordinate-based meta-analysis (PCM) of brain morphometric studies in alexithymia. The PCM method is a powerful voxel-based meta-analytic technique, which was designed

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to generate unbiased effect-size summaries of neuroimaging studies (Costafreda, 2012). By using the effect-size based algorithm, the PCM method can integrate neuroimaging findings from both Region-Of-Interest (ROI)-based and coordinate-based individual studies, integrate neuroimaging findings with different statistical thresholds under different multiple comparison corrections, and integrate both significant and non-significant findings. The aim of the present meta-analysis was to identify consistent structural brain abnormalities associated with alexithymia across published VBM studies. Based on previous VBM studies of alexithymia and a recent meta-analysis study of brain function in alexithymia (van der Velde et al., 2013), we hypothesized that alexithymia is associated with structural brain alterations. More specifically, we aimed to test for the presence of consistent changes in the volumes of brain areas related to emotional processing in alexithymia, such as the insula, amygdala, ACC, striatal and orbitofrontal regions.

2. Method

2.1. Study identification

A step-wise procedure was used to identify structural imaging studies of alexithymia. First, articles were searched on PubMed and ISI Web of Science published before the 21st of April, 2017. Search items included ["alexithymia" OR "alexithymic"] AND ["neuroimaging" OR "structural imaging" OR "magnetic resonance imaging" OR "MRI" OR "cortical thickness" OR "volume" OR "morphometry" OR "VBM"]. A total of 394 publications were identified (Fig. 1). After removing 110 duplicates between Pubmed and Web of Science, articles were assessed by reviewing their titles and abstracts for matching the following inclusion criteria: 1) written in English language; 2) reported empirical results; 3) making use of MRI and VBM; 4) included human subjects. Studies meeting these criteria were selected for full-text review and were included in the meta-analysis if they also met the following criteria: 5) investigated associations between brain volume and alexithymia; 6) assessment of alexithymia using the Toronto Alexithymia Scale (TAS-20) or the cognitive dimension of the Bermond-Vorst Alexithymia Questionnaire (BVAQ); 7) investigated alexithymia in healthy participants; 8) had an independent sample from any other included study. This step-wise procedure was conducted by two independent assessors (PX and EO).

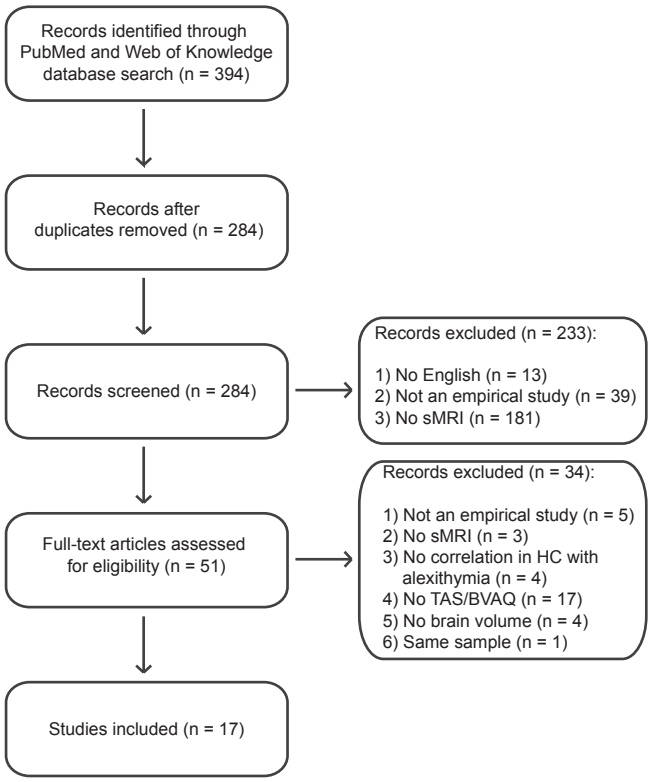

Fig. 1. PRISMA flow diagram of study selection procedure.

2.2. Data extraction

For each study, we extracted the following data: 1) study ID (first author and publication year); 2) sample size; 3) contrast (positive or negative correlations of alexithymia, increased or decreased volume of high compared to low alexithymia); 4) normalization space (MNI or Talairach); 5) size of mask (Whole Brain (WB) or Region of Interest (ROI)); 6) smoothing kernel; 7) whether findings were significant or not; 8) brain region location information (x/y/z coordinates of the peak coordinates and the corresponding automated anatomical label (Tzourio-Mazoyer et al., 2002); 9) statistical values (*p*, *r*, *T*, *F* or *Z*), threshold and correction methods (uncorrected, FDR or FWE). If there were no significant findings, the information of 8) and 9) was left empty.

2.3. Statistical analysis

To obtain a consistent neuroanatomical representation of alexithymia, we conducted a parametric coordinate-based meta-analysis (PCM) (Costafreda, 2012) using the algorithms implemented in the R statistical software (http://www.r-project.org). The PCM approach quantitatively incorporates neuroimaging findings while taking into account varied statistical thresholds across studies. Coordinates reported in Talairach space were converted to MNI space by using a nonlinear transformation (Brett et al., 2001). Using the cumulative probability function for the *T* distribution or for the standard normal distribution, effect sizes and statistical threshold values (i.e. *p*, *T*, *r* or *F*) were converted into *Z* values. To create a *Z* value summary map of each study for each contrast, the *Z* value of each reported coordinate was distributed across voxels within a 20 mm radius sphere (Radua et al., 2012; Salimi-Khorshidi et al., 2009), bounded by the field of view (FOV; either WB or ROI). For voxels located outside the sphere, the effect size estimate was a threshold-dependent interval (e.g., a non-significant finding with an uncorrected threshold of $p < 0.001$ is approximately equivalent to a *Z*-interval of [−Inf 3.09]). A pooled summary map of each contrast was then created by obtaining the maximum likelihood estimates of the mean and standard deviation of the *Z* values across studies for each voxel, through the optimization of the likelihood function based on the normal distribution. The contribution of each study to the pooled summary map was weighted by its sample size.

Pooled summary *Z* maps were created for the contrast of a positive correlation with alexithymia or greater gray matter volume in high compared to low alexithymic individuals. Moreover, pooled summary *Z* maps were also created for the contrast of a negative correlation with alexithymia or smaller gray matter volume in high compared to low alexithymic individuals. A two tailed *t*-test was performed for each voxel of the summary map to examine whether the *Z*-mean value was significantly different from zero (i.e. voxels showing evidence of differential brain volume). Two meta-analyses were conducted: 1.) including only WB-based studies; 2.) including both WB-based and ROI-based studies. To correct for multiple comparisons, the resulting *T* and *r* effect size summary maps calculated from the *Z*-values were thresholded using a $p < 0.05$ false discovery rate (FDR) and a minimum cluster size of 50 mm^3. Clusters of voxels with a positive or negative value indicated greater or smaller brain volume in alexithymia, respectively.

2.4. Publication bias test

Because the published results were primarily statistically significant

Table 1
Characteristics of studies included in the meta-analysis.

Study	Sample size	Female	Age (M ± SD)	Dimension	FOV	ROIs	Direction	Findings	Kernel
Aust et al., 2014	50 (25 HA; 25 LA)	25	34.35 ± 9.9	Cog & Aff*	ROI (Region)	Hipp, Amyg	Positive	Not Significant	–
Borsci et al., 2009	44 (14 HA; 30 LA)	44	49.85 ± 14.35	Cog	WB	–	Negative	Significant	8
D'Agata et al., 2015	17	17	23 ± 4	Cog	WB	–	Negative	Not Significant	–
Dickey et al., 2012	19	–	32 ± 11.4	Cog & Aff*	ROI (Region)	Oper	Negative	Significant	–
Goerlich-Dobre et al. 2014	40 (20 HA; 20 LA)	21	25.25 ± 6.5	Cog & Aff	WB	–	Positive	Significant	8
Goerlich-Dobre et al., 2015b	118	67	25.19 ± 5.36	Cog & Aff	WB	–	Negative	Significant	8
Grabe et al. 2014	1685	841	47.38 ± 11.15	Cog	WB	–	Negative	Significant	8
Gündel et al., 2004	100	51	25.6 ± 4.2	Cog	ROI (Region)	ACC; PCC	Positive	Significant	–
Heinzel et al. 2012	64 (33 HA; 31 LA)	–	26.85 ± 4.5	Cog	WB	–	Negative	Not Significant	8
Ihme et al., 2013	34 (17 HA; 17 LA)	16	38 ± 11	Cog	WB	–	Negative	Significant	8
Kubota et al., 2011	24	16	37.4 ± 11.5	Cog	WB	–	Negative	Significant	12
Laricchiuta et al., 2015	60	35	58 ± 17.2	Cog	ROI (Coordinate)	Amyg, INS, ACC, FFG, PHG	Negative	Significant	6
Paradiso et al., 2008	24	15	53.7 ± 17.1	Cog	ROI (Region)	ACC	Negative	Significant	–
Schneider-Hassloff et al., 2016	195	97	24 ± 3.2	Cog	ROI (Coordinate)	SPL	Negative	Significant	8
Sturm and Levenson, 2011	7	–	56 ± 18.4	Cog	ROI (Region)	ACC	Negative	Significant	–
van der Velde et al., 2014	57	28	34.1 ± 10.9	Cog & Aff	ROI (Coordinate)	ACC, mOFC, INS, Amyg	Negative	Significant	8
Zhang et al., 2011	48	24	31.1 ± 8.8	Cog	ROI (Coordinate)	INS	Positive	Not Significant	8

Abbreviations: FOV, field of view for the VBM analysis or multiple comparison corrections; WB, whole brain; ROIs, regions of interest; HA, high alexithymia; LA, low alexithymia; Cog, cognitive; Aff, affective; Hipp, hippocampus; Amyg, amygdala; INS, insula; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; FFG, fusiform gyrus; PHG, parahippocampal gyrus; Oper, pars opercularis; SPL, superior parietal lobule; mOFC, medial orbital frontal cortex.

findings based on small sample size, which might indicate publication bias, we used regression-based techniques proposed by Jennings and Van Horn (2012) to examine the effect of publication bias. Specifically, Cohen's *d* effect size estimate was computed for the volume size of each contrast of each study and compared to the sample size using Egger's regression and the 'Trim and Fill' method.

3. Results

Of the 394 publications initially found by the systematic search in the databases, 356 were excluded after reviewing the titles and abstracts (Fig. 1). After examining the full texts of the remaining 51 publications, seventeen studies with 8 WB-based and 9 ROI-based studies were identified that examined the morphometric characteristics of alexithymia. See Fig. 1 for details on the inclusion procedure and see Table 1 for characteristics of included studies. The total sample comprised 2593 subjects (age, M ± SD, 36.58 ± 9.99; see Table 1 for demographic details of the participants). Five studies measured both cognitive and affective dimensions of alexithymia. Three of these five studies measured the associations between the brain volume and two dimensions separately, but the other two ROI-based studies measured the associations between the brain volume and the sum of the two dimensions. Two studies had almost identical samples (Goerlich-Dobre et al., 2015a; Goerlich-Dobre et al., 2015b), from these we selected Goerlich-Dobre et al. (2015b) for the meta-analysis, because Goerlich-Dobre et al. (2015a) focused on the sex-specific effect of alexithymia, which was not investigated in the present study. Goerlich-Dobre et al. (2014) collected the data from a completely independent sample.

The meta-analysis including only WB-based studies showed smaller gray matter volume of the left insula, putamen, orbital frontal cortex (OFC) and right caudate in high compared to low alexithymic individuals (Table 2a and Fig. 2A). Similar results were found for the meta-analyses including both WB-based and ROI-based studies (Table 2b and Fig. 2B). Considering that there are only 8 WB-based studies and the contribution of studies to the summary findings was weighted by the sample size and the WB-based study of Grabe et al. (2014) included a huge sample size (n = 1685) comprising 70% of the total number of subjects included in the meta-analysis, the meta-analysis was repeated 8 times by excluding one study each time. The main results of this analysis were stable and robust (Table S1). Given the spread ages in the selected study of the current meta-analysis, we also analyzed age-related modulation of the observed effects (i.e. age-by-alexithymia interactions). However, we did not find any effects survived the threshold of the multiple comparison correction.

Table 2
Brain areas showing smaller gray matter volume in alexithymia.

Region	L/R	x	y	z	*Z*-score	Volume (mm^3)
With only WB-based studies						
Caudate Nucleus	R	6	10	8	−4.85	104
Caudate Nucleus	R	8	8	10	−4.85	–
Caudate Nucleus	R	8	16	14	−4.82	64
Caudate Nucleus	R	10	14	14	−4.82	–
Caudate Nucleus	R	12	−2	−16	−4.33	1016
Caudate Nucleus	R	6	8	−6	−4.33	–
Olfactory Cortex	–	0	8	−6	−4.29	–
Olfactory Cortex	R	2	10	−4	−4.29	–
Insula	L	−32	10	−12	−3.97	2488
Superior Frontal gyrus (Orbital)	L	−24	12	−14	−3.97	–
Inferior Frontal gyrus (Orbital)	L	−32	16	−20	−3.97	–
Insula	L	−30	14	−20	−3.97	–
Putamen	L	−24	6	−8	−3.97	–
Superior Temporal Pole	L	−32	14	−20	−3.97	–
With both WB-based studies and ROI-based studies						
Caudate Nucleus	R	8	16	14	−4.48	64
Caudate Nucleus	R	10	14	14	−4.48	–
Caudate Nucleus	R	6	10	8	−4.21	104
Caudate Nucleus	R	8	8	10	−4.21	–
Insula	L	−42	8	−12	−3.98	1608
Insula	L	−32	12	−14	−3.93	2488
Insula	L	−32	10	−12	−3.52	–
Insula	L	−24	12	−14	−3.52	–
Inferior Frontal gyrus (Orbital)	L	−32	16	−20	−3.52	–
Putamen	L	−24	6	−8	−3.52	–
Superior Temporal Pole	L	−32	14	−20	−3.52	–
Caudate Nucleus	R	6	0	−16	−3.75	816
Caudate Nucleus	R	6	8	−6	−3.75	–
Olfactory Cortex	–	0	8	−6	−3.69	–
Olfactory Cortex	R	2	10	−4	−3.69	–

The mixed-effect Egger regression model did not show significant publication bias ($z = 0.14$, $p = 0.89$). The plot of effect sizes (Cohen's *d*) by sample size and the funnel plot for assessing potential publication

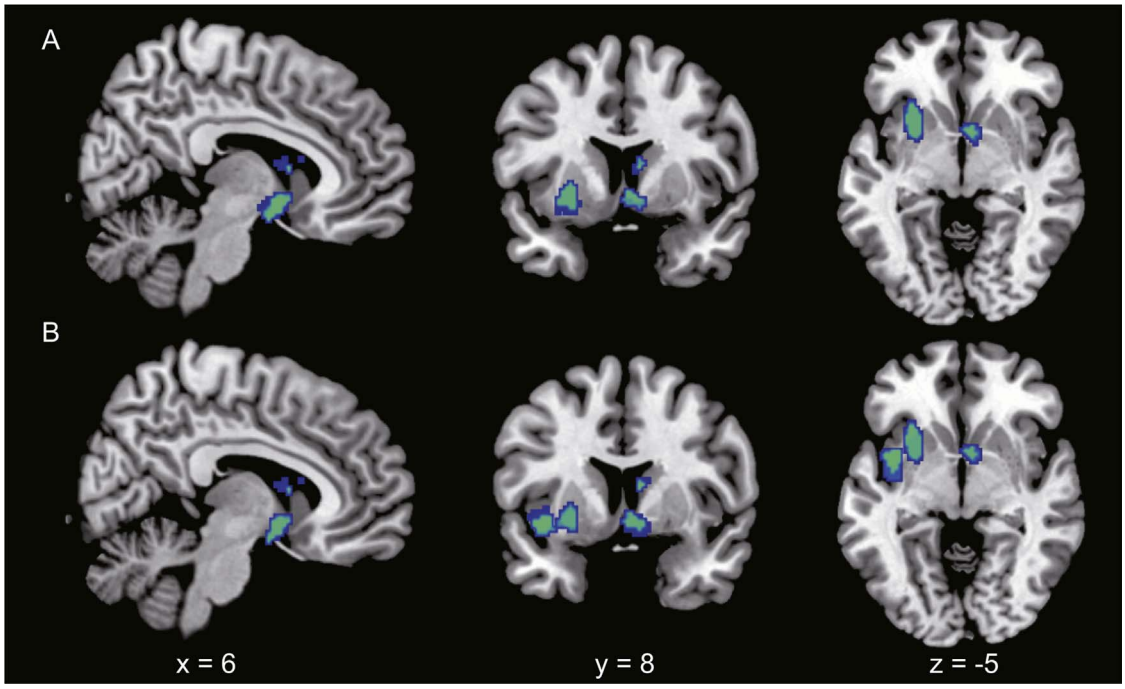

Fig. 2. Brain areas showing decreased gray matter volume in alexithymia including A) only WB-based studies and B) including both WB-based studies and ROI-based studies.

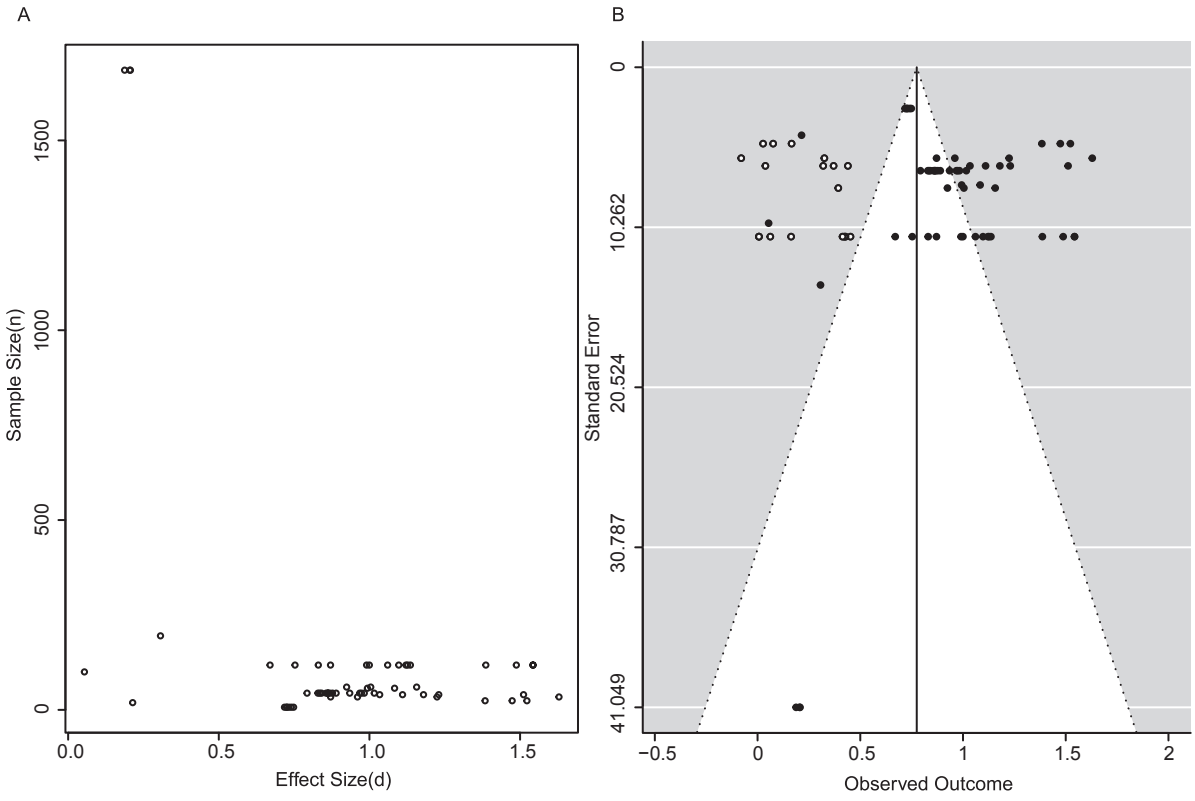

Fig. 3. A)Funnel plot of Cohen's d by sample size for studies included for meta-analysis. B) Regression tests for funnel plot asymmetry for assessing potential publication bias.

bias based on the Trim and Fill method are shown in Fig. 3, providing evidence against the presence of publication bias in the current meta-analysis.

4. Discussion

The present meta-analysis aimed to quantitatively integrate previously heterogeneous morphometric brain imaging findings in order to identify consistent brain structural alterations associated with alexithymia. Across previous studies on regional gray matter correlates of alexithymia, we found consistently smaller gray matter volumes of the insula, amygdala, OFC and striatum with higher levels of alexithymia. These brain regions may thus compose the structural basis of reduced capacities to identify and express emotions characteristic of this personality trait.

Our meta-analysis revealed a large cluster in the left insula showing

smaller structural volume associated with higher alexithymia. The insula, especially the anterior insular cortex, plays a key role in emotional awareness, which has been defined as the conscious experience and evaluation of emotions (Gu et al., 2013). Functional abnormalities of the insula have been consistently described in alexithymic individuals during emotion processing (for a meta-analysis, see van der Velde et al., 2013). Reduced activity specifically within the left insula in relation to alexithymia has been predominantly observed in tasks that require emotion processing at a cognitive level and in those assessing empathy for others (Bird et al., 2010; Enzi et al., 2016; Feldmanhall et al., 2013; Feng et al., 2016; Silani et al., 2013). Recently, a lesion study reported that the degree of damage in the insula could predict levels of alexithymia in brain-injured patients (Hogeveen et al., 2016). Thus, smaller volumes of the left insula may be associated with lower capacities in cognitive emotion processing and reduced empathic capabilities characteristic of alexithymia.

The present meta-analysis also revealed smaller volume of the left amygdala in alexithymia. The amygdala is well known as a key region for emotion processing, including emotion perception (Anderson and Phelps, 2001), emotional conflict (Etkin et al., 2006), fear conditioning/aversive leaning (LeDoux, 2003; Resnik and Paz, 2015), and reward learning (Baxter and Murray, 2002; Paton et al., 2006). Amygdalar volume has been found to be positively correlated with the size of the individual social network, which suggests a key role of the amygdala in social behavior (Bickart et al., 2011). As previously pointed out by Goerlich-Dobre et al. (2015a), smaller volume of the amygdala may be related to blunted neural responses to socio-affective stimuli in alexithymic individuals. Notably, the left amygdala has been suggested to be involved in cognitive processing of emotion to a stronger extent than the right amygdala (Baas et al., 2004), which may be particularly relevant in the context of alexithymia. Moreover, amygdalar hypo-responsiveness in relation to alexithymia, specifically difficulty in identifying feelings, has been observed not only during conscious but also during subconscious, automatic emotion processing (see Donges and Suslow, 2017 for a review on early, automatic emotion processing in alexithymia; Kugel et al., 2008; Reker et al., 2010). Together, these findings suggest that difficulties in identifying one's feelings may stem from a deep-rooted impairment in the subconscious appreciation of emotions.

The consistently smaller volume of the OFC (including inferior and superior parts) in the current meta-analysis might reveal a potential neural mechanism of hypofunctioning reward and emotional evaluation and regulation in alexithymic individuals. The OFC reflects the core neural representation of the value of stimuli (Li et al., 2015; Rudebeck et al., 2013), especially responses to interoceptive information (Hurliman et al., 2005), and also contributes to emotion regulation (Davidson et al., 2000). Smaller OFC volume may give rise to insufficient participation of the OFC in the neural circuitry valuating and mediating emotions, resulting in blunted or even absent emotional responses.

This meta-analysis also identified consistent reductions of striatal volume in alexithymia, including both the caudate and putamen. The striatum has been associated with the detection of reward, emotional value or other salient features of stimuli (Hikosaka et al., 2014) as well as with classification learning (Seger, 2008; Seger and Cincotta, 2005) and reward learning (Haruno et al., 2004). Previous findings have shown that the putamen is involved in the stimulus-action-reward association and action evaluation (Haruno and Kawato, 2006), whereas the caudate nucleus was shown to participate more in anticipation and the ventral striatum in emotion experience (Salimpoor et al., 2011). Therefore, volumetric reductions in all of these striatal areas might indicate the neurological structures of alexithymic individuals' failure to pair feelings/sensations with given triggering events, and to recruit the corresponding emotion repertoire and behavioral expression of emotions. Weaker reaction of the striatum to emotional stimuli in alexithymia has been found in several functional neuroimaging studies (Ihme et al., 2014; Lee et al., 2011; Suslow et al., 2015). Moreover, a recent study observed that during the anticipation of monetary rewards, higher levels of alexithymia were associated with reduced activity in the ventral tegmental area, from which the striatal and frontal regions receive dopaminergic input (Goerlich et al., 2017). Extending previous findings of blunted neural activity of the caudate in response to emotional stimuli, their findings suggest that such blunting occurs already during the anticipation of rewarding stimuli in alexithymia. Collectively, smaller striatal volume may contribute to devaluation of emotions, dissociation between emotional experience and emotional expression in alexithymia.

Contrary to Lane's conceptualization of alexithymia as a deficit in emotional self-awareness mediated by the ACC (Lane et al., 1997), the present meta-analysis did not confirm aberrant gray matter volumes in the ACC. Although alexithymia-related gray matter volume differences in this region were observed by several VBM studies, both reduced (Borsci et al., 2009; Grabe et al., 2014; Ihme et al., 2013; van der Velde et al., 2014) and increased (Gündel et al., 2004; Goerlich-Dobre et al., 2015b) ACC volumes have been reported. This inconsistency in the directionality of ACC volume differences may have prevented the detection of a consistent effect in the present meta-analysis. One reason for this inconsistency could be that volume differences in this region might depend on sex, as reduced ACC volumes were found in a female sample (Borsci et al., 2009) but not in a male sample (Heinzel et al., 2012). Supporting this suggestion, (Goerlich-Dobre et al., 2015a) observed smaller gray matter volume in the middle cingulate cortex, overlapping with the dorsal ACC only in males, along with sex-specific differences in several other brain regions underlying alexithymia. Thus, the potential relevance of the ACC for alexithymia cannot be discarded and deserves further scrutiny, particularly with respect to sex differences.

One limitation of the present meta-analysis is that we did not distinguish the brain structures linked to cognitive and affective dimensions of alexithymia because there were only three studies that independently measured affective (and two studies measured the sum scores of affective and cognitive) dimensions of alexithymia. It will be of relevance for future studies to make this distinction.

In conclusion, our meta-analysis suggests that alexithymia is linked to smaller gray matter volumes in core areas of the (conscious and subconscious) processing of emotions as well as in key regions of the brain's reward system. Reduced amygdalar volume might underlie the difficulties in emotion perception and identification that alexithymic individuals experience. Smaller insular volume may be associated with lower emotional awareness and impaired empathic capabilities, whereas smaller ventral striatal volume might contribute to deficient emotional learning and to blunted reward processing in alexithymia. These findings provide neuroanatomical substrates for an inability to recognize emotions, incapacity for precise descriptions of emotion, dissociation between exteroceptive cues and interoceptive emotional information, and disruption of transmission between emotional experience and emotional expression in alexithymia.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2018.01.004.

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