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Review article

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

Pengfei Xu[a,b,c,*], Esther M. Opmeer[b], Marie-José van Tol[b], Katharina S. Goerlich[d], André Aleman[a,b,e]

[a] Shenzhen Key Laboratory of Affective and Social Neuroscience, Shenzhen University, Shenzhen, China
[b] Department of Neuroscience, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[c] Center for Neuroimaging, Shenzhen Institute of Neuroscience, Shenzhen, China
[d] Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, RWTH Aachen University, Aachen, Germany
[e] Department of Psychology, University of Groningen, The Netherlands

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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

* Corresponding author at: Shenzhen Key Laboratory of Affective and Social Neuroscience, Shenzhen University, NO. 3688 Nanhai Ave., Nanshan District, Shenzhen 518060, China/ Neuroimaging Center, University Medical Center Groningen, Department of Neuroscience, University of Groningen, Antonius Deusinglaan 2, 9713AW Groningen, The Netherlands.
E-mail addresses: xupf@szu.edu.cn, p.xu@umcg.nl (P. Xu).

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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).

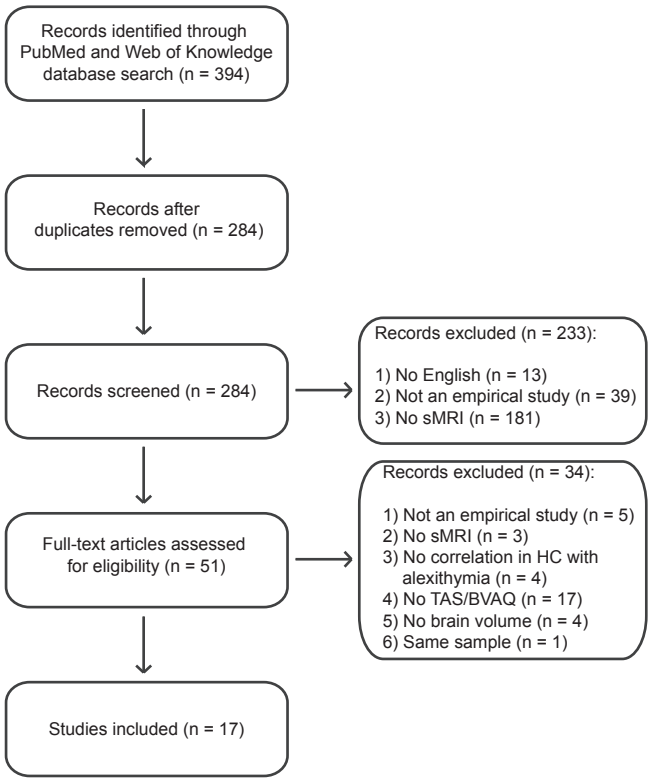

Fig. 1. PRISMA flow diagram of study selection procedure.

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