Metabolic mapping reveals sex-dependent involvement of default mode and salience network in alexithymia

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Abstract

Alexithymia, a personality construct marked by difficulties in processing one’s emotions, has been linked to the altered activity in the anterior cingulate cortex (ACC). Although longitudinal studies reported sex differences in alexithymia, what mediates them is not known. To investigate sex-specific associations of alexithymia and neuronal markers, we mapped metabolites in four brain regions involved differentially in emotion processing using a point-resolved spectroscopy MRS sequence in 3 Tesla. Both sexes showed negative correlations between alexithymia and N-acetylaspartate (NAA) in pregenual ACC (pgACC). Women showed a robust negative correlation of the joint measure of glutamate and glutamine (Glx) to NAA in posterior cingulate cortex (PCC), whereas men showed a weak positive association of Glx to NAA in dorsal ACC (dACC). Our results suggest that lowered neuronal integrity in pgACC, a region of the default mode network (DMN), might primarily account for the general difficulties in emotional processing in alexithymia. Association of alexithymia in women extends to another region in the DMN-PCC, while in men a region in the salience network (SN) was involved. These observations could be representative of sex specific regulation strategies that include diminished internal evaluation of feelings in women and cognitive emotion suppression in men.

Key words: alexithymia; sex differences; magnetic resonance spectroscopy (MRS); anterior cingulate cortex (ACC)

Introduction

Alexithymia (‘without words for feelings’) is a personality construct first termed by Sifnos (1972) to describe difficulties in emotional regulation of psychosomatic patients (Bagby et al., 1994a,b; Parker et al., 2003). It is characterized by difficulties in identifying and describing feelings, a diminished imagination and stimulus bound cognitive thinking (Lane et al., 1998; Campanella et al., 2012).

Functional MRI studies of emotional regulation in alexithymia reported that the anterior cingulate cortex (ACC) and the frontal cortex show both increased and decreased activation patterns (Berrino et al., 2002; Heinzel et al., 2010; Liemburg et al., 2012; Deng et al., 2013; Moriguchi and Komaki, 2013; van der Velde et al., 2013). Generally, the ACC is a structure involved in evaluation, regulation and cognitive control of emotions (Lane et al., 1998; Vogt 2005; McRae et al., 2008a; Etkin et al., 2011). It is
subdivided into several regions (Bush et al., 2000; Vogt 2005; Taylor et al., 2009) which belong to different networks. The rostral ACC is part of the so-called ‘default mode network’ (DMN), involved in various internally driven processes (Schilbach et al., 2008; Laird et al., 2009), while its caudal portion aligns with the ‘salience network’ (SN) engaged in detection and modulation of the response to internal and external salient events (Seeley et al., 2007; Taylor et al., 2009; Menon and Uddin, 2010).

To elucidate behavioural and functional deficiencies, we investigated neurobiological substrates of alexithymia using magnetic resonance spectroscopy (MRS) (Kim et al., 2009; Grimm et al., 2012a; Ernst et al., 2013). This way, we could overcome the conceptual problem that a specific task may bias towards findings involving a very specific region. Because one of the most prominent and widely described manifestations of alexithymia is the inability to process and distinguish feelings, we used a metabolic assessment of several networks involved in both internal and external emotional evaluation (Schneider et al., 2008). A study by Ernst et al. (2013) reported elevated levels of gamma-amnibutyric acid (GABA) in the ventral ACC which indicates the inhibition of that area (Moriguchi et al., 2007b) and elevated glutamate in the insula which coincides with the enhanced activity in this region as reported by functional studies (Moriguchi et al., 2007b; van der Velde et al., 2013; Goerlich-Dobre et al., 2014a). With the help of MRS, we measured neuronal integrity using N-acetylaspartate (NAA) as a marker of neuronal integrity and used Glx (a sum measure of glutamate and glutamine [Glu]) as a marker of local metabolism in distinct regions involved in emotional recognition and appraisal (Lane et al., 1998; Ochsner and Gross, 2005; Vogt, 2005; Etkin et al., 2011). Metabolites were measured using a finer parcellation of the cingulate cortex: the pregenual ACC (pgACC) and posterior cingulate cortex (PCC) as important hubs of the DMN and dorsal ACC (dACC) as SN constituent. These subregions of ACC have been regionally characterized extensively in task fMRI studies, and they have also been assessed in terms of covariance networks that are stable across modalities and confine to inter-subject variability (Taylor et al., 2012). We also measured in the left dorsolateral prefrontal cortex (dlPFC). dlPFC shows functional lateralization, where right was found to be more connected to attention and left to emotion regulation (Grimm et al., 2008; Cieslik et al., 2013; Takeuchi et al., 2013). To account for possible macroscopic changes, we additionally measured cortical thickness (CTh) (Gundel, 2004; Borsci et al., 2009; Thambisetty et al., 2010). The regional specificity was then complemented by a molecular specificity for distinct pathomechanisms.

Alexithymia is present in ~10% of the general population (Honkalampi et al., 2000; Mattila et al., 2006; Moriguchi et al., 2007a; Franz et al., 2008) and it is frequently more reported in men than in women (Mattila et al., 2006; Levant et al., 2009). The developmental and the biological mechanisms are not well understood (Larsen et al., 2003; Gundel 2004; Levant et al., 2009) and possible explanations include sex differences in the biological causes such as hormonal balance (Spitzer et al., 2005) or the environmental influences such as upbringing (Mattila et al., 2006; Levant et al., 2009; Campanella et al., 2012). Levant et al. (2009) speculated that the patterns of socialization in men that include restrictive emotionality could contribute to the development of alexithymia (Levant, 1992; Levant et al., 2009). Task fMRI studies of emotional processing in alexithymia were mostly focused on one sex and did not investigate if men and women are functionally affected in the same way or have the same regional associations to alexithymia (Levant et al., 2009; van der Velde et al., 2013).

Best to our knowledge, there were no reports on functional correlates of alexithymia between sexes. Therefore, we aimed to find out whether men and women have specific regional changes of metabolic activity, characterized via MRS and structural measures.

In principle both primarily transient activation related markers such as CIX (Li et al., 2014) and long term changes reflected by NAA or measures of CTh were considered as potential correlates of alexithymia. We assumed that the level of alexithymia would be reflected in these markers especially in regions involved in emotion processing. These regions comprise of those related to affect regulation and those related to affect experience, as previously discerned for several cingulate sub-regions (Bush et al., 2000; Margules et al., 2007; Walter et al., 2008a,b). If males and females differ in their mechanisms contributing to alexithymia, we expected this to lead to a sex-specific pattern of associated neuronal mechanism related to alexithymia in the four selected subregions engaged in default mode and cognitive control functions.

In addition, we explored how different facets of alexithymia, measured by the subscales, correspond to these regional and metabolic profiles of the TAS-20 score.

Materials and methods

Subjects

Thirty-six healthy subjects, 18 women (range from 25 to 51 years, mean age = 37.17 ± 10.27) and 18 men (range from 25 to 43 years, mean age = 32.00 ± 4.97), all right handed, without any prior neurological or psychiatric disorders took part in the study between 2008 and 2012. Subjects were assessed with the German Version 5.0.0 of the M.I.N.I. Mini International Neuropsychiatric Interview (Ackenberg, et al., 1999) and underwent additional interview by the study physician (M.W.). The study design included a magnetic resonance session with the MRS and the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994a; German version by Bach et al., 1996). The study was approved by the institutional ethical review board of the University of Magdeburg and all subjects gave written, informed consent.

Psychometric assessment

The TAS-20 is a self-reported questionnaire that measures three subscales: ‘Difficulties in describing feelings’ (DDF), ‘Difficulties in identifying feelings’ (DIF) and ‘Externally oriented thinking style’ (EOTS) (Bagby et al., 1994a). Each question is rated on a five-point Likert scale (from ‘1-strongly disagree’ to ‘5-strongly agree’), and the items loading on the subscale EOTS are inverted. The TAS-20 has, in its original English form, a good cross item consistency and reliability (Bagby et al., 1994b; Parker et al., 2003) which was replicated for the German version (Bach et al., 1996; Taylor et al., 2003; Franz et al., 2008). The TAS-20 total score ranges from 20 to 100 and subjects scoring 61 or higher have been suggested to be alexithymic, while those scoring 51 or lower are considered non-alexithymic (Parker et al., 1993, 2003).

MRS data acquisition and analysis

The measurements were done on a 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany). Proton MRS spectra were acquired for each participant in four different regions: (i) bilateral pgACC $10 \times 20 \times 20 \text{mm}^3 = 4.0 \text{ml}$, (ii) bilateral dACC $10 \times 20 \times 20 \text{mm}^3 = 4.0 \text{ml}$, (iii) bilateral PCC $10 \times 20 \times 20 \text{mm}^3 = 4.0 \text{ml}$ and (iv) left dlPFC $20 \times 20 \times 10 \text{mm}^3 = 4.0 \text{ml}$ (Figure 1). The bilateral voxels...
were centred on the sagittal midline to maximize the coverage of the relevant grey matter areas. A PRESS (point-resolved spectroscopy) sequence was used for all the voxels with the following parameters: echo time (TE) = 80 ms, repetition time (TR) = 2000 ms, 256 averages, band width = 1200 Hz, acquisition time for one image = 853 ms (Schubert et al., 2004). Manual shimming was performed to improve the magnetic field homogeneity by an automatic shim routine. The water reference data (TR = 10 s, four averages) were obtained for eddy current correction (Klose, 1990). The acquisition time for each voxel added up to 8 min and 40 s. To place voxels based on an established protocol of anatomical landmarks (Dou et al., 2013), a high-resolution structural scan was acquired at the beginning of this session (magnetization-prepared rapid gradient echo sequence: TE 4.77 ms, TR 2.5 s, TI 1.1 s, flip angle = 7°, bandwidth = 140 Hz/pixel, acquisition matrix = 256 × 256 × 192, isometric voxel-size = 1.0 mm³). Manual shimming took 1–5 min per voxel, varying from subject to subject, thus the total acquisition time amounted to around 50 min. A basis set was stimulated and measured, including sixteen metabolites (Creatine, Glutamate, Myo-Inositol, Lactate, N-acetylaspartate (NAA), Phosphocholine, Taurine, Aspartate, γ-Aminobutyric acid, Glx, Glucose, Alanine, N-acetylaspartylglutamate, Phosphocreatine, Guanine and Glycerophosphocholine). The spectra were analysed with LCMemod version 6.1.0 (Provencher, 1993). In our further analysis we included metabolites NAA and a joint measurement of glutamate and Glx. Values were calculated as ratios to the value of Creatine + Phosphocreatine (Cr) (Yildiz-Yesiloglu and Ankerst, 2006; Alger, 2010; Zhu and Barker, 2011). We also used the ratio of Glx to NAA (Savic et al., 2000; Duncan et al., 2013) to check the relation between these markers. A single metabolite measure was excluded as an unreliable result if (i) the signal to noise ratio was smaller than 8, (ii) a full-width-at-half maximum was bigger than 12 Hz and (iii) it didn’t meet the criteria of Cramer-Rao lower bound estimate of the fitting error (<20%) (Cavasilla et al., 2003).

To control for the underlying effects of macroscopic grey matter structure, we calculated correlation coefficients of the CTh and the TAS-20 scales. The CTh was estimated and extracted for the single voxels following the protocol as described in Li et al. (2014). Briefly, all MR-images were processed with the CIVET pipeline, developed by the McConnell Brain Imaging Centre (Zijdenbos et al., 2002). Individual voxels for every subject were co-registered first to the original T1 image, after which an affine transformation matrix was applied. The co-registered voxels were then projected to the normalized surface. Finally, the GM proportion of the individual voxel was calculated as the segmented grey matter divided by the total volume within voxels.

**Statistical analysis**

Statistical analysis was performed in SPSS for Windows (version 15.0; SPSS, Inc., Chicago, IL). Sex comparisons of the TAS-20 scores were analysed with independent sample t-tests. The tests were done on a two-tailed level of significance of \( P < 0.05 \). We tested the relationship between metabolites of interest in the above-described regions and the TAS-20 total score using partial rank correlations. To control for the possible effect of the individual differences of placed voxels on the metabolites, we used relative grey matter and white matter tissue composition as covariates in all analyses. Previous investigations showed that age is connected to the alexithymia scores (Mattila et al., 2006; Moriguchi et al., 2007a) and to the metabolite concentrations (Fouwels and Frahm, 1998; Schuff et al., 2001), thus age was added as a nuisance factor. To address the problem of multiple comparisons, we used Bonferroni correction. Due to the fact that the measured metabolites are not independent variables across regions, a classical Bonferroni correction would be too conservative (Sankoh et al., 1997). Therefore, we had to calculate the mean correlation coefficient of the metabolites correlation matrix (men \( r = 0.387 \), women \( r = 0.395 \)) and incorporate the degree of interdependence into our model for Bonferroni correction for each sex independently (number of comparisons = 12, \( df = 14 \)) following formulas: \( \gamma_k = 1 - (1 - r)^{m_k} \) where \( m_k = K^{1/k} \) (Sankoh et al., 1997). The significance threshold was adjusted accordingly to \( P < 0.011 \) for both women and men, representing a corrected \( P < 0.05 \), two sided. The correlation coefficient difference between the sexes was calculated following Fischer’s transformation and significance values were obtained from the computed z-values (Chalmer, 1986). Partial rank correlation of the regional CTh and the TAS-20 scale with age as a covariate was obtained on a two-tailed level of significance of \( P < 0.05 \). Additionally, an exploratory correlation analysis was performed with the TAS-20 subscales and the metabolites from four regions. Exploratory analysis was corrected with the same adjusted statistical threshold of \( P \leq 0.011 \).

**Results**

**Behavioural data**

Data are summarized in Table 1. There were no significant differences in the TAS-20 total score (\( P = 0.99 \)) or the subscales score (\( DFF, P = 0.27 \); \( DIF, P = 0.24 \); \( EOTS, P = 0.97 \)) between male and female participants. In a post-hoc test we ran a correlation

![Fig. 1. Single voxel proton MRS placed in (a) pgACC; (b) dACC; (c) PCC and (d) dIPFC.](Image)
between age and TAS-20 scores and the two variables didn’t correlate significantly.

**Association of metabolite levels and alexithymia**

This sex difference of network Fischer’s test revealed significant differences of the correlation scores for men and women in the PCC, where the Glx/ NAA measures correlated significantly stronger with the TAS-20 in women ($P = 0.018$) (Table 2). Correlations of the NAA/Cr in the pgACC and the Glx/ NAA in the dACC with the TAS-20 did not differ significantly between the sexes. We did not find any association between the metabolites in the dlPFC and the TAS-20 in either sex.

As a control analysis, we also calculated differences in metabolite ratios between men and women using relative grey matter and white matter tissue composition and age as covariates. There were no statistically significant differences ($P < 0.05$).

**Cortical thickness**

In women, we observed a correlation on a trend level for the TAS-20 total score and the CTh in the PCC ($P = 0.07, r = 0.45$). In men, no significant correlation was found between the CTh and the TAS-20 total score (all $P > 0.05$).

**Exploratory analysis**

In an exploratory investigation, we found that the alexithymia subscales had similar correlates as the TAS-20 total score. The subscale on DDF showed similar effects but on an uncorrected level of statistical significance (Table 3). In women, correlations of the Glx/ NAA in the PCC ($P = 0.027, R = -0.59$) and the NAA/Cr in the pgACC ($P = 0.013, R = -0.64$) were also found with DDF.

Furthermore, DDF correlations mirrored the general TAS-20 correlation with the Glx/ NAA in the dACC ($P = 0.06, R = 0.52$) for men. However, there was an additional trend for the Glx/ Cr in the pCC correlating with the DDF in women ($P = 0.085, R = -0.48$), which was not found for the general TAS-20 (Table 3). For the DDF, group difference in the correlation scores for the Glx/ NAA in the PCC was replicated ($P = 0.032$) and additionally there was a trend difference for the Glx/ NAA in the dACC ($P = 0.067$). The subgroup DIF was robustly negatively correlated with the Glx/ NAA in the PCC ($P = 0.001, R = -0.79$) and with the NAA/ Cr in the pgACC ($P = 0.007, R = -0.69$) in women, and, trend wise, with the Glx/ NAA in the dACC for men ($P = 0.09, R = 0.46$). The only significant difference of the correlation coefficients between the sexes was again found for Glx/ NAA in the PCC ($P = 0.0002$). The third subscale on EOTS replicated the correlations of the NAA/ Cr in the pgACC both for women and men ($P = 0.015, R = -0.63$ and $P = 0.062, R = -0.49$, respectively) at a uncorrected statistical threshold, but in contrast to the other scales, not the correlation with Glx/NAA in the PCC for women nor the correlations with Glx/NAA in the dACC for men (Table 3). Consistently, the three TAS-20 subscales also did not show any associations with the markers measured in the dlPFC.

**Discussion**

Using a metabolic mapping across regions involved in internally and externally oriented evaluation of feelings (Schneider et al., 2008) we found that NAA/Cr, a sensitive marker of neuronal integrity in the pgACC showed a consistent negative correlation with the alexithymia scores in both men and women (Figure 2). This negative correlation extended towards the PCC, where the Glx/NAA levels were inversely associated with the TAS-20 scores specifically in women while in men the Glx/NAA exerted an additional positive correlation with the TAS-20 in the dACC (Figure 2) but only on a lower statistical threshold. This metabolic modulation was found independent from any significant modulation by CTh within these areas in either women or men.

pgACC, the region where we observed changes in the NAA to creatine ratio, frequently aligns with the DMN (Northoff et al., 2007; Yu et al. 2011) which has been connected to various self-referential processes, i.e. emotion processing, planning and rumination (Raichle et al., 2001; Fox et al., 2005; Laird et al., 2009; Andrews-Hanna et al., 2010). The pgACC was shown to be specifically

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**Table 1.** Mean values $\pm$ SD of variables

| Region       | Metabolite | Mean $\pm$ SD | Women (N = 18) | Men (N = 18) |
|--------------|------------|---------------|----------------|--------------|
|              |            | Age           | 37.17 $\pm$ 10.27 | 32.00 $\pm$ 4.97 |
|              |            | Total TAS-20  | 40.83 $\pm$ 11.18 | 40.89 $\pm$ 7.56 |
|              |            | DDF           | 10.11 $\pm$ 3.32  | 11.44 $\pm$ 3.68 |
|              |            | DIF           | 13.17 $\pm$ 5.22  | 11.83 $\pm$ 3.70 |
|              |            | EOTS          | 17.56 $\pm$ 4.29  | 17.61 $\pm$ 3.42 |

**Table 2.** The metabolite values and the correlation difference between the sexes with the TAS-20 total score

| Region       | Metabolite | Mean $\pm$ SD | Women | Men | Correlation with TAS-20 | Fishers’s test (P) |
|--------------|------------|---------------|-------|-----|------------------------|-------------------|
|              |            |               |       |     |                        |                   |
| PCC          | NAA/Cr     | 1.18 $\pm$ 0.09 | 1.23 $\pm$ 0.12 | 0.26 | -0.19 |
|              | Glx/Cr     | 1.19 $\pm$ 0.12 | 1.20 $\pm$ 0.12 | -0.40 | 0.23 |
|              | Glx/NAA    | 1.01 $\pm$ 0.09 | 0.99 $\pm$ 0.10  | -0.72* | 0.28 |
| dIPFC        | NAA/Cr     | 1.38 $\pm$ 0.10 | 1.38 $\pm$ 0.15 | 0.12 | -0.20 |
|              | Glx/Cr     | 1.17 $\pm$ 0.16 | 1.17 $\pm$ 0.15 | 0.04 | -0.15 |
|              | Glx/NAA    | 0.85 $\pm$ 0.08 | 0.86 $\pm$ 0.08 | -0.13 | 0.13 |
| pgACC        | NAA/Cr     | 1.09 $\pm$ 0.09 | 1.07 $\pm$ 0.06  | -0.71* | -0.49* |
|              | Glx/Cr     | 1.32 $\pm$ 0.15 | 1.34 $\pm$ 0.17 | -0.07 | -0.13 |
|              | Glx/NAA    | 1.21 $\pm$ 0.13 | 1.25 $\pm$ 0.14  | 0.37 | 0.11 |
| dACC         | NAA/Cr     | 1.10 $\pm$ 0.06 | 1.09 $\pm$ 0.07  | -0.15 | -0.07 |
|              | Glx/Cr     | 1.21 $\pm$ 0.11 | 1.23 $\pm$ 0.15 | 0.01 | 0.45 |
|              | Glx/NAA    | 1.10 $\pm$ 0.07 | 1.13 $\pm$ 0.13  | 0.03 | 0.50b |

Correlation is indicated as a result of partial correlation, controlling for age and tissue composition.

*Denotes $P < 0.011$, statistical threshold with the Bonferroni correction, **denotes $0.1 > P > 0.011$, Fisher test ‘*’ $P < 0.05$, ‘**’ $P < 0.005$. 

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engaged in mood regulation and identification of affective internal states (Lane et al., 1998; Medford and Critchley, 2010; Etkin et al., 2011; Sturm et al., 2012). fMRI studies found reduced activation of the pgACC during visual emotional processes in alexithymic individuals (Deng et al., 2013; Moriguchi and Komaki, 2013) and Ernst et al. (2013) reported a decreased GABA to creatine ratio in the pgACC which was correlated to the TAS-20 score. Higher concentrations of GABA, mediating neuronal inhibition, might consequently decrease activity in the specific area. Although we did not measure GABA due to the technical limitations of our multi-voxel mapping approach, one could consider our findings generally concomitant in indicating a reduced activity either by neurotransmitter mediation or by the diminished neuronal integrity in the pgACC. Ernst et al., however, did not find changes in the neuronal marker NAA. This seems to stand in relevant contrast of the strong, consistent and robust correlation found in our study across sex and subscales. We are thus considering methodological aspects to contribute to the different observation. Our sample was considerably better powered in terms of sample size. Furthermore, we used a smaller voxel, which might be able to address any regionally focused observation in an anatomically defined subregion, namely Brodmann areas (BA) 24a-d, while the JPRESS assessment used by Ernst et al. had to integrate signals from ACC and large parts of BA10. Moreover, we here considered important potentially confounding factors such as age, gray matter voxel composition and potential influence of local CTh. Incorporating inter-individual variations of voxel tissue composition not only preserves against potentially spurious correlations but further can increase detection of true associations as it denoises the metabolite levels from variations merely attributed to varying gray matter content, due to voxel positioning and anatomical variability. Therefore, we interpret our finding as sufficiently robust to discuss it even in the light of previous negative findings.

It has been proposed that NAA is linked to neuronal viability and integrity (Lin et al., 2005; Kalra et al., 2006; Oz et al. 2014) and is considered to be a neuronal marker (Moffett et al., 2008). Alterations in NAA concentration have been reported for affective and metabolic disorders (Sassi et al., 2005; Shinno et al., 2007; Moffett et al., 2008; Walter et al., 2009, Horn et al., 2010) and for longitudinal neurobiological changes such as aging (Schuff et al., 2001; Kaiser et al., 2005). Although alexithymia has been associated with increasing age (Mattila et al., 2006) it would be difficult to disentangle weather this is due to decreased NAA levels (neuronal integrity) or both processes are parallel in the aging brain. In our study, we did not observe association of age and alexithymia, possibly due to small age and TAS-20 span in our sample.

Our finding points in the direction of a lower neuronal integrity of the pgACC in alexithymic individuals. Interestingly, we did not find a converging conformation for substrate-based macroscopic changes via examination of CTh. In both groups there was no correlation of the alexithymia scale and the CTh measured in the pgACC. This could speak for a very subtle effect in a generally healthy population. Extension towards a clinical population or use of a higher spatial resolution might resolve the question of whether the metabolic association with a putative marker of neuronal integrity is independent from the structural changes or if subtle regional alterations can be first observed on this metabolic marker. Voxel-based morphometric studies found decreased grey matter volume in the ACC alexithymic people (Borsci et al., 2009; Ihme et al., 2013). We did not observe decreased CTh in association with alexithymia. One reason for this difference could be intermediate scores (41) of our healthy participants whereas above mentioned studies used alexithymic individuals with values over 50 of the TAS-20.

Best to our knowledge, we for the first time found evidence for a sex-specific extension of regional abnormalities towards either the DMN or the SN. In women specifically, we found a robust negative correlation of the PCC measure of Glx relative to NAA with TAS-20 scores which were significantly stronger than in males, whereas men showed additional regional positive correlation of the Glx relative to NAA in the dACC, although on an uncorrected trend level. The ratio of Glx/ NAA can be considered as a measure of the dynamics of neuronal and glial processes (Savic et al., 2000; Walter et al., 2009; Wiebking et al., 2014) indicating an activation related state of the measured regions. Here, it needs to be noted that at least for the PCC the critical metabolic function related to alexithymia is reflected by the ratio itself and not increased or decreased Glx. While of course this marker is still reflecting activation related mechanism (YükSEL and Öngür, 2010) interpretation of this ratio will have to remain

Table 3. The correlation difference between the sexes with the TAS-20 subscales

| Region | Metabolite | DDF            | DIF            | EOTS            |
|--------|------------|----------------|----------------|-----------------|
|        |            | Women | Men | Fisher’s test | Women | Men | Fisher’s test | Women | Men | Fisher’s test |
| PCC    | Glx/Cr     | -0.48b | 0.04 | 0.16 | -0.79a | 0.30 | 0.0002** | -0.63b | -0.49c | 0.6 |
|        | Glx/NAA    | -0.59b | 0.13 | 0.032 | -0.69a | -0.26 | 0.1 | -0.01 | -0.48c | 0.2 |
| pgACC  | NAA/Cr     | -0.64b | -0.35 | 0.28 | -0.01 | -0.48c | 0.2 |
| dACC   | Glx/Cr     | 0.025 | 0.52c | 0.067*** | 0.11 | 0.46c | 0.1 |
|        | Glx/NAA    | 0.63c | -0.35 | 0.28 | -0.01 | -0.48c | 0.2 |

The table is restricted to results with a significance of P < 0.1 only.

*Denotes P < 0.011, statistical threshold with the Bonferroni correction; †denotes 0.05 > P > 0.011; ‡denotes 0.1 > P > 0.011; Fisher test: *P < 0.05; **P < 0.005; ***P < 0.1.
more carefully in relating it to a single neuronal mechanism but might also point towards more complex adaptation mechanisms involving both neuronal integrity and metabolism. In any case the finding may have implications on interpreting PCC functionality. The PCC is part of the DMN and was linked to heterogeneous self-relevant mental processes including autobiographical memory and internally directed attention (Vogt et al., 2006; Leech and Sharp, 2014). Lower levels of the Glx to NAA ratio could mark a lower activity of that region and indeed, fMRI studies showed decreased activation during an imagery task in the PCC in alexithymia (Mantani et al., 2005). Female participants have been characterized by an increased self-focus and high directed attention towards their own emotions via processes such as introspection and rumination (McRae et al., 2008a, b; Moriguchi et al., 2014). This general tendency could be a reason why the microstructural deficits (measured by NAA/Cr in the pgACC) and lower neuronal-glial dynamic (measured by Glx/NAA in the PCC) in the DMN (Liemburg et al., 2012) are more prominently correlated with the alexithymia in women.

This sex difference of network extension was further reflected by enhanced Glx to NAA ratio in men with higher scores of alexithymia. Although, the findings where not on a corrected statistical level, they could point to a regional activation of the dACC in those subjects. The dACC together with the insula composes a so-called ‘salience network’ (Seeley et al., 2007) which monitors external and internal cues directing attention to the appropriate stimulus (Taylor et al., 2009; Medford and Critchley, 2010; Menon and Uddin, 2010). It is also involved in the cognitive control of affective states (Lane et al., 1998; McRae et al., 2008b; Lane, 2008) and a differential activation for men and women has been shown for this area (Lane et al., 1998; McRae et al., 2008; Biswal et al., 2010). Goerlich-Dobre et al. (2014a) reported a larger dACC volume in regards to the affective alexithymia dimension, supporting the notion of the enhanced activity of this region in alexithymia (Gundel, 2004; Goerlich-Dobre et al., 2014a). The observed higher Glx/NAA could be the consequence of a compensation mechanism of the hypothesized general arousal in alexithymia (Lane et al., 2000; Lane, 2008; Medford and Critchley, 2010; Ernst et al., 2013) or of an emotion regulatory mechanism of suppression (Ochsner and Gross, 2005; Goldin et al., 2007; Swart et al., 2009; Liemburg et al., 2012; Goerlich-Dobre et al., 2014b).

Taken together, these network differences of the neurobiological correlates of alexithymia between the sexes could be an extension of the frequently observed sex differences in emotional processing (Lane et al., 1998; Hyde, 2005; Koch et al., 2007; McRae et al., 2008a; Kret and De Gelder, 2012; Moriguchi et al., 2014). Most importantly, these effects need to be seen in the context of a general, sex-independent effect in a region crucial for the establishment of mood states, namely the pgACC. Decline of the neuronal integrity in the pgACC could be a starting point of the observed alexithymia difficulties (Sturm and Levenson, 2011). Sex-specific emotion regulation strategies may then correlate with the alternating, specific regional patterns of activation and consecutively explain network-specific variation of MRS activity markers.

Our findings may also have more certain clinical implications. Although considered a separate personality construct (Bagby et al., 1994a,b; Saarijärvi et al., 2001; Celikel et al., 2010) alexithymia shows a high comorbidity with psychopathological syndromes and affective disorders (Honkalampi et al. 2000; Larsen et al., 2006; Sturm and Levenson, 2011; Shibata et al., 2014). In recent years, there has been a wide range of evidence for connotations between dysfunctional neurotransmission and affective disorders (Ende et al., 2006; Yildiz-Yesiloglu and Ankerst, 2006; Sanacora et al., 2008; Walter et al., 2009; Yüksel and Ongür, 2010; Grimm et al., 2012b). Men and women have different prevalence and treatment patterns for example in depression (Addis, 2008) and it has been suggested that comorbidity between depression and alexithymia could affect treatment outcomes (Carpenter and Addis, 2000). Our results point into direction that different metabolic patterns in alexithymia between men and women are contributing to the reported treatment outcomes. Thus, investigations of differential metabolic profiles in alexithymia for men and women could contribute to a better understanding of the development of dysfunction in emotion regulation (Hauwel-Fantini and Pedinielli, 2008) and future research should incorporate the evidence of sex specificity in network associations in our moderately alexithymic subjects. Our findings indicate that DMN and SN contribute in different amounts to the overall aspect of deficient identification of own emotional states in men and women.

In the left dIPFC, an area involved in emotional regulation and executive function (MacDonald et al., 2000; Grimm et al., 2008; Cieslik et al., 2013), we did not find any metabolic correlates with the TAS-20. This may suggest that alexithymia varies primarily as a construct of difficulties in the cognitive evaluation of feelings at the level of introspection or suppression of emotions and less at the level of higher-order control processes. This conclusion needs however to be made with considerable caution. While we can assess high regional correspondence between MRS voxels and regions previously involved in alexithymia or associated cognitive processes, the localization of dIPFC is less stringent and furthermore subject to increased inter-individual variability. It is thus possible, that despite focusing on a localization which well corresponds with previously reported changes related to emotion regulation we did not manage to capture its location in all subjects with the same level of anatomical preciseness.

On an exploratory level we also found that two subscales of the TAS-20, the DDF and the DIF, showed the same pattern of activity as the total score in both sexes (although on a differential statistical threshold). The correlational patterns for DDF and DIF are involving regions in ACC, structure that has role in various steps of emotion processing (Vogt, 2005; Etkin et al., 2011). On the other hand subscale EOTS was often reported as a separate item in the TAS-20 (Kooiman et al., 2002; Müller et al., 2003) and our finding also points in direction that other regions are mediating this facet in the sense that EOTS was not correlated with the MRS findings in the same regions as DDF/DIF or at least to a weaker extent. Although this finding may be intriguing in support of discussions on the validity of different subscales, one has to acknowledge that a lack of significance in one subscale provides very indirect evidence for a difference in underlying constructs and demands for further follow up investigations.

Limitation

Besides the general limitations arising from the moderate effective sample sizes of our study, there are some conceptual limitations arising from our choice of (effect maximizing) midline voxels. While we did not hypothesize an additional effect of hemisphere on different association of alexithymia within the SN and the DMN networks, this may be an interesting question to follow up in another study. Both emotion processing and brain maturation have been shown to lead to differences in lateralization between the sexes (Wager et al., 2003; Plessen et al., 2014) and other studies investigating influence of the
metabolite markers on brain function indeed found different effects for between hemispheres (Nagae-Poetscher et al., 2004; Falkenberg et al., 2012). The use of high field MRS at 7 Tesla may provide an opportunity for such investigation by allowing a smaller voxel size with equally high SNR (Dou et al., 2013). This may further allow investigation of other metabolites, namely GABA (Ernst et al., 2013; Wiebking et al., 2014), in relation to alexithymia which is hard to accomplish using a multivoxel MRS sequence at 3 Tesla. We didn’t control for the effects of menstrual cycle in our female participants which might impact the MRS measures (Batra et al., 2008). However, we do not expect that these would explain the additional correlation in the PCC given that for such a spurious correlation one would have to expect similar fluctuations in alexithymia along the normal cycle and this would still not explain the appearance of correlation in the males for dACC. Additionally, interpreting our results one should bear in mind that our sample didn’t contain individuals with very high TAS-20 scores. This may explain the absence of a correlation with the CTh, which once clinical dimensions are reached, may follow after the metabolite deviations (Li et al., 2013). Future investigation thus should incorporate bigger samples with wider TAS-20 distribution and ideally combine MRS with the additional measurements of a functional response to tasks of emotional processing and/or resting state fMRI.

Conclusion

In summary, we reported a converging, sex-independent negative association between alexithymia and the marker of neuronal integrity (NAA) in the pgACC, which could be a substrate for the observed deficit in processing of feelings in alexithymia. Moreover, we found sex-specific association of alexithymia and the Glx/NAA ratio in distinct nodes implying differential compensation or activation of the emotion modulation pathways in men and women. A functional conclusion of our observation may take the differences in men and women as a suggestion that women experience alexithymia predominantly as a function of reduced internal evaluation, mediated in the DMN, particularly in the PCC while men employ regulation strategies via dACC. These specific derangements of networks would then also suggest specific routes of affective impairments in clinical populations (van Tol et al., 2013).

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Conflict of interest.

None declared.

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