Psychological Medicine

cambridge.org/psm

Impaired cognitive self-awareness mediates the association between alexithymia and excitation/inhibition balance in the pgACC

A. Kühnel[1,2,*], A. Widmann[1,3,4,*], L. Colic[1,5,6], L. Herrmann[3], L. R. Demenescu[1], A. L. Leutritz[1], M. Li[3,7], S. Grimm[8,9,10], T. Nolte[11,12], P. Fonagy[11,13] and M. Walter[1,3,5,14,15]

[1]Clinical Affective Neuroimaging Laboratory, Magdeburg, Germany; [2]Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry and International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany; [3]University Department of Psychiatry and Psychotherapy, University Tübingen, Tübingen, Germany; [4]Experimental and Molecular Psychiatry, LWL University Hospital, Ruhr University Bochum, Bochum, Germany; [5]Leibniz Institute for Neurobiology, Magdeburg, Germany; [6]Department of Psychiatry, Mood Disorders Research Program, Yale School of Medicine, New Haven, CT, USA; [7]Department of Psychiatry and Psychotherapy, OVGU Magdeburg, Magdeburg, Germany; [8]Department of Psychiatry, Charité, CBF, Berlin, Germany; [9]MSB Medical School Berlin, Calandrellistraße 1-9, 12247 Berlin, Germany; [10]Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, 8032 Zurich, Switzerland; [11]The Anna Freud National Centre for Children and Families, London, UK; [12]Wellcome Trust Centre for Neuroimaging, University College London, London, UK; [13]Research Department of Clinical, Educational and Health Psychology, University College London, London, UK; [14]Center for Behavioral Brain Sciences (CBBS), Magdeburg, Germany and [15]Max Planck Institute for Biological Cybernetics, Tübingen, Germany

Original Article

*Shared first authorship.

Cite this article: Kühnel A *et al* (2020). Impaired cognitive self-awareness mediates the association between alexithymia and excitation/inhibition balance in the pgACC. *Psychological Medicine* **50**, 1727–1735. https://doi.org/10.1017/S0033291719001806

Received: 8 October 2018
Revised: 10 May 2019
Accepted: 1 July 2019
First published online: 22 July 2019

Key words:
Alexithymia; anterior cingulate cortex (ACC); emotion regulation; magnetic resonance spectroscopy (MRS)

Author for correspondence:
M. Walter,
E-mail: martin.walter@uni-tuebingen.de

Abstract

Background. Previous research showed that automatic emotion regulation is associated with activation of subcortical areas and subsequent feedforward processes to cortical areas. In contrast, cognitive awareness of emotions is mediated by negative feedback from cortical to subcortical areas. Pregenual anterior cingulate cortex (pgACC) is essential in the modulation of both affect and alexithymia. We considered the interplay between these two mechanisms in the pgACC and their relationship with alexithymia.

Method. In 68 healthy participants (30 women, age = 26.15 ± 4.22) we tested associations of emotion processing and alexithymia with excitation/inhibition (E/I) balance represented as glutamate (Glu)/GABA in the pgACC measured via magnetic resonance spectroscopy in 7 T.

Results. Alexithymia was positively correlated with the Glu/GABA ratio ($N = 41$, $p = 0.0393$). Further, cognitive self-awareness showed an association with Glu/GABA ($N = 52$, $p = 0.003$), which was driven by a correlation with GABA. In contrast, emotion regulation was only correlated with glutamate levels in the pgACC ($N = 49$, $p = 0.008$).

Conclusion. Our results corroborate the importance of the pgACC as a mediating region of alexithymia, reflected in an altered E/I balance. Furthermore, we could specify that this altered balance is linked to a GABA-related modulation of cognitive self-awareness of emotions.

Introduction

Emotion regulation is one of the main processes of behavioral functioning and deficits in related circuitry might contribute to the development of affective disorders. Neural models propose an interplay of feedforward and feedback processes between subcortical areas, especially the amygdala and cortical areas such as the prefrontal or orbitofrontal cortex to be essential for successful emotion regulation (Phillips *et al*., 2008). A ventral area of the anterior cingulate cortex (ACC), the pregenual ACC (pgACC), is suggested as an integrative hub between subcortical and cortical areas (Phillips *et al*., 2008). Automatic emotion regulation is thought to be mediated by stimulating feedforward processes from subcortical to cortical areas, while voluntary cognitive mechanisms are mediated by downregulating feedback from cortical to subcortical areas (Fig. 1).

Automatic or 'intrinsic' emotion regulation is closely related to the direct experience of emotions. It starts automatically, is effortless and without awareness (Gyurak *et al*., 2011). It is considered as a protective factor against the development of depression (Joormann and Gotlib, 2010), while its absence is related to alexithymia and increased psychopathology (Green *et al*., 2007; Angst, 2008). Neuroimaging investigations of automatic emotion regulation revealed that glutamate (Glu) concentrations in the pgACC were related to emotional dysregulation in youth (Wozniak *et al*., 2012). Furthermore, depression, a disorder marked by aberrant automatic emotion regulation, has been found to be associated with activity and

CAMBRIDGE UNIVERSITY PRESS

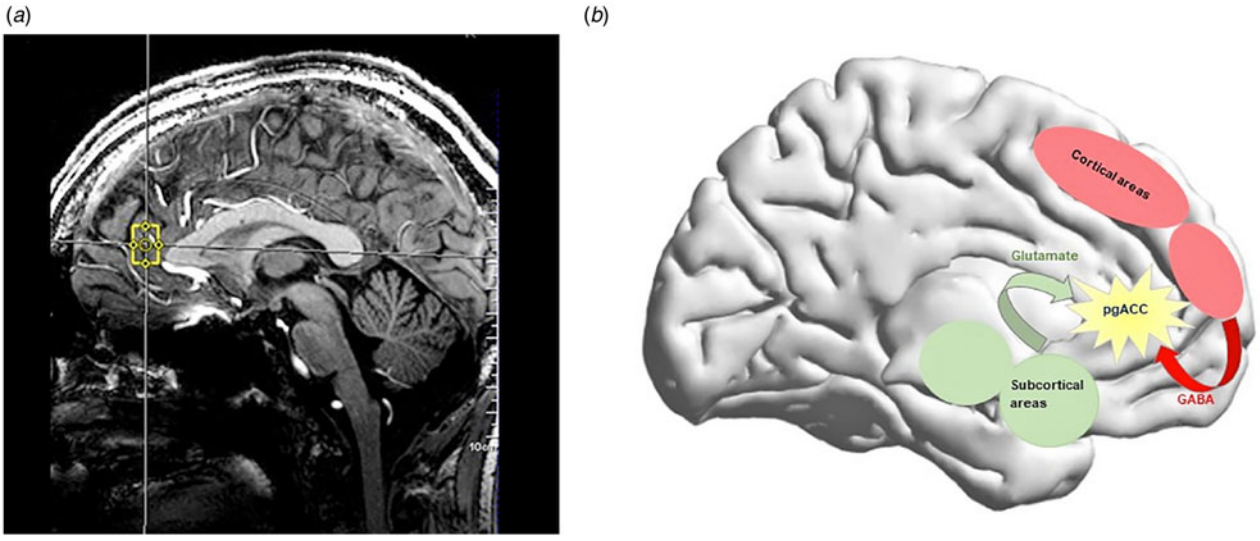

Fig. 1. (*a*) Voxel position of the spectroscopy voxel in the pgACC. (*b*) Schematic representation of GABAergic feedback projections and Glutamatergic feedforward projections. Adapted from Phillips *et al.* (2008), schematic brain figure from BrainNet Viewer (http://www.nitrc.org/projects/bnv/, Xia *et al.*, 2013).

glutamatergic neurotransmission in the pgACC (Horn *et al.*, 2010; Peng *et al.*, 2012; Victor *et al.*, 2013; Li *et al.*, 2014; Philippi *et al.*, 2015; Colic *et al.*, 2019).

A second aspect of emotion processing is voluntary or cognitive emotion regulation. In contrast to automatic emotion regulation, this process is consciously evoked and effortful (Gross, 1998; Gyurak *et al.*, 2011; Braunstein *et al.*, 2017). One aspect of voluntary emotion regulation is self-awareness – a cognitive process closely associated with reflective functioning (RF) (Gyurak *et al.*, 2011). RF is defined as ability to mentalize – the capacity to understand one's own and other's behaviors as expressions of mental states and feelings (Fonagy and Target, 1997) and reflects a cognitive understanding of emotions. Studies showed that mentalizing is an important factor for psychological well-being as low RF is associated with psychiatric conditions, such as depression (Toth *et al.*, 2008) or borderline personality disorder (Guttman and Laporte, 2002; Deborde *et al.*, 2012; New *et al.*, 2012). Mentalizing was associated with activity in ventromedial prefrontal and orbitofrontal cortex (Schurz *et al.*, 2015) and was affected by interpersonal stress (Nolte *et al.*, 2013). Moriguchi *et al.* (2007) reported a hypoactivation in these areas during mentalizing tasks in alexithymic subjects, indicating a possible disturbance in metabolic excitation/inhibition (E/I) balance. Local inhibitory metabolites were shown to correlate with the activity of the pgACC during emotional tasks (Northoff *et al.*, 2007), thus further emphasizing the importance of pgACC metabolism in emotion processing. In conclusion, voluntary cognitive emotion processing is in part mediated by projections from prefrontal areas to the cingulate cortex and further to subcortical structures, which are hypothesized to be modulated by GABAergic local circuitry (Northoff *et al.*, 2007; Phillips *et al.*, 2008; Wiebking *et al.*, 2014).

Deficits in emotion processing, regulation or experience are features of alexithymia, a personality trait describing a general lack of emotional understanding that is present in about 10% of population. Alexithymia is a multifaceted construct and integrates a cognitive emotion regulation deficit and an automatic emotion regulation deficit (Taylor, 2000). In line with this theory, general emotion regulation was repeatedly shown to be dysfunctional in alexithymia (Taylor and Bagby, 2004; Vermeulen *et al.*, 2006; Swart *et al.*, 2009; Venta *et al.*, 2013) and impairments in both types of emotion processing have been reported. Regarding cognitive emotion processing, it has been shown that reflective functioning is negatively associated with alexithymia (Antonsen *et al.*, 2014; Rothschild-Yakar *et al.*, 2018) and lower mentalizing skills are a risk factor for alexithymia (Moriguchi *et al.*, 2006; Swart *et al.*, 2009). Regarding automatic emotion regulation, it has been reported that behavior and neural activity (Pollatos and Gramann, 2012; van der Velde *et al.*, 2013) are altered in experiments eliciting automatic emotion processing (e.g. priming, masked emotional stimuli, Donges and Suslow, 2017). Additionally, alexithymia has been associated with habitual suppressive emotion regulation (Lane *et al.*, 2000; Swart *et al.*, 2009; Chen *et al.*, 2011; Walker *et al.*, 2011), which has been proposed as a primarily automatic process impairing emotional experience (Mauss *et al.*, 2007*a*, 2007*b*; Abler *et al.*, 2010). Alexithymia was previously described as a risk factor for affective disorders (Conrad *et al.*, 2009; Luminet, 2010; Leweke *et al.*, 2012). Nonetheless, the underlying mechanisms of alexithymia are still not fully understood (Salminen *et al.*, 1999). Neuroimaging investigations pointed toward ACC as a region of interest, identifying overlapping neuronal substrate for emotion regulation processes and alexithymia (Berthoz *et al.*, 2002; Leweke *et al.*, 2004; van der Velde *et al.*, 2013; Grabe *et al.*, 2014).

Inconsistent results of increased (Berthoz *et al.*, 2002; Mériau *et al.*, 2006; Heinzel *et al.*, 2012) or decreased ACC activity (Leweke *et al.*, 2004; Silani *et al.*, 2008; Bird *et al.*, 2010; Reker *et al.*, 2010) during emotional tasks have been reported in subjects with alexithymia. To overcome a potential task bias, magnetic resonance spectroscopy (MRS) studies subsequently showed an association between GABA concentration in the pgACC and alexithymia (Ernst *et al.*, 2014). Moreover, a general shift in neuronal integrity markers was found in the pgACC (Colic *et al.*, 2016). The latter study revealed pgACC as region of general association with alexithymia regardless of sex while other cingulate regions, such as dorsal ACC and posterior ACC had sex-specific associations. Congruently, volumetric studies also showed a negative association between pgACC volume and alexithymic features (Sturm and Levenson, 2011), specifying this region as a starting point of emotion regulation deficits, as expressed in alexithymia.

https://doi.org/10.1017/S0033291719001806 Published online by Cambridge University Press

Within the framework of emotion regulation proposed by Phillips *et al.* (2008), we attempt to offer a more integrated explanation of alexithymia, considering both voluntary and automatic emotion regulation processes and their differential biological substrates. We suggest that alexithymia is related to alterations in emotional experience in two complementary dimensions: automatic emotion regulation, characterized by a more immediate emotional experience, and cognitive regulation, characterized by self-awareness. We propose that these two regulation processes are linked to subcortical–cortical feedforward processes (automatic emotion experience) and cortical–subcortical feedback mechanisms (voluntary emotion regulation), which are in turn reflected by excitatory (glutamatergic) and inhibitory (GABAergic) inputs, respectively. We therefore focused on the pgACC as key region integrating these signals on both the metabolic and the behavioral level. We first tested an association between E/I balance, measured as glutamate to GABA ratio (Glu/GABA), in the pgACC and alexithymia. We additionally used the dorsal ACC (dACC) as a control region, to corroborate the regional specificity of both processes. Second, we assessed associations of emotion regulation facets with alexithymia and their respective metabolic contributions. We predicted that cognitive self-awareness would be associated with GABA, whereas we expected automatic emotion regulation to correlate with Glu levels in the pgACC.

Methods

Participants

Participants were 68 healthy volunteers (age = 26.15 ± 4.22, 30 women), recruited through advertisement and reimbursed for their participation. All subjects were screened for prior neurological or psychiatric illnesses with the German Version 5.0.0 of the Mini International Neuropsychiatric Interview (M.I.N.I.) (Ackenheil *et al.*, 1999) and underwent an interview with the study physician. The subjects completed three questionnaires concerning alexithymia, reflective functioning and emotional experience. Participants underwent a magnetic resonance session in the 7 T, where anatomical and MRS data were acquired. The ethical committee of the University of Magdeburg reviewed and approved the study. The study was conducted in accordance with the Declaration of Helsinki and all subjects gave written informed consent.

Psychometric tests

The Toronto Alexithymia Scale (TAS-20) has 20 items with a 5-point Likert scale. We used the total alexithymia score in our analysis. The original English version has good reliability and item consistency (Bagby *et al.*, 1994*a*, 1994*b*; Parker *et al.*, 2003) and comparable results were obtained for the German version (Bach *et al.*, 1996; Taylor *et al.*, 2003; Franz *et al.*, 2008).

The 'Skalen zum Erleben von Emotionen' [SEE, Emotional Experience Scales (Behr and Becker, 2004)] were employed to measure habitual emotion regulation experience. The questionnaire consists of 42 items divided into seven subscales, which are rated on a 5-point Likert scale. We used the subscale 'Experiencing Emotion Regulation' (EER), as alexithymia has been previously shown to be associated with deficient emotion regulation (Taylor and Taylor, 1997).

To measure mentalizing capacities, we used the Reflective Functioning Questionnaire, RFQ (Fonagy *et al.*, 2016). It uses a 7-point Likert scale and consists of 54 items. The scores are non-polar and higher scores represent lower mentalizing capacity. For analysis, we used the subscale assessing uncertainty about the mental state of oneself (LRFuS), as a measure for impaired self-awareness. The RFQ has satisfactory internal consistency and test-retest reliability (Fonagy *et al.*, 2016).

MRS data acquisition

MRI data were acquired with a Siemens 7T scanner using a 32-channel head array coil (Siemens, Erlangen, Germany). High-resolution *T*1-weighted anatomical MR images were obtained with magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TE = 2.73 ms, TR = 2300 ms, TI = 1050 ms, flip angle = 5°, bandwidth = 150 Hz/pixel, isotropic voxel size = 0.8 mm). The MR spectra were acquired from pgACC ($20 \times 15 \times 10$ mm^3) and dACC ($25 \times 15 \times 10$ mm^3) voxels with a STEAM sequence. The following scan parameters were used: TE = 20 ms, TR = 3000 ms, TM = 10 ms and 128 averages. Tissue water spectra were measured to serve as an internal concentration reference for quantification. LCModel (Stephen Provencher, Inc., Oakville, ON, Canada, V6.3.0) was used to analyze the spectral data (0.6–4.0 ppm). Concentrations were obtained for GABA and Glu [expressed using institutional units (i.u.)] together with their Cramér-Rao Lower Bound (CRLB) and full width at half maximum (FWHM) values. To ensure sufficient data quality, measurements with CRLB > 20%, FWHM > 24 Hz or signal-to-noise ratio (SNR) < 20 were excluded and data were visually inspected by two independent raters and excluded if both agreed on insufficient data (Li *et al.*, 2018; Ristow *et al.*, 2018). The ratio of glutamate to GABA was calculated as a representation of the E/I balance. The gray matter proportions used for tissue content correction were obtained from segmented anatomical *T*1 images using VBM8 (www.neuro.uni-jena.de/vbm) in SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). Co-registration of voxel location and *T*1 images was performed using an in-house script.

Statistical analysis

Several subjects had to be excluded for each analysis because of either incomplete questionnaires ($N_{TAS} = 1$, $N_{EER} = 12$, $N_{LRFuS} = 4$) or insufficient MRS data quality pgACC: $N = 4$ (2 FWHM, 2 insufficient curves), dACC: $N = 19$ (4 SNR, 3 CRLB, 12 insufficient curves). As some participants had multiple measures missing, the final sample sizes are stated for each analysis. The primary hypothesis of a differential association of alexithymia with the E/I balance in the pgACC compared to the dACC was assessed in a subsample ($N = 46$) with satisfactory MRS data quality in both regions. Subsequent analyses were focused only on pgACC, thereby increasing the sample size.

First, data were tested for distribution with the Smirnov–Kolmogorov test. Psychometric data were not normally distributed, thus nonparametric partial Spearman-rank correlations were used, thereby accounting for outliers. Age, sex and gray matter proportions were included as covariates. Furthermore, we calculated bootstrapped confidence intervals for all effects. The *p*-levels were adjusted for multiple comparisons by applying Bonferroni correction for each hypothesis separately. As the metabolite measures are not independent, we used an adjusted

https://doi.org/10.1017/S0033291719001806 Published online by Cambridge University Press

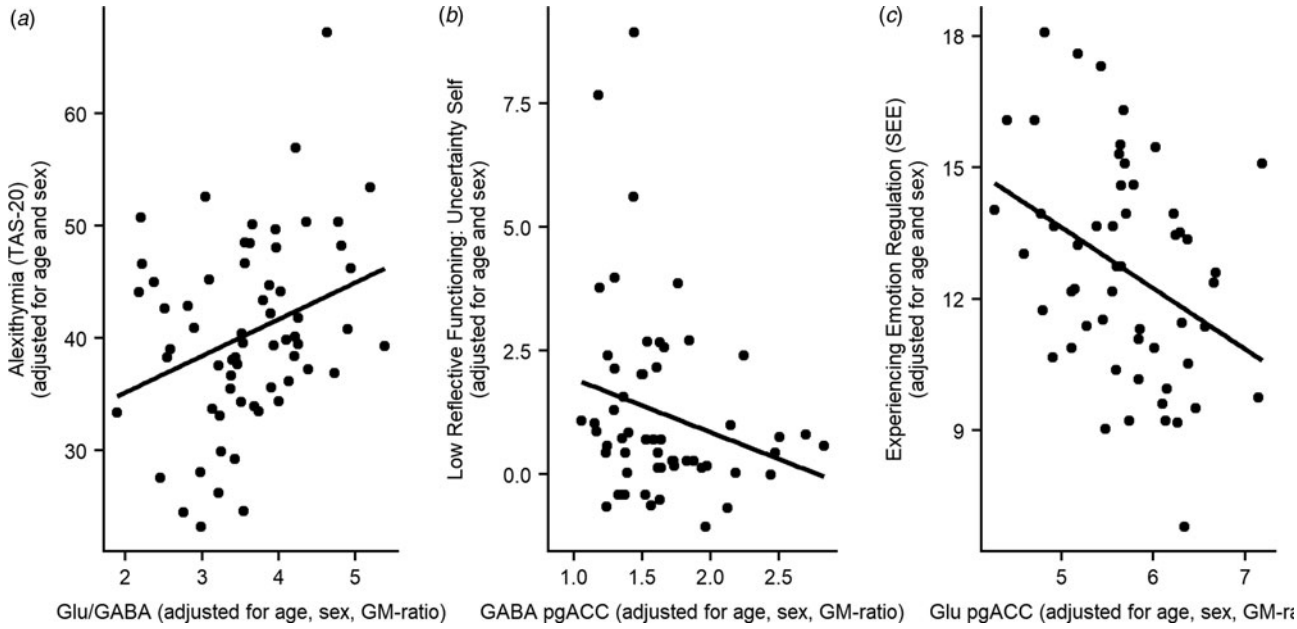

Fig. 2. Scatterplots of correlations between metabolite concentrations in the pgACC (corrected for age, sex and gray matter ratio) and alexithymia, automatic emotion regulation and reflective functioning (all corrected for age and sex). (*a*) Partial Spearman-rank correlation between alexithymia (TAS-20) and Glu/GABA corrected for age, sex and gray matter ratio, $\rho(58) = 0.30$, $p = 0.019$. (*b*) Spearman-rank correlation between experiencing emotion regulation (EER) and Glu corrected for age, sex and gray matter ratio, $\rho(49) = -0.37$, $p = 0.008$. (*c*) Spearman-rank correlation between Low Reflective Functioning: Uncertainty Self (LRFuS) and GABA corrected for age, sex and gray matter ratio, $\rho(52) = -0.28$, $p = .041$.

Bonferroni correction (Sankoh *et al.*, 1997) considering the mean correlation of $r = 0.35$ between metabolites (Glu/GABA, GABA and Glu). The significance threshold was $p_{corr} = 0.027$ for correlations regarding alexithymia, automatic emotion regulation or cognitive self-awareness with metabolite concentrations and $p_{corr} = 0.025$ for the correlations between TAS-20 and EER or LRFuS. Correlations between dACC/pgACC metabolite concentrations and alexithymia were compared with Steiger's *Z* coefficient for dependent correlations. All analyses were performed with SPSS (Release 20.0, SPSS, Inc., Chicago, IL, USA). Subsequently, we tested the specificity of the associations between questionnaires and metabolites by evaluating three multiple regressions, one for each metabolite including all three scales as independent variables and age, sex and gray matter ratio as covariates. To assess if the relationship of TAS-20 and the E/I balance is explained by alterations in reflective functioning or emotion regulation, we tested a mediation model with the same covariates and EER and LRFuS as proposed mediators. Significance of indirect effects was tested using bootstrapping.

Results

First, we determined the relationship of alexithymia with emotion regulation and reflective functioning. TAS-20 correlated with low levels of self-awareness characterized by high uncertainty [LRFuS, $N = 60$, $\rho(56) = 0.30$, $p = 0.024$, CI_{boot} (0.01–0.54)], corrected for multiple comparisons. In contrast, there was no association with emotion regulation [EER, $N = 56$, $\rho(52) = -0.14$, $p = 0.30$, CI_{boot} (−0.43 to 0.15)]. Explorative analysis revealed that EER and LRFuS were negatively correlated with each other [$N = 51$, $\rho(47) = -0.38$, $p = 0.006$, CI_{boot} (−0.62 to −0.11)].

We then tested the association between alexithymia and E/I balance in a subsample ($N = 46$) with data from pgACC and dACC, to elucidate regional specificity of pgACC. There TAS-20 correlated with the pgACC Glu/GABA ratio [$\rho(41) = 0.393$, $p = 0.009$, CI_{boot}(0.10–0.65)]. In contrast, the correlation between TAS-20 and the Glu/GABA ratio in the dACC was not significant [$\rho(41) = 0.015$, $p = 0.923$, CI_{boot} (−0.32 to 0.34)]. The regional specificity was confirmed by a significant difference in correlations ($Z = -2.11$, $p = 0.017$). Therefore, follow-up analyses focused on metabolites in the pgACC, which lead to an increased sample size ($N = 64$). In this larger sample Glu/GABA ratio was still significantly correlated to TAS-20 [$\rho(59) = 0.30$, $p = 0.019$, CI_{boot} (0.05–0.58), Fig. 2*a*]. Further analysis revealed an association of TAS-20 with GABA concentration in the pgACC on trend-level [uncorrected, $\rho(59) = -0.223$, $p = 0.087$, CI_{boot} (−0.46 to 0.04)], and no association with Glu [$\rho(59) = 0.043$, $p = 0.798$, CI_{boot} (−0.22 to 0.34)]. Similar results were found in the subsample of the primary analysis [GABA: $\rho(41) = -0.314$, $p = 0.04$, CI_{boot} (−0.58 to −0.003); Glu: $\rho(41) = 0.092$, $p = 0.557$, CI_{boot} (−0.23 to 0.43)].

After confirming that alexithymia is associated with E/I balance in the pgACC, we analyzed correlations between possibly implicated emotion regulation facets and metabolite concentrations in subsamples with complete data for the respective measures.

We found that higher experience of emotion regulation (EER) was significantly correlated with lower Glu levels in pgACC [N = 54, $\rho(49) = -0.37$, $p = 0.008$, CI_{boot} (−0.56 to −0.08)], Fig. 2*b*) on a corrected level, correlated with Glu/GABA on an uncorrected trend-level ($\rho(49) = -0.24$, $p = 0.095$, CI_{boot} (−0.51 to 0.05)], and not correlated with GABA levels [$\rho(49) = 0.06$, $p = 0.674$, CI_{boot} (−0.21 to 0.35)].

In contrast, cognitive contributions were more strongly related to the E/I balance. The Glu/GABA ratio was significantly correlated with low reflective functioning due to high uncertainty about mental states of oneself [$N = 57$, $\rho(52) = 0.398$, $p = 0.003$, CI_{boot} (0.14–0.58)], surviving Bonferroni-correction. A significant negative correlation with GABA [$\rho(52) = -0.28$, $p = 0.041$, CI_{boot} (−0.47 to −0.021), Fig. 2*c*] was additionally accompanied by a

https://doi.org/10.1017/S0033291719001806 Published online by Cambridge University Press

Table 1. Correlations of alexithymia, reflective functioning and emotion regulation with metabolite concentrations in pgACC

	Metabolite concentrations in pgACC					
	Glu		GABA		Glu/GABA	
	ρ	p	ρ	p	ρ	p
TAS-20 (alexithymia) $N = 58$	0.043	0.798	−0.223	0.087	0.300	0.019[A*]
SEE: experiencing emotion regulation (EER) $N = 49$	−0.370[A**]	0.008	0.060	0.674	−0.236	0.095
RFQ: uncertainty self (LRFuS) $N = 52$	0.264	0.053	−0.279[B*]	0.041	0.398	0.003[A**]

All correlations are partial spearman-rank correlations corrected for age, sex, and gray matter proportion.
[A*] $p < 0.05$, Bonferroni corrected, [A**] $p < 0.01$, Bonferroni corrected; [B*] $p < 0.05$, uncorrected.

trend-level correlation with Glu levels [$\rho(52) = 0.26$, $p = 0.053$, CI_{boot} (−0.0012 to 0.51)], although both correlations were on an uncorrected level (Table 1).

Lastly, we confirmed the general pattern of the correlation analyses in the subset ($N = 49$) with complete data for all variables using multiple regression analyses. The associations between Glu and EER [$\beta = -0.274$, $p = 0.09$, CI_{boot} (−0.534 to 0.033)] as well as GABA and LRFuS [$\beta = -0.361$, $p = 0.066$, CI_{boot} (−0.750 to −0.030)] were still significant on trend-level, while the other psychometric scales were not (Table 2). Critically, the association between alexithymia and Glu/GABA was not significant [$\beta =$ 0.003, $p = .985$, CI_{boot} (−0.361 to 0.257)] anymore when self-awareness [LRFuS, $\beta = 0.459$, $p = 0.011$, CI_{boot} (0.137–0.884)] was added as additional predictor, indicating that the relationship between alexithymia and E/I balance is partly explained by self-awareness. Indeed, a mediation model revealed a significant indirect [2.32, CI_{boot} (0.29–5.14), Fig. 3] effect for LRFuS as a mediator between pgACC Glu/GABA levels and alexithymia (TAS-20). In contrast, no significant indirect effect [0.11, CI_{boot} (−0.83 to 1.23)] was found for EER.

Table 2. Multiple regression analyses of metabolite concentrations in the pgACC by alexithymia and emotion regulation facets

	β	t	p	LCI_{boot}	UCI_{boot}
Glu/GABA					
TAS-20	0.003	0.019	0.985	−0.361	0.257
RFQ: LRFuS	0.459	2.648	0.011	0.137	0.884
SEE: EER	−0.130	−0.893	0.377	−0.460	0.214
GABA					
TAS-20	0.02	0.112	0.911	−0.285	0.388
RFQ: LRFuS	−0.361	−1.888	0.066	−0.750	−0.030
SEE: EER	0.007	0.045	0.964	−0.307	0.342
Glu					
TAS-20	−0.032	0.688	0.85	−0.459	0.321
RFQ: LRFuS	0.129	−0.182	0.49	−0.192	0.545
SEE: EER	−0.274	−1.730	0.09	−0.534	0.033

All models include covariates for age, sex, and gray matter proportion.

Discussion

By combining behavioral and metabolic profiling, we have shown that the pgACC E/I profile correlated with alexithymia. Furthermore, proposed constructs implicated in alexithymia were distinctively correlated with inhibitory and excitatory transmitter concentrations. Impaired autonomic emotion regulation was associated with Glu. In contrast, lack of cognitive self-awareness was most strongly correlated with the E/I balance, which seems to be mainly driven by an association with GABA. However, additional contributions of Glu could not be excluded.

Our findings add to recent observations outlining the importance of the pgACC in alexithymia, in terms of brain activity (van der Velde *et al.*, 2013) and metabolic associations (Ernst *et al.*, 2014; Colic *et al.*, 2016). The relationship between E/I balance in the pgACC (Table 1) and alexithymia supports our hypothesis that such an imbalance might represent an underlying mechanism in the complex pathophysiology of alexithymia. Multimodal imaging studies investigating E/I balance are still rare due to technical requirements for such MRS studies. Most commonly used editing sequences such as MEGA-PRESS, allowing sufficient detection accuracies for GABA also at 3 T, normally limit the accuracy for isolated glutamate measurements and allow solely the assessment of combined glutamine–glutamate (Glx) levels. Alternatives, e.g. 2D resolved spectroscopy would in principle overcome this problem, however, the inference on regional specificity is not possible, given the increased acquisition times per voxel (Dou *et al.*, 2013). We benefited from equally well-suited measurements for both components of the E/I balance and for the first time investigated its regional profile in alexithymia. We found that associations between alexithymia and Glu/GABA levels differed significantly between pgACC and dACC. Similarly, using multiple single voxel PRESS sequences at 3 T, Colic *et al.* (2016) found, that the association of alexithymia with N-acetylaspartate (NAA), a subtle indicator of neuronal integrity, was sex unspecific and restricted to the pgACC, while the association with Glx/NAA was specific for male participants in the dACC. Although extensive, our sample was not large enough to segregate sex-specific effects on the E/I balance; however, sex was considered as a covariate in our analysis. This and a more detailed investigation of relationships between subtle molecular and structural markers will have to be subject of future investigations.

Most importantly, different emotion regulation processes (automatic and cognitive) that are altered in alexithymia were indirectly related to the E/I balance through respective inhibitory and excitatory metabolites (Table 1). The sign of correlations herein needs to be interpreted in the context of the respective scaling: EER scores lowest for highest impairments in emotion regulation, while high-RFQ values indicate strongest deficits in self-awareness.

https://doi.org/10.1017/S0033291719001806 Published online by Cambridge University Press

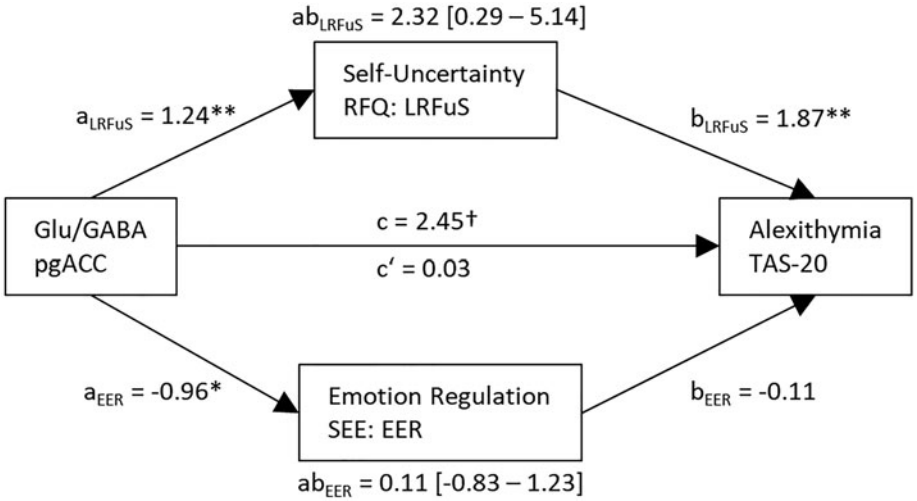

Fig. 3. The association between alexithymia (TAS-20) and Glu/GABA is mediated by Reflective Functioning (LRFuS). *$p < 0.05$, †$p < 0.10$.

The negative correlation of experiencing emotion regulation and Glu levels in the pgACC (Table 1) supports our hypothesis that deficits related to automatic emotion processing might be related to excitatory inputs to the pgACC. The importance of the pgACC in emotion regulation and experience has been extensively reported (Etkin *et al.*, 2011; Lee *et al.*, 2012; Victor *et al.*, 2012). Specifically, this association corresponds well with the emotion regulation model described by Phillips *et al.* (2008) which postulated that feedforward mechanisms, initiating in the amygdala, passing through the pgACC and ending in medial prefrontal areas, are essential for automatic emotion regulation. These connections have been found directly affected, e.g. in bipolar patients, where anatomical fiber connections of the uncinate fasciculus, linking hippocampus and amygdala with the orbitofrontal cortex, showed altered fractional anisotropy in diffusion tensor imaging (DTI) (Versace *et al.*, 2008; Lin *et al.*, 2011). The functional importance of Glu in the pgACC has been shown in functional connectivity between cortical and subcortical regions (Duncan *et al.*, 2011, 2013), activity at rest (Enzi *et al.*, 2012), neural activity in response to emotional stimuli (Walter *et al.*, 2009) and abnormal functional coupling (Horn *et al.*, 2010) of the pgACC to the anterior insula, another region associated with alexithymia (Ernst *et al.*, 2014). Importantly, glutamate metabolism of the pgACC is also altered in depressive disorders (Yüksel and Öngür, 2010; Taylor, 2014; Moriguchi *et al.*, 2018), for which alexithymia is a risk factor (Conrad *et al.*, 2009).

Surprisingly, the direct association of automatic emotion regulation and alexithymia was not significant. One possible explanation is that alexithymia, at least measured with TAS-20, reflects cognitive and self-aware aspects of deficits in emotional understanding. Other questionnaires, such as Bermond–Vorst Alexithymia Questionnaire, measure automatic processing deficits in alexithymia more directly (Goerlich-Dobre *et al.*, 2014) and thus might be better suited to assess associations with EER.

In contrast to automatic emotion processing, self-uncertainty was correlated with the Glu/GABA and, at least on a trend-level, with Glu (positive) and GABA (negative) concentrations separately (Table 1). While this suggests that cognitive emotion regulation is not only related to inhibitory top-down signaling, GABAergic processes may still dominate this relationship. Nonetheless, the positive correlation with Glu/GABA and the negative correlation with GABA indicate that subjects with low GABA levels show strongest deficits in self-awareness. This strengthens the idea that the association of Glu/GABA and alexithymia also reflects GABAergic top-down processes from the cognitive control network (Northoff *et al.*, 2007; Wiebking *et al.*, 2014) involved in generating self-awareness of emotions. The involvement of cognitive affect processing at the level of emotional self-awareness in alexithymia was supported by their positive correlation. More generally, the association between GABA and self-certainty corresponds to the emotion regulation model proposed by Phillips *et al.* (2008), in which voluntary emotion regulation processes are mediated by feedback mechanisms from lateral and medial prefrontal areas to the ACC. Additionally, these cognitive control networks and the related pgACC have been implicated in the cognitive experience of emotions and self-judgments (Kjaer *et al.*, 2002; Onoda *et al.*, 2009; Denny *et al.*, 2012; D'Argembeau *et al.*, 2012).

The positive relationship between alexithymia and uncertainty about one's own mental states replicates findings from Badoud *et al.* (2015), who observed a positive correlation of alexithymia with the RFQ uncertainty scale. Further, this corresponds well to the previously described cognitive dimension of alexithymia, which is characterized by diminished abilities to name, evaluate and express one's own feelings (Aleman and Kahn, 2005; Swart *et al.*, 2009).

Critically, cognitive self-awareness almost completely mediated the association between alexithymia and the E/I balance, whereas the experience of automatic emotion regulation did not. This suggests that the increased E/I balance in high alexithymia is predominantly driven by GABAergic processes of cognitive emotion regulation and self-awareness about feelings. In contrast, while automatic emotion regulation is related to Glu levels in pgACC, this relationship is not significantly reflected in alexithymia related alterations of the Glu/GABA ratio.

We could not explicitly replicate the previously reported specific association between the GABA concentration in pgACC and alexithymia in 22 subjects using MRS at 3 T by Ernst *et al.* (2014) Instead we found an association of Glu/GABA ratio in the pgACC with alexithymia, while GABA was only correlated on trend-level (Table 1). Methodological differences between the two studies might contribute to discrepant findings; next to a much smaller sample size the voxel position was considerably different. In the present study outlines of the ACC subregions were confined to histoarchitectural and receptor-architectural boundaries (Dou *et al.*, 2013), whereas Ernst *et al.* (2014) relied on larger voxels to

https://doi.org/10.1017/S0033291719001806 Published online by Cambridge University Press

reach sufficient SNR given the low field strengths. Furthermore, inclusion of correction for gray matter content in the respective voxels, which was not done by Ernst *et al.* (2014), has become feasible for most institutions and will hopefully lead to more consistent findings. Those limitations of the initial results by Ernst *et al.* (2014) on isolated GABAergic effects may explain the difference to our finding of a more general effect of the Glu/GABA ratio.

To the best of our knowledge, a relationship between self-uncertainty and experience of emotion regulation has so far not been reported. A negative correlation between these two scales indicates that high uncertainty regarding the mental and emotional state of oneself is associated with the reduced experience of emotion regulation. While implications of both concepts in psychopathologies are often investigated separately, this finding is in accordance with the emotion regulation theories proposing that self-awareness and introspection are essential for the regulation of emotions (Koole, 2009). Further evidence comes from a study by Sharp *et al.* (2011) describing a correlation between mentalizing and emotion regulation.

Limitations

The results and conclusions should be interpreted with caution, considering the demographic characteristics of the sample. The sample included only healthy subjects in the normal range of alexithymia. Accordingly, range and distribution included here (TAS-20: mean 40.33, S.D. 8.26, range 23–68) varied from large scale epidemiological samples as reported in Franz *et al.* (2008) (TAS-20: mean 48.8, S.D. 9.3; range 22–85). The screening for psychiatric disorders excluded participants with pathologic autistic characteristics, nonetheless there is considerable overlap between alexithymia and autism that we have not assessed with additional questionnaires. Therefore, further research is necessary to delineate alexithymia and autism-related processes. However, it has previously been shown, that alexithymia but not autism is related to emotion processing deficits (Bird *et al.*, 2010; Bird and Cook, 2013; Cook *et al.*, 2013). Subjects were within the age range of 18–40 and thus results are not representative for children, adolescents or elderly, who can have distinct metabolite profiles (Brooks *et al.*, 2001) and have been shown to differ in alexithymia scores and associated ACC gray matter volume (Paradiso *et al.*, 2008). Further, values for all scales, but most prominently cognitive self-awareness, were not normally distributed. While we used appropriated non-parametric statistical methods that are robust to outliers, e.g. Spearman-rank correlations and bootstrapping, replication in a more heterogeneous sample would be advisable. Finally, it should be considered that data measured in this study representing excitation or inhibition, is not assessing the neuronal activity of regions or fiber connectivity between regions, but rather reflects average metabolite concentrations regardless of neuron or glia-specific origin. This makes MRS a non-specific measurement and individual differences in MRS transmitter estimates do not directly measure differences in synaptic/vesicular concentrations from one represented neural subtype (e.g. long-range projections from the prefrontal cortex) within a region. This may be crucial particularly when interpreting the lack of specificity for GABAergic mechanisms related to RFQ. Furthermore, regional metabolite concentrations, while used to decipher the state of the region of interest, do not explain the direct structural connectivity underlying the hypothesized bottom up and top-down processes. It would be necessary to perform studies using DTI, to further determine the connectivity leading to metabolite profiles and explain underlying mechanisms of autonomic and cognitive aspects of emotion processing.

Conclusion

We demonstrated that alexithymia is associated with the pgACC E/I balance. Variance in E/I balance seems to incorporate individual variations of GABA and Glu levels, which were shown to correlate differentially with automatic emotional experience and cognitive self-awareness. Although scales of automatic emotional experience and cognitive self-awareness dimensions were correlated with each other, their contribution to alexithymic features seems to reflect distinct biological mechanisms of feedforward and feedback control, which are integrated in this area and are important for general emotion regulation.

References

Abler B, Hofer C, Walter H, Erk S, Hoffmann H, Traue HC and Kessler H (2010) Habitual emotion regulation strategies and depressive symptoms in healthy subjects predict fMRI brain activation patterns related to major depression. *Psychiatry Research: Neuroimaging* **183**, 105–113.

Ackenheil M, Stotz-Ingenlath G, Dietz-Bauer R and Vossen A (1999) MINI Mini International Neuropsychiatric Interview, German version 5.0. 0 DSM IV. *Psychiatrische Universitätsklinik München, Germany*.

Aleman A and Kahn R (2005) Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? *Progress in Neurobiology* **77**, 283–298.

Angst J (2008) Bipolar disorder-methodological problems and future perspectives. *Dialogues in Clinical Neuroscience* **10**, 129.

Antonsen BT, Klungsøyr O, Kamps A, Hummelen B, Johansen MS, Pedersen G, Urnes Ø, Kvarstein EH, Karterud S and Wilberg T (2014) Step-down versus outpatient psychotherapeutic treatment for personality disorders: 6-year follow-up of the Ullevål personality project. *BMC Psychiatry* **14**, 119.

Bach M, Bach D, de Zwaan M, Serim M and Böhmer F (1996) Validation of the German version of the 20-item Toronto Alexithymia Scale in normal persons and psychiatric patients. *Psychotherapie, Psychosomatik, Medizinische Psychologie* **46**, 23–28.

Badoud D, Luyten P, Fonseca-Pedrero E, Eliez S, Fonagy P and Debbané M (2015) The French version of the Reflective Functioning Questionnaire: validity data for adolescents and adults and Its association with non-suicidal self-injury. *PLoS ONE* **10**, e0145892.

Bagby RM, Parker JDA and Taylor GJ (1994*a*) The twenty-item Toronto Alexithymia scale – I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research* **38**, 23–32.

Bagby RM, Taylor GJ and Parker JDA (1994*b*) The twenty-item Toronto Alexithymia scale – II. Convergent, discriminant, and concurrent validity. *Journal of Psychosomatic Research* **38**, 33–40.

Behr M and Becker M (2004) *SEE: Skalen zum Erleben von Emotionen*. Göttingen: Hogrefe, Verlag für Psychologie.

Berthoz S, Artiges E, Van de Moortele P-F, Poline J-B, Rouquette S, Consoli SM and Martinot J-L (2002) Effect of impaired recognition and expression of emotions on frontocingulate cortices: an fMRI study of men with alexithymia. *American Journal of Psychiatry* **159**, 961–967.

Bird G and Cook R (2013) Mixed emotions: the contribution of alexithymia to the emotional symptoms of autism. *Translational Psychiatry* **3**, e285.

Bird G, Silani G, Brindley R, White S, Frith U and Singer T (2010) Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain* **133**, 1515–1525.

Braunstein LM, Gross JJ and Ochsner KN (2017) Explicit and implicit emotion regulation: a multi-level framework. *Social Cognitive and Affective Neuroscience* **12**, 1545–1557.

Brooks JCW, Roberts N, Kemp GJ, Gosney MA, Lye M and Whitehouse GH (2001) A proton magnetic resonance spectroscopy study of age-related

https://doi.org/10.1017/S0033291719001806 Published online by Cambridge University Press

changes in frontal lobe metabolite concentrations. *Cerebral Cortex* **11**, 598–605.

Chen J, Xu T, Jing J and Chan RC (2011) Alexithymia and emotional regulation: a cluster analytical approach. *BMC Psychiatry* **11**, 33.

Colic L, Demenescu LR, Li M, Kaufmann J, Krause AL, Metzger C and Walter M (2016) Metabolic mapping reveals sex-dependent involvement of default mode and salience network in alexithymia. *Social Cognitive and Affective Neuroscience* **11**, 289–298.

Colic L, von Düring F, Denzel D, Demenescu LR, Lord A, Martens L, Lison S, Frommer J, Vogel M, Kaufmann J, Speck O, Li M and Walter M (2019) Rostral anterior cingulate Gln/Glu disbalance in major depressive disorder depends on symptom severity. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, in press.

Conrad R, Wegener I, Imbierowicz K, Liedtke R and Geiser F (2009) Alexithymia, temperament and character as predictors of psychopathology in patients with major depression. *Psychiatry Research* **165**, 137–144.

Cook R, Brewer R, Shah P and Bird G (2013) Alexithymia, not autism, predicts poor recognition of emotional facial expressions. *Psychological Science* **24**, 723–732.

D'Argembeau A, Jedidi H, Balteau E, Bahri M, Phillips C and Salmon E (2012) Valuing one's self: medial prefrontal involvement in epistemic and emotive investments in self-views. *Cerebral Cortex* **22**, 659–667.

Deborde A-S, Miljkovitch R, Roy C, Dugré-Le Bigre C, Pham-Scottez A, Speranza M and Corcos M (2012) Alexithymia as a mediator between attachment and the development of borderline personality disorder in adolescence. *Journal of Personality Disorders* **26**, 676–688.

Denny BT, Kober H, Wager TD and Ochsner KN (2012) A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of Cognitive Neuroscience* **24**, 1742–1752.

Donges U-S and Suslow T (2017) Alexithymia and automatic processing of emotional stimuli: a systematic review. *Reviews in the Neurosciences* **28**, 247–264.

Dou W, Palomero-Gallagher N, van Tol M-J, Kaufmann J, Zhong K, Bernstein H-G, Heinze H-J, Speck O and Walter M (2013) Systematic regional variations of GABA, glutamine, and glutamate concentrations follow receptor fingerprints of human cingulate cortex. *Journal of Neuroscience* **33**, 12698–12704.

Duncan NW, Enzi B, Wiebking C and Northoff G (2011) Involvement of glutamate in rest-stimulus interaction between perigenual and supragenual anterior cingulate cortex: a combined fMRI-MRS study. *Human Brain Mapping* **32**, 2172–2182.

Duncan NW, Wiebking C, Tiret B, Marjańska M, Hayes DJ, Lyttleton O, Doyon J and Northoff G (2013) Glutamate concentration in the medial prefrontal cortex predicts resting-state cortical-subcortical functional connectivity in humans. *PLoS ONE* **8**, e60312.

Enzi B, Duncan NW, Kaufmann J, Tempelmann C, Wiebking C and Northoff G (2012) Glutamate modulates resting state activity in the perigenual anterior cingulate cortex – a combined fMRI–MRS study. *Neuroscience* **227**, 102–109.

Ernst J, Böker H, Hättenschwiler J, Schüpbach D, Northoff G, Seifritz E and Grimm S (2014) The association of interoceptive awareness and alexithymia with neurotransmitter concentrations in insula and anterior cingulate. *Social Cognitive and Affective Neuroscience* **9**, 857–863.

Etkin A, Egner T and Kalisch R (2011) Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences* **15**, 85–93.

Fonagy P and Target M (1997) Attachment and reflective function: their role in self-organization. *Development and Psychopathology* **9**, 679–700.

Fonagy P, Luyten P, Moulton-Perkins A, Lee Y-W, Warren F, Howard S, Ghinai R, Fearon P and Lowyck B (2016) Development and validation of a self-report measure of mentalizing: the reflective functioning questionnaire. *PLoS ONE* **11**, e0158678.

Franz M, Popp K, Schaefer R, Sitte W, Schneider C, Hardt J, Decker O and Braehler E (2008) Alexithymia in the German general population. *Social Psychiatry and Psychiatric Epidemiology* **43**, 54–62.

Goerlich-Dobre KS, Bruce L, Martens S, Aleman A and Hooker CI (2014) Distinct associations of insula and cingulate volume with the cognitive and affective dimensions of alexithymia. *Neuropsychologia* **53**, 284–292.

Grabe HJ, Wittfeld K, Hegenscheid K, Hosten N, Lotze M, Janowitz D, Völzke H, John U, Barnow S and Freyberger HJ (2014) Alexithymia and brain gray matter volumes in a general population sample. *Human Brain Mapping* **35**, 5932–5945.

Green MJ, Cahill CM and Malhi GS (2007) The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. *Journal of Affective Disorders* **103**, 29–42.

Gross JJ (1998) The emerging field of emotion regulation: an integrative review. *Review of General Psychology* **2**, 271–299.

Guttman H and Laporte L (2002) Alexithymia, empathy, and psychological symptoms in a family context. *Comprehensive Psychiatry* **43**, 448–455.

Gyurak A, Gross JJ and Etkin A (2011) Explicit and implicit emotion regulation: a dual-process framework. *Cognition and Emotion* **25**, 400–412.

Heinzel A, Minnerop M, Schäfer R, Müller H-W, Franz M and Hautzel H (2012) Alexithymia in healthy young men: a voxel-based morphometric study. *Journal of Affective Disorders* **136**, 1252–1256.

Horn DI, Yu C, Steiner J, Buchmann J, Kaufmann J, Osoba A, Eckert U, Zierhut K, Schiltz K, He H, Biswal B, Bogerts B and Walter M (2010) Glutamatergic and resting-state functional connectivity correlates of severity in major depression – the role of pregenual anterior cingulate cortex and anterior insula. *Frontiers in Systems Neuroscience* **4**, 33.

Joormann J and Gotlib IH (2010) Emotion regulation in depression: relation to cognitive inhibition. *Cognition and Emotion* **24**, 281–298.

Kjaer TW, Bertelsen C, Piccini P, Brooks D, Alving J and Lou HC (2002) Increased dopamine tone during meditation-induced change of consciousness. *Cognitive Brain Research* **13**, 255–259.

Koole SL (2009) The psychology of emotion regulation: an integrative review. *Cognition and Emotion* **23**, 4–41.

Lane R, Sechrest L, Riedel R, Shapiro D and Kaszniak A (2000) Pervasive emotion recognition deficit common to alexithymia and the repressive coping style. *Psychosomatic Medicine* **62**, 492–501.

Lee H, Heller AS, van Reekum CM, Nelson B and Davidson RJ (2012) Amygdala–prefrontal coupling underlies individual differences in emotion regulation. *NeuroImage* **62**, 1575–1581.

Leweke F, Stark R, Milch W, Kurth R, Schienle A, Kirsch P, Stingl M, Reimer C and Vaitl D (2004) Neuronale Aktivitätsmuster auf affektinduktive Reize bei Alexithymie. *PPmP - Psychotherapie · Psychosomatik · Medizinische Psychologie* **54**, 437–444.

Leweke F, Leichsenring F, Kruse J and Hermes S (2012) Is alexithymia associated with specific mental disorders? *Psychopathology* **45**, 22–28.

Li M, Metzger CD, Li W, Safron A, van Tol M-J, Lord A, Krause AL, Borchardt V, Dou W, Genz A, Heinze H-J, He H and Walter M (2014) Dissociation of glutamate and cortical thickness is restricted to regions subserving trait but not state markers in major depressive disorder. *Journal of Affective Disorders* **169**, 91–100.

Li M, Woelfer M, Colic L, Safron A, Chang C, Heinze H-J, Speck O, Mayberg HS, Biswal BB, Salvadore G, Fejtova A and Walter M (2018) Default mode network connectivity change corresponds to ketamine's delayed glutamatergic effects. *European Archives of Psychiatry and Clinical Neuroscience*, in press.

Lin F, Weng S, Xie B, Wu G and Lei H (2011) Abnormal frontal cortex white matter connections in bipolar disorder: a DTI tractography study. *Journal of Affective Disorders* **131**, 299–306.

Luminet O (2010) Commentary on the paper 'Is alexithymia a risk factor for major depression, personality disorder, or alcohol use disorders? A prospective population-based study'. *Journal of Psychosomatic Research* **68**, 275–277.

Mauss IB, Bunge SA and Gross JJ (2007*a*) Automatic emotion regulation. *Social and Personality Psychology Compass* **1**, 146–167.

Mauss IB, Cook CL and Gross JJ (2007*b*) Automatic emotion regulation during anger provocation. *Journal of Experimental Social Psychology* **43**, 698–711.

Mériau K, Wartenburger I, Kazzer P, Prehn K, Lammers C-H, van der Meer E, Villringer A and Heekeren HR (2006) A neural network reflecting individual differences in cognitive processing of emotions during perceptual decision making. *NeuroImage* **33**, 1016–1027.

Moriguchi Y, Ohnishi T, Lane RD, Maeda M, Mori T, Nemoto K, Matsuda H and Komaki G (2006) Impaired self-awareness and theory of mind: an fMRI study of mentalizing in alexithymia. *NeuroImage* **32**, 1472–1482.

Moriguchi Y, Maeda M, Igarashi T, Ishikawa T, Shoji M, Kubo C and Komaki G (2007) Age and gender effect on alexithymia in large,

Japanese community and clinical samples: a cross-validation study of the Toronto Alexithymia Scale (TAS-20). *Biopsychosocial Medicine* **1**, 7.

Moriguchi S, Takamiya A, Noda Y, Horita N, Wada M, Tsugawa S, Plitman E, Sano Y, Tarumi R, ElSalhy M, Katayama N, Ogyu K, Miyazaki T, Kishimoto T, Graff-Guerrero A, Meyer JH, Blumberger DM, Daskalakis ZJ, Mimura M and Nakajima S (2018) Glutamatergic neurometabolite levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. *Molecular Psychiatry* **24**, 952–964.

New AS, aan het Rot M, Ripoll LH, Perez-Rodriguez MM, Lazarus S, Zipursky E, Weinstein SR, Koenigsberg HW, Hazlett EA, Goodman M and Siever LJ (2012) Empathy and alexithymia in borderline personality disorder: clinical and laboratory measures. *Journal of Personality Disorders* **26**, 660–675.

Nolte T, Bolling DZ, Hudac C, Fonagy P, Mayes LC and Pelphrey KA (2013) Brain mechanisms underlying the impact of attachment-related stress on social cognition. *Frontiers in Human Neuroscience* **7**, 816.

Northoff G, Walter M, Schulte RF, Beck J, Dydak U, Henning A, Boeker H, Grimm S and Boesiger P (2007) GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. *Nature Neuroscience* **10**, 1515–1517.

Onoda K, Okamoto Y, Nakashima K, Nittono H, Ura M and Yamawaki S (2009) Decreased ventral anterior cingulate cortex activity is associated with reduced social pain during emotional support. *Social Neuroscience* **4**, 443–454.

Paradiso A, Berardino R, de Pinto MC, Sanita di Toppi L, Storelli MM, Tommasi F and De Gara L (2008) Increase in ascorbate-glutathione metabolism as local and precocious systemic responses induced by cadmium in durum wheat plants. *Plant and Cell Physiology* **49**, 362–374.

Parker JDA, Taylor GJ and Bagby RM (2003) The 20-item Toronto Alexithymia Scale. *Journal of Psychosomatic Research* **55**, 269–275.

Peng D-H, Shen T, Zhang J, Huang J, Liu J, Liu S-Y, Jiang K, Xu Y-F and Fang Y-R (2012) Abnormal functional connectivity with mood regulating circuit in unmedicated individual with major depression: a resting-state functional magnetic resonance study. *Chinese Medical Journal* **125**, 3701–3706.

Philippi CL, Motzkin JC, Pujara MS and Koenigs M (2015) Subclinical depression severity is associated with distinct patterns of functional connectivity for subregions of anterior cingulate cortex. *Journal of Psychiatric Research* **71**, 103–111.

Phillips M, Ladouceur C and Drevets W (2008) A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry* **13**, 829–857.

Pollatos O and Gramann K (2012) Attenuated modulation of brain activity accompanies emotion regulation deficits in alexithymia. *Psychophysiology* **49**, 651–658.

Reker M, Ohrmann P, Rauch AV, Kugel H, Bauer J, Dannlowski U, Arolt V, Heindel W and Suslow T (2010) Individual differences in alexithymia and brain response to masked emotion faces. *Cortex* **46**, 658–667.

Ristow I, Li M, Colic L, Marr V, Födisch C, von Düring F, Schiltz K, Drumkova K, Witzel J, Walter H, Beier K, Kruger THC, Ponseti J, Schiffer B and Walter M (2018) Pedophilic sex offenders are characterised by reduced GABA concentration in dorsal anterior cingulate cortex. *NeuroImage: Clinical* **18**, 335–341.

Rothschild-Yakar L, Peled M, Enoch-Levy A, Gur E and Stein D (2018) 'Eating me up from inside': a pilot study of mentalization of self and others and emotion regulation strategies among young women with eating disorders. *The Israel Journal of Psychiatry and Related Sciences* **55**, 35–43.

Salminen JK, Saarijärvi S, Äärelä E, Toikka T and Kauhanen J (1999) Prevalence of alexithymia and its association with sociodemographic variables in the general population of Finland. *Journal of Psychosomatic Research* **46**, 75–82.

Sankoh AJ, Huque MF and Dubey SD (1997) Some comments on frequently used multiple endpoint adjustment methods in clinical trials. *Statistics in Medicine* **16**, 2529–2542.

Schurz M, Kogler C, Scherndl T, Kronbichler M and Kühberger A (2015) Differentiating self-projection from simulation during mentalizing: evidence from fMRI. *PLoS ONE* **10**, e0121405.

Sharp C, Pane H, Ha C, Venta A, Patel AB, Sturek J and Fonagy P (2011) Theory of mind and emotion regulation difficulties in adolescents with borderline traits. *Journal of the American Academy of Child & Adolescent Psychiatry* **50**, 563–573, e1.

Silani G, Bird G, Brindley R, Singer T, Frith C and Frith U (2008) Levels of emotional awareness and autism: an fMRI study. *Social Neuroscience* **3**, 97–112.

Sturm VE and Levenson RW (2011) Alexithymia in neurodegenerative disease. *Neurocase* **17**, 242–250.

Swart M, Kortekaas R and Aleman A (2009) Dealing with feelings: characterization of trait alexithymia on emotion regulation strategies and cognitive-emotional processing. *PLoS ONE* **4**, e5751.

Taylor GJ (2000) Recent developments in alexithymia theory and research. *The Canadian Journal of Psychiatry* **45**, 134–142.

Taylor MJ (2014) Could glutamate spectroscopy differentiate bipolar depression from unipolar? *Journal of Affective Disorders* **167**, 80–84.

Taylor GJ and Taylor HL (1997) Alexithymia. In McCallum M and Piper W (eds), *Psychological Mindedness: A Contemporary Understanding*. Munich: Lawrence Erlbaum, pp. 77–104.

Taylor GJ and Bagby RM (2004) New trends in alexithymia research. *Psychotherapy and Psychosomatics* **73**, 68–77.

Taylor GJ, Bagby RM and Parker JDA (2003) The 20-item Toronto Alexithymia Scale. *Journal of Psychosomatic Research* **55**, 277–283.

Toth E, Gersner R, Wilf-Yarkoni A, Raizel H, Dar DE, Richter-Levin G, Levit O and Zangen A (2008) Age-dependent effects of chronic stress on brain plasticity and depressive behavior: coping with chronic stress. *Journal of Neurochemistry* **107**, 522–532.

van der Velde J, Servaas MN, Goerlich KS, Bruggeman R, Horton P, Costafreda SG and Aleman A (2013) Neural correlates of alexithymia: a meta-analysis of emotion processing studies. *Neuroscience & Biobehavioral Reviews* **37**, 1774–1785.

Venta A, Hart J and Sharp C (2013) The relation between experiential avoidance, alexithymia and emotion regulation in inpatient adolescents. *Clinical Child Psychology and Psychiatry* **18**, 398–410.

Vermeulen N, Luminet O and Corneille O (2006) Alexithymia and the automatic processing of affective information: evidence from the affective priming paradigm. *Cognition & Emotion* **20**, 64–91.

Versace A, Almeida JRC, Hassel S, Walsh ND, Novelli M, Klein CR, Kupfer DJ and Phillips ML (2008) Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. *Archives of General Psychiatry* **65**, 1041–1052.

Victor TA, Furey ML, Fromm SJ, Bellgowan PSF, Öhman A and Drevets WC (2012) The extended functional neuroanatomy of emotional processing biases for masked faces in major depressive disorder. *PLoS ONE* **7**, e46439.

Victor TA, Furey ML, Fromm SJ, Öhman A and Drevets WC (2013) Changes in the neural correlates of implicit emotional face processing during antidepressant treatment in major depressive disorder. *The International Journal of Neuropsychopharmacology* **16**, 2195–2208.

Walker S, O'Connor DB and Schaefer A (2011) Brain potentials to emotional pictures are modulated by alexithymia during emotion regulation. *Cognitive, Affective, & Behavioral Neuroscience* **11**, 463–475.

Walter M, Henning A, Grimm S, Schulte RF, Beck J, Dydak U, Schnepf B, Boeker H, Boesiger P and Northoff G (2009) The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. *Archives of General Psychiatry* **66**, 478–486.

Wiebking C, Duncan NW, Qin P, Hayes DJ, Lyttelton O, Gravel P, Verhaeghe J, Kostikov AP, Schirrmacher R, Reader AJ, Bajbouj M and Northoff G (2014) External awareness and GABA-A multimodal imaging study combining fMRI and [^{18}F]flumazenil-PET: GABA and External Awareness. *Human Brain Mapping* **35**, 173–184.

Wozniak J, Gönenç A, Biederman J, Moore C, Joshi G, Georgiopoulos A, Hammerness P, McKillop H, Lukas SE and Henin A (2012) A magnetic resonance spectroscopy study of the anterior cingulate cortex in youth with emotional dysregulation. *The Israel Journal of Psychiatry and Related Sciences* **49**, 62–69.

Xia M, Wang J and He Y (2013) BrainNet viewer: a network visualization tool for human brain connectomics. *PLOS ONE* **8**, e68910.

Yüksel C and Öngür D (2010) Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biological Psychiatry* **68**, 785–794.

https://doi.org/10.1017/S0033291719001806 Published online by Cambridge University Press