The association of interoceptive awareness and alexithymia with neurotransmitter concentrations in insula and anterior cingulate

Jutta Ernst,1 Heinz Böker,1 Joe Hättenschwiler,2 Daniel Schüpbach,1 Georg Northoff,3 Erich Seifritz,1 and Simone Grimm1,4,5

1Clinic for Affective Disorders and General Psychiatry, Department of Psychiatry, Psychotherapy, and Psychosomatics, Psychiatric University Hospital, 8029 Zurich, Switzerland, 2Center for Anxiety and Depression, 8008 Zurich, Switzerland, 3University of Ottawa, Institute of Mental Health Research, Ottawa K1Z 7K4, Canada, 4Department of Psychiatry, Campus Benjamin Franklin, Charité, 14050 Berlin, and 5Languages of Emotion Cluster of Excellence, Freie Universität Berlin, 14195 Berlin, Germany

Alexithymia and increased interoceptive awareness have been associated with affective disorders as well as with altered insula and anterior cingulate cortex (ACC) function. Brain imaging studies have demonstrated an association between neurotransmitter function and affective disorders as well as personality traits. Here, we first examined the relationship between alexithymic facets as assessed with the Toronto Alexithymia Scale (TAS-20) and interoceptive awareness (assessed with the Body Perception Questionnaire) in 18 healthy subjects. Second, we investigated their association with glutamate and gamma-aminobutyric acid (GABA) concentrations in the left insula and the ACC using 3-Tesla proton magnetic resonance spectroscopy. Behaviorally, we found a close association between alexithymia and interoceptive awareness. Furthermore, glutamate levels in the left insula were positively associated with both alexithymia and awareness of autonomic nervous system reactivity, while GABA concentrations in ACC were selectively associated with alexithymia. Although preliminary, our results suggest that increased glutamate-mediated excitatory transmission related to enhanced insula activity reflects increased interoceptive awareness in alexithymia. Suppression of the unspecific emotional arousal evoked by increased awareness of bodily responses in alexithymics might thus be reflected in decreased neuronal activity mediated by increased GABA concentration in ACC.

Keywords: alexithymia; interoceptive awareness; neurotransmitter; proton magnetic resonance spectroscopy

INTRODUCTION

The biological underpinnings of individual differences in personality traits are incompletely understood. Although there have been several functional imaging studies investigating the neuronal activity signatures of personality traits (Johnson et al., 1999; Canli et al., 2001, Canli and Amin, 2002; Canli, 2004; Kumari et al., 2004; Deckersbach et al., 2006; Vaidya et al., 2007; Simon et al., 2010; Brühl et al., 2011), less is known about their association with neurotransmitter concentrations. Specific personality traits such as low extraversion, high neuroticism (Watson and Clark, 1997; Kotov et al., 2010) and alexithymia (Luminit, 2010; Leweke et al., 2012) have been linked to increased vulnerability to psychiatric disorders, specifically affective disorders, which are in turn associated with dysfunctional neurotransmission (Mathew et al., 2008; Sanacora et al., 2008; Walter et al., 2009; Hashimoto et al., 2010; Grimm et al., 2012a). Of specific relevance with regard to affective disorders are findings of a negative correlation between prefrontal glutamate (Glu) concentrations, mental perspective taking and extraversion (Montag et al., 2008; Grimm et al., 2012b). In addition, decreased and increased ACC gamma-aminobutyric acid (GABA) concentrations, respectively, have been associated with extraversion and harm avoidance (Kim et al., 2009; Goto et al., 2010) in healthy subjects. Thus, the investigation of alexithymia might be promising, since it is marked by cognitive and affective features including difficulties in identifying and describing feelings as well as in distinguishing feelings from bodily sensations of emotional arousal (Franz et al., 2008). Alexithymics can be characterized by low extraversion, high neuroticism, high harm avoidance, low self-directedness and low perspective taking (Wise et al., 1992; Guttmann and Laporte, 2002; Picardi et al., 2005). This personality trait is prevalent in 10% of the general population (Linden et al., 1995; Salminen et al., 1999) and its facets have been identified as a risk factor for affective disorders (Conrad et al., 2009; Luminit, 2010; Leweke et al., 2012). Results from neuroimaging studies indicate a crucial role of insula and ACC in mediating alexithymic features. In both regions, heterogeneous findings with either increased (Berthoz et al., 2002; Mériaux et al., 2006; Frewen et al., 2008; Karlsson et al., 2008; Heinzel et al., 2010) or decreased (Leweke et al., 2004; Karlsson et al., 2008; Silani et al., 2008; Bird et al., 2010; Reker et al., 2010) response to emotion stimuli have been reported in alexithymic individuals. Data on structural changes in alexithymia are inconsistent, with studies reporting a correlation between alexithymia and the size of the right ACC (Gündel et al., 2004), smaller volumes of ACC, medial temporal gyrus and anterior insula in alexithymic women (Borsci et al., 2009) as well as no volume difference in alexithymic men (Heinzel et al., 2012). Reduced gray matter volume in the ACC has been recently associated with an interaction between two polymorphisms on the BDNF and DRD2/ANKK1 gene (Montag et al., 2010) which in turn are also associated with alexithymia (Walter et al., 2011). Insula and ACC are implicated in processing of affect, self-awareness and mood and show functional alterations in affective disorders (Bush et al., 2000; Mayberg, 2003; Phillips et al., 2003; Grimm et al., 2009, 2011; Horn et al., 2010; Wiebking et al., 2010). A recently proposed model by Medford and Critchley (2010) states that the conjoint activity of insula and ACC is crucial for the production of subjective feelings and co-ordinating appropriate responses to internal and external stimuli, thereby providing the neural basis of self-awareness. The insula also has a central role in attention to interoceptive states (Critchley et al., 2004; Pollatos et al., 2007; Menon and Uddin, 2010;
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Materials and methods

Subjects

Healthy subjects [13 women and 9 men, mean age 27.12 (s.d. 7.6)] were recruited through online study advertisements. Exclusion criteria were major medical illnesses, histories of seizures, head trauma with loss of consciousness and pregnancy. In addition, subjects who met criteria for any psychiatric or neurologic disorder or had a history of substance dependence were excluded from the study. All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). The study was performed in accordance with the latest version of the Declaration of Helsinki and approved by the State of Zurich’s Review Board. All subjects gave written informed consent. Subjects were investigated with proton magnetic resonance spectroscopy (1H-MRS), the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994a, German version by Bach et al., 1996) and the Body Perception Questionnaire (BPQ; Porges, 1993). The TAS-20 is a self-administered questionnaire that captures two affective and one cognitive alexithymic facets, respectively: difficulties identifying feelings (e.g. I am often confused about what emotion I am feeling), difficulties describing feelings (DDF, e.g. it is difficult for me to find the right words for my feelings) and a concrete, externally oriented thinking (EOT) style (e.g. being in touch with emotion is essential; inverted item). The scale has a good psychometric quality (Cronbach’s α > 0.80; Bagby et al., 1994b) and is widely used in emotion research, so that comparability with previous studies is assured. Its psychometric properties have previously been investigated in healthy subjects (Franz et al., 2008). Each item of the TAS-20 is rated on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The BPQ (Porges, 1993) is a 96 item self-report instrument to assess body perception and interoceptive awareness on four subscales [awareness subscale: subjects are asked to imagine how aware they are of their bodily processes (e.g. swallowing frequently); stress response: subjects are asked to imagine being in a very stressful situation and rate their bodily changes due to that situation (e.g. emotional problems such as more frequent feelings of depression, frustration, rage or anger); autonomic nervous system reactivity: requires that subjects answer items about their own autonomous nervous system reactions (e.g. ‘my heart often beats irregularly’); stress style subscale: evaluates the manner in which the subject responds to stress (e.g. ‘I have difficulty speaking’)]. Each item is rated on a five-point Likert scale ranging from 1 (never) to 5 (always).

Spectroscopic data acquisition and analysis

Single voxel 1H-MRS data were acquired at rest from two volumes of interest (VOI) in each subject using a Philips Achieva 3-T whole-body MR unit (Philips Medical Systems, Best, The Netherlands) equipped with a birdcage transmit-receive head coil. One VOI of 32 × 21 × 24 mm³ = 16.128 ml was placed in the left insula, while a second one (25 × 25 × 25 mm³ = 15.625 ml) was placed in the ACC (Figure 1). To enable an unambiguous measurement of metabolites, data from each VOI were acquired using a 2D JPRESS sequence (Schulte and Boesiger, 2004), which encodes the J coupling along the indirect spatial dimension by acquiring data with multiple echo times. This approach allows for a significant reduction of spectral overlap by spreading multiple resonances along two frequency axes. The sequence was preceded by water suppression using frequency-selective excitation and gradient spoiling followed by adiabatic frequency-selective rephasing and gradient spoiling. The echo times for the JPRESS experiment ranged from 28 to 228 ms with a step size of 2 ms and a phase cycling of 16 for each TE. Other parameters included a bandwidth in the direct dimension of 2 kHz and 2048 sample points. Using 100 encoding steps and eight averages per encoding step at a repetition time of TR = 2000 ms, the acquisition time for one voxel accounted to 24 min. JPRESS data were quantified using ProFit (Schulte and Boesiger, 2006), a two-dimensional fitting procedure, which applies the full amount of prior knowledge by fitting a linear combination of simulated two-dimensional basis metabolite spectra. Simulation of the basis metabolite spectra was performed with GAMMA (Smith et al., 1994). Cramer-Rao lower bounds, an estimate of the fitting error, were used as a quality criterion to exclude data sets with unreliable quantification results. Hence, analyses were restricted to subjects who met strict quality criteria to indicate reliable spectral quantification (Cramer-Rao lower bounds 20%) for each metabolite and four subjects had to be excluded from the analysis. Because determination of absolute metabolite concentrations in millimolars requires a reliable T1 and T2 relaxation correction, while relaxation times of coupled metabolites are hardly known for spectroscopy at 3-T, all metabolite concentrations are given relative to creatine levels. Creatine was proven to be an appropriate internal reference for the ProFit analysis (Schulte and Boesiger, 2006).

Statistical analyses

Statistical calculations were carried out as indicated in the ‘Results’ section using SPSS for Windows (Release 18.0; SPSS, Inc., Chicago, IL, USA). Within-group comparisons were performed using paired t-tests. Pearson correlation coefficients were computed to assess the relationship between neurotransmitter concentrations in both regions.
and the association between these concentrations and TAS-20 and BPQ scores. In an exploratory analysis, median split was used to create two groups of subjects with high and low scores on the TAS-20. Independent-sample t-tests were performed to analyze group differences between these subjects. Bonferroni corrections were used to counteract the problem of multiple comparisons. All tests were performed at a two-tailed level of significance of 5%.

RESULTS

Behavioral data
TAS-20 and BPQ total scores and subscores are summarized in Table 1. The total score of the TAS-20 correlated significantly with the BPQ total score ($r=0.70$, $P<0.01$) as well as with the BPQ subscales for awareness ($r=0.55$, $P<0.05$), stress response ($r=0.73$, $P<0.05$), autonomic nervous system reactivity ($r=0.65$, $P<0.05$; Figure 2) and stress style ($r=0.66$, $P<0.05$). There were no effects of age and gender on TAS-20 and BPQ scores.

MRS data
First, concentrations of glutamate (Glu) and GABA did not differ significantly between the two investigated regions (Table 2). Glu concentrations in both regions were correlated ($r=0.74$, $P<0.01$), whereas GABA concentrations were not ($r=0.33$, $P>0.05$). Regarding the association of neurotransmitters with alexithymia and measures of sensitivity for bodily processes, we found a significant positive correlation between TAS total score and Glu concentrations in insula ($r=0.59$, $P<0.05$; Figure 2), which was mainly due to a strong correlation with the DDF ($r=0.49$, $P<0.05$) and EOT ($r=0.53$, $P<0.05$) subscores.
Furthermore, there was a significant positive correlation between TAS total score and GABA concentrations in ACC \((r = 0.52, P < 0.05;\) Figure 2), which was mainly due to a strong correlation with the DDF subscore \((r = 0.57, P < 0.05)\). The BPQ subscore for autonomic nervous system reactivity also correlated with Glu concentration in insula \((r = 0.47, P < 0.05)\), whereas no correlation was found with GABA concentrations in ACC (Figure 2). In an exploratory analysis, we investigated differences between subjects scoring high and low, respectively, on the TAS-20. High scoring subjects not only showed significantly higher BPQ scores (total score: \(P < 0.01\); awareness score: \(P < 0.05\); autonomic nervous system reactivity: \(P < 0.01\)) but also significantly higher Glu concentrations in insula, but not in ACC \((P < 0.05)\). Strikingly, these subjects also showed a higher GABA concentration in ACC, but not in insula \((P < 0.07;\) Figure 3).

DISCUSSION

The main goal of this study was to test the interconnection between alexithymic features, interoceptive awareness and concentrations of Glu and GABA in ACC and insula. As hypothesized, alexithymia was closely related to the different facets of interoceptive awareness. Glu levels in left insula and GABA concentrations in ACC were positively associated with alexithymia. Furthermore, there was a double dissociation of GABA and Glu concentrations in insula and ACC as a function of alexithymia: subjects scoring high on the TAS-20 showed high Glu concentration in insula, but not in ACC and high GABA concentration in ACC, but not in insula. Finally, Glu levels in left insula, but not in ACC, were positively associated with the awareness of autonomic nervous system reactivity.

### Table 2 Metabolite concentrations in insula and ACC

|          | Left insula | ACC  |
|----------|-------------|------|
| Glu/Cr   | 1.62 (±0.32) | 1.59 (±0.26) |
| GABA/Cr  | 0.23 (±0.07) | 0.25 (±0.06) |

ACC, anterior cingulate cortex; Glu, glutamate; GABA, gamma-aminobutyric acid.

Fig. 3 Bar diagrams show (a) glutamate and (b) GABA concentrations in ACC and insula in subjects scoring high and low, respectively, on the TAS-20. Differences in glutamate concentration between these two groups were observed in insula \((P < 0.05)\), but not ACC, whereas differences in GABA concentration were observed in ACC \((P < 0.07)\), but not in insula. TAS-20, Toronto Alexithymia Scale; ACC, anterior cingulate cortex. \(^* P < 0.05\).
et al., 2010; Gutzeit et al., 2011), which is supported by our finding of a relationship between insula Glu concentration and awareness of autonomic nervous system reactivity. High interoceptive awareness, which in turn might be related to a Glu-mediated increase in insula activity, has been associated with higher emotional arousal (Wiens and Palmer, 2001; Pollatos et al., 2005). Likewise, the positive association reported between insula Glu concentration and alexithymia might reflect enhanced insula activity in alexithymia related to increased Glu-mediated excitatory transmission. The role of insula Glu in alexithymia is further emphasized by the region-specific elevation in Glu levels in subjects scoring high on the TAS-20.

Thus, we propose that the interconnection observed between alexithymia, interoceptive awareness and Glu concentration in insula reflects increased awareness of bodily and stress responses as well as enhanced insula activity due to increased Glu-mediated excitatory transmission, which in turn might lead to a high unspecific arousal in alexithymic subjects. To the best of our knowledge, no studies have yet investigated the modulation of alexithymic features by neurotransmitter concentrations. However, alexithymics show increased vulnerability to affective disorders (Luminet, 2010; Leweke et al., 2010), which are characterized by dysfunctional Glu and GABA-ergic neurotransmission (Sanacora et al., 2008; Mathew et al., 2008; Walter et al., 2009; Hashimoto et al., 2010; Grimm et al., 2012; Scheidegger et al., 2012). Furthermore, alexithymics show low extraversion, high neuroticism, high harm avoidance, low self-directedness and impaired perspective taking (Wise et al., 1992; Guttman and Laporte, 2002; Picardi et al., 2005). The correlation observed between Glu and alexithymic features is therefore well in accordance with previous studies investigating these traits and showing a negative correlation between prefrontal Glu and mental perspective taking as well as extraversion (Montag et al., 2008; Grimm et al., 2012b). Harm avoidance and extraversion have been associated with increased and decreased ACC GABA concentrations (Kim et al., 2009; Goto et al., 2010), respectively, which fits well with the reported correlation between ACC GABA and alexithymia. The ACC is a crucial region for emotion processing and for constituting our sense of self (McKiernan et al., 2006; Northoff et al., 2006). It has been hypothesized that while insula is involved in the generation of all subjective feeling states, combined action of insula and ACC might provide the neural basis of self-awareness (Craig, 2009). Medford and Critchley (2010) proposed that awareness of self, i.e. an integrated awareness of cognitive, affective and physical state is generated by the integrative functions of the insula and then re-represented in ACC as a basis for responses to inner or outer events. Back-projections from the ACC may then allow the insular representation of the feeling state to be modulated by circulate activity. The proposed reciprocity between ACC and insula is supported by neuroanatomical studies (Nieuwenhuys et al., 2008; Moisset et al., 2010), findings of correlated BOLD signal fluctuations (Taylor et al., 2009; Horn et al., 2010) and joint activity of these areas during emotional experience (Harrison et al., 2008). Menon and Uddin (2010) characterize insula and ACC as a ‘salience network’ that functions to segregate the most relevant among internal and external stimuli in order to guide behavior. Insula activity modulates autonomic reactivity to salient stimuli and Glu-mediated increased insula activity in alexithymia might reflect the misattribution of emotional salience to mundane events or bodily responses. A similar overdrive in the salience network has also been discussed in neuroticism, increased anxiety and depression (Paulus and Stein, 2006; Stein et al., 2007; Horn et al., 2010), all of which are closely related to alexithymia (Picardi et al., 2005; Luminet, 2010; Leweke et al., 2012). Our results show an association between GABA concentrations in ACC and alexithymic features. Since increased GABA transmission mediates a decrease in neuronal activity our finding is therefore well in accordance with previous studies showing lower ACC activation in response to emotion stimuli in alexithymia (Leweke et al., 2004; Moriguchi et al., 2007; Karlsson et al., 2008; Silani et al., 2008; Bird et al., 2010; Reker et al., 2010). Although we investigated Glu and GABA concentrations in the ventral ACC, a region crucially involved in emotional experience (Lane et al., 1998; Larisch et al., 1997; Bush et al., 2000; Northoff et al., 2007; Grimm et al., 2009), several previous studies reported increased activity in dorsal ACC in alexithymia (Berthoz et al., 2002; Mériau et al., 2006; Frewn et al., 2008; Karlsson et al., 2008; Heinzl et al., 2010). The dorsal region of the ACC provides a cognitive processing of emotions (Bush et al., 2000; Beauregard et al., 2001) and is especially relevant for emotion regulation (Ochsner et al., 2002; Phan et al., 2005; Kim and Hamann, 2007; Wager et al., 2008). Alexithymia has been conceptualized as a disorder of emotion regulation (Swart et al., 2009), since it is associated with maladaptive coping strategies, notably emotional inhibition and immature defensive styles (Helmes et al., 2008). Increased activity in dorsal ACC might represent an effort to suppress the unspecific emotional arousal that results from increased interoceptive awareness and Glu-mediated enhanced insula activity (Swart et al., 2009; Heinzl et al., 2010) and eventually lead to GABA-mediated decreased activity in ventral ACC, which prevents excessive experience of negative emotions (Urry et al., 2009; Abler et al., 2010). Increased GABA concentrations in alexithymia might therefore indicate increased inhibitory control of ACC activity as a neuronal correlate of impoverished conscious experience of emotion in alexithymia (blindfeel) (Lane et al., 1997, 1998). This hypothesis is supported first by the region-specific elevation in GABA levels in subjects scoring high on the TAS-20. Second, previous findings show that signal changes in ventral ACC during emotional processing are meditated by GABA (Northoff et al., 2007). Third, a recent study by Kupers et al. (2009) reports that acute pain and associated aversive emotional experience induced a significant increase in GABA in ACC. Finally, a recent study reported lower connectivity in ventral ACC in alexithymia (Liemburg et al., 2012).

There are several limitations to this study. The rather small sample size has to be considered when interpreting the results. We did not control for phase effects within our female participants, which might be of importance since it has been demonstrated that luteal and follicular phases impact MRS metabolites (Batra et al., 2008). Additionally, although we investigated two regions related to alexithymia and interoceptive awareness, future studies should include a further control region and also investigate the right insula, since specifically right insula might support interoceptive awareness and integrate it with other information to form the basis of the subjective experience of an emotional state (Craig, 2003). Future studies should also consider including additional scales to shed further light on the association between other personality dimensions related to increased vulnerability to affective disorders (e.g. neuroticism) and neurotransmitter concentrations. In sum, this study indicates for the first time a close relationship between alexithymia, interoceptive awareness and GABA and Glu concentrations in ACC and insula. Increased Glu-mediated excitatory transmission and related enhanced insula activity might reflect increased interoceptive awareness in alexithymia. We assume that increased awareness of bodily and stress responses in alexithymics results in unspecific emotional arousal. Alexithymics mainly use suppression as a strategy to down-regulate emotional arousal, which might be reflected in neuronal activity decreases as mediated by the here reported increased GABA concentration in ACC. These hypotheses should be tested in further studies, though, that combine neuroimaging during emotional processing and interoceptive awareness with MRS measurements in insula and ACC in healthy subjects as well as in patients with affective disorders.
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Association of interoceptive awareness and alexithymia

SCAN (2014) 863

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