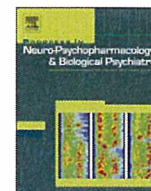




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Gastric dysmotility in major depression

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ABSTRACT

Background: Somatic symptoms of the gastrointestinal tract occur frequently in major depressive disorder (MDD) and might be associated with the known autonomic imbalance in the disease. Hence, we have investigated gastric electrical activity in patients suffering from major depression before and after treatment by means of electrogastrography (EGG) to investigate a putative association with either the disease state and its symptoms or its relation to the treatment.

Methods: EGG readings before and after ingestion of a test meal of 27 patients suffering from major depression were recorded before and after treatment with antidepressants and compared with age-matched controls. Abdominal symptoms were rated by a specific Autonomic Nervous Symptom-score.

Results: We found a significantly increased amount of tachygastria before and after medication, indicating increased sympathetic modulation. A significant difference was observed for the instability coefficients before and after medication, indicating gastric dysmotility in our patients prior to treatment. The elevated approximate entropy measure points to increased complexity and dysregulation. Furthermore, we have observed a correlation between subjective sensation of sweating and dry mouth with the sympathetic parameter tachygastria.

Discussion: Our results suggest that major depression is associated with gastric dysrhythmia possibly caused by increased sympathetic modulation. Linear and non-linear EGG measures emphasize a possible role of the autonomic nervous system in the development of gastric symptoms. The treatment with antidepressants seems to increase the activity of the sympathetic nervous system, without aggravating gastric symptoms. The association of increased sympathetic modulation with somatic symptoms was indicated by correlation analysis with these symptoms.

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1. Introduction

Altered autonomic neurocardiac regulation is controversial in major depression (Yeragani et al., 1995; Tulen et al., 1996; Bär et al., 2004; Voss et al., 2006; Boettger et al., 2008). While some studies reported decreased parasympathetic modulation (Guinjoan et al.,

1995; Rechlin et al., 1994), others could not detect any change at all (Bär et al., 2004; Moser et al., 1998). Similarly, contradictory results have been presented for sympathetic function. There are reports of increased (Guinjoan et al., 1995), decreased (Tulen et al., 1996) or unchanged (Moser et al., 1998) sympathetic modulation under resting conditions in depressed patients. Furthermore, a recent meta-analysis revealed relatively modest effect sizes for depression on cardiac vagal control (Rottenberg, 2007).

Decreased parasympathetic modulation has been demonstrated by means of heart rate variability applying linear and non-linear measures (Agelink et al., 2001; Yeragani et al., 2003; Bär et al., 2004; Boettger et al., 2008; Koschke et al., 2009). Overall, treatment using antidepressants shifted this imbalance towards sympathetic modulation in relation to the specific receptor profile of drugs (Koschke et al., 2009).

The autonomic imbalance of the enteric nervous system in major depressive disorder (MDD) has not been studied in more detail.

Abbreviations: ANOVA, Analysis of variance; ANS-score, Autonomic Nervous Symptom-score; ApEn, Approximate Entropy; BDI, Beck's Depression Inventory; EGG, Electrogastrography; HAMD, Hamilton Depression Rating Scale; ICDF, Instability coefficient of the dominant frequency; MANOVA, Multivariate analysis of variance; ICDP, Instability coefficient of the dominant power; MDD, Major depressive disorder; SCID, Structured Clinical Interview for DSM-IV; SSRI, Serotonin reuptake inhibitors; SNRI, Serotonin and noradrenaline selective reuptake inhibitors.

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Table 1

Clinical and demographic data of participants as well as obtained parameters of patients and controls.

| | Controls | Patients | | | |
|-----------------------------------|-------------------|-------------------|----------|----------------|-----------|
| Participants | 27 | 27 | | | |
| (male/female) | (8/19) | (8/19) | | | |
| Age (years) \pm SD | 39.33 \pm 15.85 | 40.48 \pm 13.86 | | | |
| | (22–59 years) | (23–59 years) | | | |
| Body mass index \pm SD | 23.08 \pm 0.75 | 23.93 \pm 0.85 | | | |
| Smoker/non-smoker | n = 7/20 | n = 9/18 | | | |
| Assessed parameters | Controls (C) | UP | C vs. UP | MP | UP vs. MP |
| | | | p | | p |
| HAMD | 1.0 \pm 0.2 | 27.7 \pm 1.4 | < 0.0001 | 20.3 \pm 1.4 | < 0.001 |
| BDI | 1.0 \pm 0.3 | 23.9 \pm 2.6 | < 0.0001 | 19.7 \pm 2.6 | < 0.034 |
| ANS- score | 0.8 \pm 0.2 | 9.3 \pm 1.0 | < 0.0001 | 6.5 \pm 1.1 | < 0.12 |
| Normogastria (%) before test meal | 73.1 \pm 4.6 | 61.5 \pm 4.6 | < 0.04 | 65.5 \pm 4.8 | < 0.19 |
| Normogastria (%) after test meal | 72.5 \pm 4.0 | 60.3 \pm 4.4 | < 0.04 | 52.9 \pm 4.6 | < 0.71 |
| Bradygastria (%) before test meal | 10.6 \pm 2.5 | 8.6 \pm 1.4 | 0.96 | 8.4 \pm 1.4 | < 0.96 |
| Bradygastria (%) after test meal | 8.8 \pm 2.0 | 10.6 \pm 2.2 | 0.55 | 8.7 \pm 1.4 | < 0.98 |
| Arrhythmia (%) before test meal | 16.9 \pm 3.6 | 17.8 \pm 2.9 | 0.48 | 17.4 \pm 3.3 | < 0.80 |
| Arrhythmia (%) after test meal | 12.0 \pm 2.6 | 19.5 \pm 3.0 | 0.19 | 19.9 \pm 2.9 | < 0.59 |
| Slow wave (%) before test meal | 42.1 \pm 5.1 | 31.6 \pm 4.4 | 0.12 | 37.4 \pm 5.1 | < 0.43 |
| Slow wave (%) after test meal | 40.6 \pm 4.8 | 31.8 \pm 3.8 | 0.19 | 31.1 \pm 4.3 | < 0.93 |

Data are presented as mean \pm standard deviation SD; C = control subjects; UP = unmedicated patients; MP = medicated patients; HAMD = Hamilton Depression Rating Scale; BDI = Beck's Depression Inventory; ANS-score = Autonomic Nervous Symptom-score.

Gorard et al. (1996) reported some evidence of a prolongation of gut transit time in these patients. Similarly, a high proportion of patients with intractable constipation are known to suffer from a previous or current affective disorder (Dykes et al., 2001). Recently, it was shown by applying electrogastrography (EGG) that unmedicated patients suffering from major depression present with alterations of the myoelectrical activity of the stomach (Ruhland et al., 2008). In particular, a significantly increased amount of tachygastria and arrhythmia during test meal digestion has been found indicating increased sympathetic modulation in unmedicated patients suffering from MDD (Ruhland et al., 2008). The influence of antidepressants like serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline selective reuptake inhibitors (SNRI) on the enteric nervous system has not been studied in patients suffering from MDD to our knowledge.

We hypothesized that autonomic modulation in the enteric nervous system of depressed patients is shifted towards sympathetic predominance in unmedicated patients which might be further exaggerated by treatment. We applied the cutaneous EGG that is a non-invasive method for quantifying the activity of the gastric myoelectrical pacemaker. In addition, we assumed that sympathetic predominance in the enteric nervous system might be related to somatic symptoms of patients since serotonin or norepinephrine play an important role in modulating autonomic and somatic symptoms in major depression (Hansen, 2003; Sussman, 2003).

2. Methods

2.1. Subjects

Twenty seven patients suffering from MDD and twenty seven matched healthy controls (sex- and age-matched) were investigated using the EGG records. Patients were admitted to our inpatient unit for affective disorders and the diagnosis was made by a staff psychiatrist. All patients fulfilled DSM-IV criteria for MDD. Diagnosis was confirmed by means of a Structured Clinical Interview for DSM-IV Axis I disorders (SCID, 1997). Any additional or confounding psychiatric condition (e.g. anxiety disorder) or other disease led to the exclusion of participants. Table 1 depicts demographic and clinical data for both groups. Patients had to be unmedicated for at least 8 weeks prior to the investigation. After administration of antidepressants (SNRI $n=21$; SSRI $n=6$; 7–12 days) a reassessment was

performed. Patients were treated with venlafaxine ($n=15$; 150–225 mg/day), mirtazapine ($n=6$; 30 mg/day) and S-citalopram ($n=6$; 10–20 mg/day). The choice of medication was based on clinical grounds. All participants were seen by a gastroenterologist (M.H.) to exclude any potential gastrointestinal disease. Control subjects were recruited from hospital staff ($n=6$), medical students ($n=7$) and the local community ($n=14$). This study complied with the Declaration of Helsinki. All participants gave written informed consent to a protocol approved by the local Ethics Committee of the University hospital, Jena.

2.2. Interview and questionnaires

The severity of depression was assessed based on a semi-structured clinical interview, the Hamilton Depression Rating Scale (HAMD-D-21; Hamilton, 1960) and Beck's Depression Inventory (BDI; Beck et al., 1961). Controls were also interviewed to assure the absence of a psychiatric disorder. The nature of the study required the exclusion of any subject with a history of peptic ulcer disease, gastroesophageal reflux disease, irritable bowel syndrome, symptoms of gastritis, diabetes mellitus or any further confounding medical or neurological condition as well as a previous gastrointestinal surgery.

In order to assess autonomic complaints, we obtained an Autonomic Nervous Symptom-score (ANS-score; Ruhland et al., 2008), which includes the following symptoms: feeling of fullness, heartburn, nausea, vomiting, dry mouth, diminished appetite, constipation, diarrhea, palpitation, sweating, back pain, muscle pain, headache and abdominal pain.

In addition, we assessed (0 = no; 1 = mild; 2 = medium; 3 = severe) the severity of these symptoms (Table 1). The structured-interview was performed before and after treatment to identify an interrelation of clinical symptoms and EGG parameters in patients. Control subjects had to have unremarkable scores on the HAMD-21 (< 7 points), BDI (< 5 points) and ANS-score (< 3 points).

2.3. Procedure of EGG recordings

Patients were studied in the morning after an overnight fast. The EGG was recorded for 30 min in fasting state and thereafter for a further 30 min during standard meal digestion (200 ml Clinutren®, 300 kcal, Vevey, Switzerland). The system exploits four channels to

record electric signals plus one filter channel for muscle movements and breathing activity. All electrodes were positioned to follow the antral axis of the stomach. The best results were obtained from channel three, because it is located above the gastric pacemaker (Ruhland et al., 2008). The gastric slow wave is a measure indicating coupling of two EGG channels. We calculated the slow wave parameter between channel one, placed over the fundus region and channel three positioned above the gastric pacemaker. Channel four was located over the antrum region.

2.4. Data acquisition and preprocessing

EGG is a non-invasive method using an electrogastragraph (Medtronic, Minneapolis, USA) to record gastric myoelectrical activity by means of cutaneous electrodes placed on the abdominal wall (Chen et al., 1995). The percentages of gastric myoelectrical activity were determined by using the adaptive running spectral analysis method. Electrodes obtain the signal of the gastric pacemaker which is located in the corpus of the stomach (Chen et al., 1995). The signal of the pacemaker contains slow waves (electrical control activity, pacesetter potential) as well as spike activity (electrical response activity).

Bauer et al. (1985) have shown that slow wave activity originates in the Auerbach's plexus region, where the interstitial cells of Cajal are located. Functionally, they may serve as mediators interposing between enteric nerves and smooth muscle cells (Huizinga, 2001). Slow waves, which are characterized by regular recurring changes in potential, originate in the upper part of the stomach constantly propagating circumferentially and distally toward the pylorus with increasing velocity and amplitude (Hinder and Kelly, 1977; Chen and McCallum, 1994). Gastric slow waves represent the dominant frequency obtained from spectral analyses corresponding with frequency of phasic gastric contractions (Chen and McCallum, 1994). The percentage of single slow wave spectra was defined as the proportion of time (in percent) in which it was present during the observation period. While the percentage of slow waves reflect the regularity of gastric myoelectrical activity (normogastria in %, 2.4–3.6 cycles/min), the superimposed spikes are associated with the magnitude of contractions of the stomach (Smout et al., 1980; Chen and McCallum, 1994). Gastric dysrhythmias include bradygastria (0.5–2.4 cycles/min), tachygastria (3.7–9.0 cycles/min) and gastric arrhythmia which is associated with a lack of a dominant frequency (0.5–9.0 cycles/min) (Chen et al., 1993). Bradygastria, is mainly associated with vagal modulation and is caused by a decreased frequency of the normal pacemaker located in the corpus (Qian et al., 2003). Tachygastria, which does not lead to abdominal contractions, arises due to additional and external pacemaker activity located in the antrum of the stomach propagating retrogradely to the corpus (Qian et al., 2003). An increased proportion of tachygastria and arrhythmia might be associated with sympathetic modulation and has frequently been observed in patients with gastric motility disorders like delayed gastric emptying and gastroparesis (Chen et al., 1993; Pfaffenbach et al., 1998).

The instability coefficient of dominant frequency (ICDF) and the dominant power (ICDP) are indicators of stability of the gastric electrical peak and reflect changes in gastric slow waves (Diamanti et al., 2003; Chen and McCallum, 1994).

The percentage of slow-wave coupling is a measure of coupling between two EGG channels and is defined as the ratio between the number of time segments during which the recorded slow waves were coupled and the total number of segments (Chen et al., 1999). It is the ultimate determinant of the frequency and direction of propagation of contractions of the mid- and distal stomach (Xu et al., 2004).

2.5. Approximate entropy (ApEn)

Besides linear electrogastragraphic parameters, which describe the frequency as well as the magnitude of gastric myoelectrical activity,

we have applied the non-linear measure approximate entropy (ApEn), to examine the regularity and complexity of the obtained signal (Pincus, 1991; Pincus, 2006). The application of these novel measures has led to a higher sensitivity for the detection of dysautonomia in patients with various physiological conditions (Makikallio et al., 1997; Radhakrishnan and Gangadhar, 1998; Yeragani et al., 2003; Pincus, 2003; Glenn et al., 2006; Bär et al., 2007d).

In the model of approximate entropy, runs of patterns in time series are compared. If these runs remain close in successive observations, regularity is high and thus complexity of the series is low, resulting in smaller ApEn values. We applied the technique previously described by Pincus (Pincus, 1991; Pincus, 2001). Given N data points $u(1), u(2), \dots, u(N)$, two input parameters should be set prior to the computation of ApEn. These are the run length m and the filter level r . From previous reports, a value of 2 for m and 0.2 times the standard deviation of the time series for the value of r have been shown to reveal reliable results. First, we obtained vector sequences from the consecutive data points, which represent m consecutive u values, beginning with the i th point. Consecutively, the distance between vectors, $x(i)$ and $x(j)$ is defined as the maximum difference in their respective scalar components. Then the sequence $x(1), x(2), \dots, x(N-m+1)$ is used to construct $\ln C^m(r) = \{\text{number of } x(j) \text{ such that } d[x(i), x(j)] \leq r\} / (N-m+1)$ for each $i \in N-m+1$.

The $Cim(r)$ values measure, within a tolerance r , the regularity or frequency of patterns similar to a given pattern of window length, m . Here, ApEn is defined as: $\text{ApEn}(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r)$.

In this equation, $\sqrt{m}(r)$ is the average value of $\ln Cim(r)$, \ln being the natural logarithm.

The value of N is fixed, typically between 100 and 5000 points but it has been shown that one can get a reliable estimate of ApEn even with a data length of <50 points, especially in studies related to endocrinology (Pincus, 1991; Pincus, 2001). In this study, 1000 data points were used.

2.6. Data analysis

For statistical analyses, SPSS for Windows (version 15.0) was used. The Kolmogorov–Smirnov-test was used to test for normal distribution of obtained parameters. The natural logarithm was applied to produce normal distribution of single EGG data. We used a probability level of 0.05 for significance.

Thereafter, we performed a multivariate analysis of variance (MANOVA) to examine the overall difference between unmedicated MDD patients and control subjects before and after test meal ingestion. Follow-up univariate analyses of variance (ANOVAs) were performed for single EGG data to compare unmedicated patients and controls.

In addition, post hoc pair-wise t -tests were performed to compare EGG data of unmedicated and medicated patients to assess the putative influence of treatment with antidepressants.

Furthermore, ratings of psychopathological scales (HAMD-21; BDI) and the ANS-score were correlated with EGG parameters using the Spearman rank order correlation coefficient. Moreover, pair-wise t -tests were performed for descriptive analysis of the effect of medication on clinical symptoms between both points in time.

3. Results

3.1. EGG measures at baseline

The MANOVA revealed a significant overall difference between unmedicated patients and controls for obtained EGG parameters (percentage of normogastria, tachygastria, bradygastria, arrhythmia, ICDF, ICDP, slow-wave coupling and ApEn before and after test meal ingestion) [$F(37,16) = 4.6; p < 0.0001$].

The follow-up univariate ANOVA revealed a significant difference for the sympathetic parameter tachygastria before [$F = 13.9; p < 0.0001$;

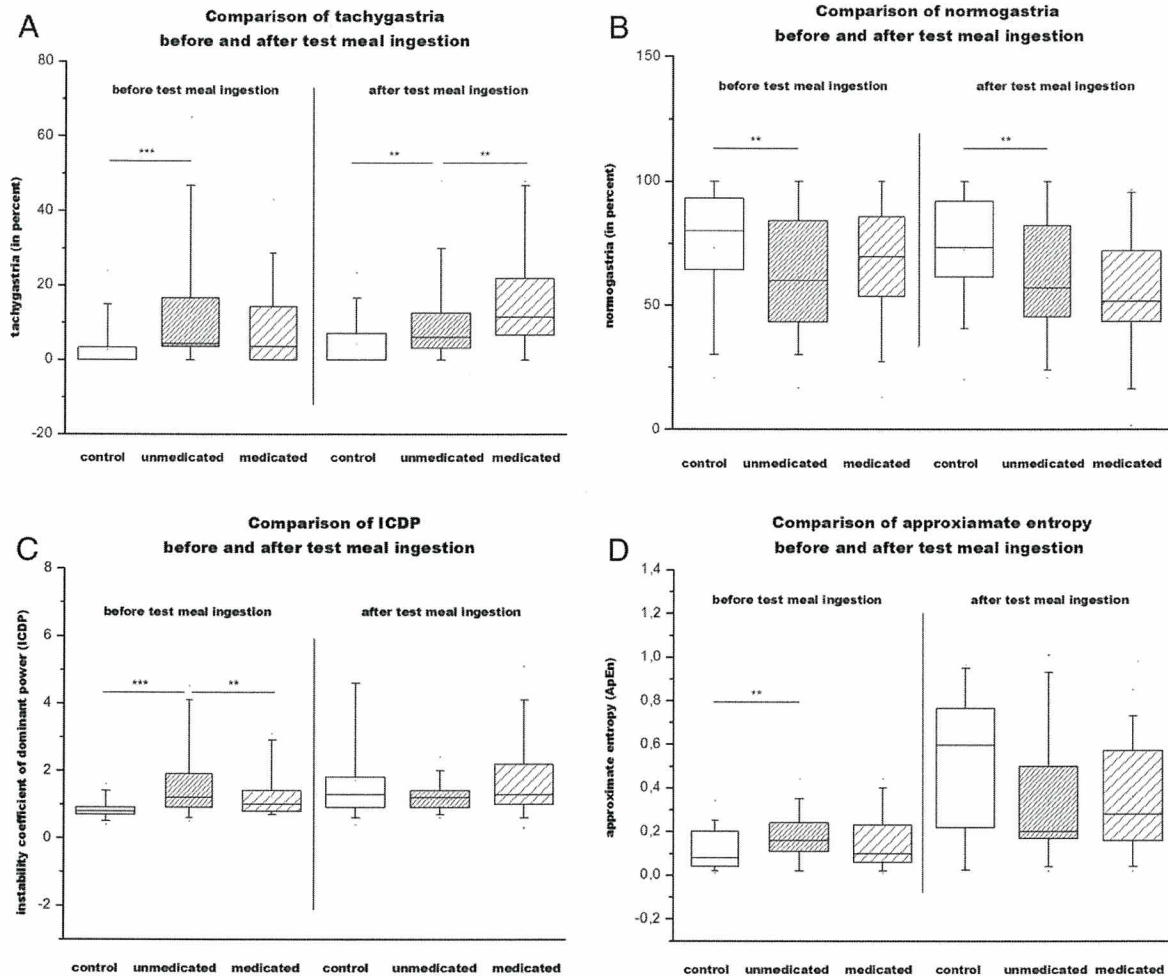


Fig. 1. Specific EGG parameters of healthy controls, unmedicated patients and medicated patients before and after test meal ingestion are displayed in Fig. 1. The percentage of tachygastria (A) was significantly elevated before and after ingestion of the test meal in unmedicated patients suggesting increased sympathetic modulation in the enteric nervous system. In medicated patients, tachygastria (%) was only significantly increased after the test meal. The significant decrease of the percentage of normogastria in unmedicated depressed patients is presented in (B). The instability coefficient (C) of dominant power (ICDP) was significantly increased before test meal ingestion in unmedicated patients. After medication, ICDP was decreased indicating stability of the myoelectrical activity. The approximate entropy (ApEn; D) was significantly increased before test meal ingestion pointing to increased complexity in unmedicated patients. Data presented as scatter-plots; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Fig. 1B) and after [$F = 6.0$; $p < 0.02$] test meal ingestion comparing unmedicated patients and controls. Similarly, a significant difference for ICDP was found before the test meal [$F = 15.1$; $p < 0.0001$; Fig. 1C] and the coefficient of dominant frequency [$F = 5.1$; $p < 0.02$] after the test meal, revealing an increased amount of instability of the gastric electrical peak. In addition, a decreased amount of normogastria was observed before [$F = 4.3$; $p < 0.04$; Fig. 1A] and after [$F = 4.2$; $p < 0.04$] the test meal. No significant difference was found for arrhythmia [$F = 1.7$; $p < 0.19$] and slow wave [$F = 1.7$; $p < 0.19$] at both points in time (Table 1).

The non-linear parameter ApEn indicated decreased regularity in the analyzed signal before the test meal [$F = 5.5$; $p < 0.02$; Fig. 1D] and a trend for irregularity after test meal ingestion [$F = 3.2$; $p < 0.08$].

3.2. Influence of medication on gastric myoelectrical activity

Post hoc pair-wise *t*-tests revealed a significant effect of medication for the parameter ICDP ($p < 0.03$) and ICDP ($p < 0.04$) being decreased in patients before the test meal ingestion.

Furthermore, an elevated amount of tachygastria ($p < 0.02$) was found after test meal ingestion indicating increased sympathetic modulation after initiation of treatment.

The pair-wise *t*-test revealed a significant reduction of disease specific symptoms assessed by the HAMD scale ($p < 0.001$) and BDI score ($p < 0.03$) after medication. In particular, we found a decreased amount of somatic symptoms ($p < 0.001$) rated in the HAMD subscale. No significant difference was observed for the ANS-score ($p < 0.12$) after treatment.

3.3. Correlation analysis

We found a significant correlation between the ANS-score [$r = 0.5$; $p < 0.02$] and the percentage of tachygastria prior to ingestion of the test meal. Similarly, we observed a correlation between the item "sweating" [$r = 0.61$; $p < 0.003$] as well as "dry mouth" [$r = 0.5$; $p < 0.02$] of the ANS-score and tachygastria, indicating sympathetic modulation of both. Furthermore, we found a positive correlation between tachygastria and the item "somatic symptoms", rated in HAMD scale [$r = 0.65$; $p < 0.001$].

4. Discussion

Autonomic disturbances of psychiatric disorders have gained increased interest during recent years (Yeragani et al., 2002; Bär et al., 2004;

Bär et al., 2006; Bär et al., 2007a; Ruhland et al., 2008). In this study, we present further evidence for an autonomic imbalance in the enteric nervous system of patients suffering from major depression. We aimed to evaluate gastric electrical activity with linear and non-linear measures in depression and additionally assessed the influence of treatment with newer antidepressants.

One of the main findings of our study was a significantly increased amount of the non-linear measure ApEn in untreated patients suffering from MDD. The increase of ApEn points to increased complexity and might indicate disturbed myoelectrical activity of the gastric pacemaker. It cannot easily be attributed to sympathetic or parasympathetic modulation within the enteric nervous system. However, non-linear measures of longitudinal data from patients with major depression may provide information not apparent from traditional techniques. ApEn indicates the regularity and complexity of the obtained signal (Pincus, 1991; Pincus, 2006) and future studies need to relate this to the underlying pathophysiology.

Increased sympathetic modulation has been reported for cardiac function (Koschke et al., 2009) in MDD. Similarly, tachygastria, which was found to be elevated in unmedicated patients in our study, is thought to reflect sympathetic modulation and arises due to external pacemaker activity located in the antrum of the stomach propagating retrogradely to the corpus (Jin et al., 2007; Hu et al., 1991). Additionally, we have found some indication for reduced vagal modulation in the enteric nervous system indicated by reduced normogastria in unmedicated patients.

The amount of tachygastria showed a positive correlation with the ANS-score. These data are consistent with previous reports, demonstrating the association of enhanced tachygastria with feelings of fullness, epigastric distress and nausea (Koch and Stern, 1996; Walsh et al., 1996; Ogawa et al., 2004). Furthermore, it is in line with our hypothesis of an association of an autonomic imbalance and somatic symptoms in MDD.

Similarly, we found a positive correlation of the items “sweating” and “dry mouth” with tachygastria in patients with MDD. Previous studies associated autonomic symptoms like diarrhea or sweating with increased sympathetic modulation, whereas symptoms like dry mouth or constipation were assumed to be related to reduced parasympathetic function (Davidson and Turnbull, 1986). We further speculate that similar to other conditions gastric dysmotility indicated by the instability coefficient of dominant frequency (ICDF) and dominant power (ICDP) might be associated with feelings of fullness and abdominal distention in MDD (Ogawa et al., 2004; Tack et al., 1998). However, a specific correlation was not observed.

Thus, our results demonstrated an autonomic dysfunction within the enteric nervous system in MDD, as previously described for heart rate variability and pupillary light reflex (Agelink et al., 2001; Koschke et al., 2009). Nevertheless, the specificity of autonomic dysfunction in psychiatric diseases needs to be determined in future studies since comparable results were reported for patients suffering from schizophrenia for the enteric nervous system (Peupelmann et al., 2009) and for the cardiac division (Bär et al., 2007a,b,d; Bär et al., 2008) as well as for patients during alcohol withdrawal (Bär et al., 2006; Bär et al., 2007c). Future research strategies might assess simultaneously different divisions of the autonomic nervous system to better discriminate the specific autonomic imbalance in a disease.

4.1. Influence of treatment

To our knowledge, this is the first study investigating the effect of antidepressants on gastric myoelectrical activity and associated abdominal symptoms in MDD.

We have found that patients had an increased amount of tachygastria after treatment with SSRI and SNRI after test meal ingestion. Thus, this treatment might lead to increased sympathetic modulation on the gastric pacemaker. However, according to our data this increase of sympathetic modulation was not accompanied by amplified somatic symptoms.

Additionally, we detected a decline of the instability coefficient ICDF and ICDP before test meal ingestion after treatment. This might suggest that antidepressants stabilize the gastric peristalsis in MDD before test meal ingestion possibly associated with reduced somatic symptoms after treatment (Goldstein et al., 2004).

Due to the small sample size we refrained from differentiating between specific effects of SNRI and SSRI. In a recent study, examining the influence of antidepressants on the cardiac division in MDD Koschke et al. (2009) found an increase of sympathetic modulation after administration of SNRI. In contrast, administration of SSRI had no significant effect on the modulation of the cardiac nervous system (Koschke et al., 2009). In order to further clarify the influence of different classes of antidepressants on the enteric nervous system, future studies are needed to include larger sample sizes to differentiate the specific influence of SSRI and SNRI possibly in contrast to tricyclic antidepressants. The inclusion of both classes of antidepressants dampens the explanatory power of the study. Therefore, results in respect to the influence of medication on the enteric nervous system need to be viewed with caution. Furthermore, results of this study are limited due to awareness of patients about their treatment regimen and the significant reduction of symptoms during the second investigation. The relatively short time interval for re-investigation was chosen, to assess patients in a comparable clinical state. However, this might further have influenced the obtained results. Furthermore, the specific explanatory power of EGG parameters is less well established in comparison to sophisticated cardiac investigations and the presented results are limited by the clinical exclusion of gastrointestinal diseases.

In conclusion, our results suggest that major depression is associated with gastric dysrhythmia possibly caused by increased sympathetic modulation. Linear and non-linear EGG measures emphasize a possible role of the autonomic nervous system in the development of gastric symptoms. The treatment with antidepressants seems to increase the activity of the sympathetic nervous system, without aggravating gastric symptoms. Nevertheless, further investigations are required to validate the utility of non-linear EGG measures and to relate those to other parameters of autonomic function such as heart rate variability in patients suffering from MDD.

References

- Agelink MW, Majewski T, Wurthmann C, Postert T, Linka T, Rotterdam S, et al. Autonomic neurocardiac function in patients with major depression and effects of antidepressive treatment with nefazodone. *J Affect Disord* 2001;62:187–98.
- Bär KJ, Greiner W, Jochum T, Friedrich M, Wagner G, Sauer H. The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters. *J Affect Disord* 2004;82:245–52.
- Bär KJ, Boettger MK, Boettger S, Grotelüschen M, Neubauer R, Jochum T, et al. Reduced baroreflex sensitivity in acute alcohol withdrawal syndrome and in abstained alcoholics. *Drug Alcohol Depend* 2006;15:66–74.
- Bär KJ, Boettger MK, Berger S, Baier V, Sauer H, Yeragani VK, et al. Decreased baroreflex sensitivity in acute schizophrenia. *J Appl Physiol* 2007a;102:1051–6.
- Bär KJ, Boettger MK, Koschke M, Schulz S, Chokka P, Yeragani VK, et al. Non-linear complexity measures of heart rate variability in acute schizophrenia. *Clin Neurophysiol* 2007b;118:2009–15.
- Bär KJ, Boettger MK, Koschke M, Boettger S, Grotelüschen M, Voss A, et al. Increased QT interval variability index in acute alcohol withdrawal. *Drug Alcohol Depend* 2007c;89:259–66.
- Bär KJ, Boettger MK, Koschke M, Schulz S, Chokka P, Yeragani VK, et al. Non-linear complexity measures of heart rate variability in acute schizophrenia. *Clin Neurophysiol* 2007d;118:2009–15.
- Bär KJ, Wernich K, Boettger S, Cordes J, Boettger MK, Löffler S, et al. Relationship between cardiovagal modulation and psychotic state in patients with paranoid schizophrenia. *Psychiatry Res* 2008;157:255–7.
- Bauer AJ, Publicover NG, Sanders KM. Origin and spread of slow waves in canine gastric antral circular muscle. *Am J Physiol Gastrointest Liver Physiol* 1985;249:G800–6.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
- Boettger S, Hoyer D, Falkenhahn K, Kaatz M, Yeragani VK, Bär KJ. Nonlinear broad band dynamics are less complex in major depression. *Bipolar Disord* 2008;10:276–84.
- Chen JDZ, McCallum RW. *Electrogastrography: principles and applications*. New York: Raven; 1994.
- Chen JDZ, McCallum RW, Richards R. Frequency components of the electrogram and their correlation with gastrointestinal contractions in humans. *Med Biol Eng Comput* 1993;31:60–7.

- Chen JD, Pan J, McCallum RW. Clinical significance of gastric myoelectrical dysrhythmias. *Dig Dis* 1995;13:275–90.
- Chen JD, Zou X, Lin X, Ouyang S, Liang J. Detection of gastric slow wave propagation from the cutaneous electrogastragram. *Am J Physiol* 1999;277:G424–30.
- Davidson J, Turnbull CD. Diagnostic significance of vegetative symptoms in depression. *Br J Psychiatry* 1986;148:442–6.
- Diamanti A, Bracci F, Gambarara M, Ciofetta GC, Sabbi T, Ponticelli A, et al. Gastric electric activity assessed by electrogastrography and gastric emptying scintigraphy in adolescents with eating disorders. *J Pediatr Gastroenterol Nutr* 2003;37:35–41.
- Dykes S, Smilgin-Humphreys S, Bass C. Chronic idiopathic constipation: a psychological enquiry. *Eur J Gastroenterol Hepatol* 2001;13:39–44.
- Glenn T, Whybrow PC, Rasgon N, Grof P, Alda M, Baethge C, et al. Approximate entropy of self-reported mood prior to episodes in bipolar disorder. *Bipolar Disord* 2006;8:424–9.
- Goldstein DJ, Lu Y, Detke MJ, Hudson J, Iyengar S, Demitrack MA. Effects of duloxetine on painful physical symptoms associated with depression. *Psychosomatics* 2004;45:17–28.
- Gorard DA, Gomborone JE, Libby GW, Farthing MJ. Intestinal transit in anxiety and depression. *Gut* 1996;39:551–5.
- Guinjoan SM, Bernabo JL, Cardinali DP. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. *J Neurol Neurosurg Psychiatry* 1995;59:299–302.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
- Hansen MB. Neurohumoral control of gastrointestinal motility. *Physiol Res* 2003;52:1–30.
- Hinder RA, Kelly KA. Human gastric pacemaker potential. *Am J Surg* 1977;133:29–33.
- Hu S, Grant WF, Stern RM, Koch KL. Motion sickness severity and physiological correlates during repeated exposures to a rotating optokinetic drum. *Aviat Space Environ Med* 1991;62:308–14.
- Huizinga JD. Physiology and pathophysiology of the interstitial cell of Cajal: from bench to bedside. II. Gastric motility: lessons from mutant mice on slow waves and innervation. *Am J Physiol Gastrointest Liver Physiol* 2001;281:1129–34.
- Jin X, Katsuura T, Iwanaga K, Shimomura Y, Inoue M. The influence of taste stimuli and illumination on electrogastragram measurements. *J Physiol Anthropol* 2007;26:191–5.
- Koch KL, Stern RM. Functional disorders of the stomach. *Semin Gastrointest Dis* 1996;7:185–95.
- Koschke M, Boettger MK, Schulz S, Berger S, Terhaar J, Voss A, et al. The autonomy of autonomic dysfunction in major depression. *Psychosomatic Medicine* 2009;71:852–60.
- Makikallio TH, Seppanen T, Airaksinen KE. Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. *Am J Cardiol* 1997;79:779–83.
- Moser M, Lehofer M, Hoehn-Saric R. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *J Affect Disord* 1998;48:115–24.
- Ogawa A, Mizuta I, Fukunaga T, Takeuchi N, Honaga E, Sugita Y, et al. Electrogastrography abnormality in eating disorders. *Psychiatry Clin Neurosci* 2004;58:300–10.
- Peupelmann J, Quick C, Berger S, Hocke M, Tancer ME, Yeragani VK, Bär KJ. Linear and non-linear measures indicate gastric dysmotility in patients suffering from acute schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33(7):1236–40.
- Pfaffenbach B, Adamek RJ, Lux G. The value of electrogastrography for the diagnosis of gastroenterologic function. *Dtsch Med Wochenschr* 1998;123:855–60.
- Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci* 1991;88:2297–301.
- Pincus SM. Assessing serial irregularity and its implications for health. *Ann N Y Acad Sci* 2001;954:245–67.
- Pincus SM. Quantitative assessment strategies and issues for mood and other psychiatric serial study data. *Bipolar Disord* 2003;5:287–94.
- Pincus SM. Approximate entropy as a measure of irregularity for psychiatric serial metrics. *Bipolar Disord* 2006;8:430–40.
- Qian LW, Pasricha PJ, Chen JD. Origins and patterns of spontaneous and drug-induced canine gastric myoelectrical dysrhythmia. *Dig Dis Sci* 2003;48:508–15.
- Radhakrishnan N, Gangadhar BN. Estimating regularity in epileptic seizure time-series data. A complexity-measure approach. *IEEE Eng Med Biol Mag* 1998;17:89–94.
- Rechlin T, Weis M, Spitzer A, Kaschka WP. Are affective disorders associated with alterations of heart rate variability? *J Affect Disord* 1994;32:271–5.
- Rottenberg J. Cardiac vagal control in depression: a critical analysis. *Biol Psychol* 2007;74:200–11.
- Ruhland C, Koschke M, Greiner W, Peupelmann J, Pietsch U, Hocke M, et al. Gastric dysmotility in patients with major depression. *J Affect Disord* 2008;110:185–90.
- Smout AJPM, VanDerSchee EJ, Grashuis JL. What is measured in electrogastrography? *Dig Dis Sci* 1980;25:179–87.
- Structured clinical interview for DSM IV axis I disorders (SCID), clinical version. (Arlington, USA). American Psychiatric Publishing. Ref Type: Generic; 1997.
- Sussman N. SNRIs versus SSRIs: mechanisms of action in treating depression and painful physical symptoms. *J Clin Psychiatry* 2003;5:19–26.
- Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in unctinal dyspepsia. *Gastroenterology* 1998;115:1346–52.
- Tulen JH, Bruijn JA, de Man KJ, Peppinkhuizen L, van den Meiracker AH, Man in 't Veld AJ. Cardiovascular variability in major depressive disorder and effects of imipramine or mirtazapine. *J Clin Psychopharmacol* 1996;16:135–45.
- Voss A, Baier V, Schulz S, Bär K. Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders. *Bipolar Disord* 2006;8:441–52.
- Walsh JW, Hasler WL, Nugent CE, Owyang C. Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy. *Am J Physiol* 1996;270:G506–14.
- Xu X, Qian L, Chen JD. Anti-dysrhythmic effects of long-pulse gastric electrical stimulation in dogs. *Digestion* 2004;69:63–70.
- Yeragani VK, Balon R, Pohl R, Ramesh C. Depression and heart rate variability. *Biol Psychiatry* 1995;38:768–70.
- Yeragani VK, Rao KA, Smith MR, Pohl RB, Balon R, Srinivasan K. Diminished chaos of heart rate time series in patients with major depression. *Biol Psychiatry* 2002;51:733–44.
- Yeragani VK, Pohl R, Mallavarapu M, Balon R. Approximate entropy of symptoms of mood: an effective technique to quantify regularity of mood. *Bipolar Disord* 2003;5:279–86.