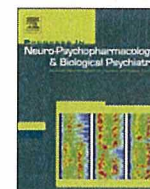




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Linear and non-linear measures indicate gastric dysmotility in patients suffering from acute schizophrenia

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ABSTRACT

Cardiac autonomic dysfunction has been reported in patients suffering from schizophrenia. The aim of the present study was to evaluate gastric electrical activity in unmedicated patients suffering from acute schizophrenia in relation to their symptoms.

Electrogastrography was performed before and after test meal ingestion in 26 patients suffering from schizophrenia and 26 matched controls. The non-linear measure approximate entropy (ApEn) was calculated for the first time from the obtained signal in addition to standardized measures. Results were correlated with the scales for the assessment of positive symptoms and negative symptoms. In addition, autonomic and abdominal symptoms were assessed by the autonomic symptom score.

We found a significantly increased amount of tachygastria and arrhythmia within the signal of the activity of the gastric pacemaker before and after test meal digestion in patients compared to controls, indicating increased sympathetic modulation within the enteric nervous system. A significant difference was observed for slow wave, which represents the dominant frequency of gastric pacemaker activity, indicating gastric dysmotility in our patients. The elevated ApEn measure points to increased complexity and dysregulation. In addition, we have observed a correlation between delusions and tachygastria.

Sympathetic function seems to be altered in the enteric nervous system of patients suffering from schizophrenia. Future studies need to explore the influence of the disease on different branches of the autonomic nervous system and clinical consequences of enteric dysfunction. Our findings point to a possible systemic autonomic imbalance that needs to be studied in respect to the neurobiology of schizophrenia.

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1. Introduction

Autonomic imbalance has been reported in various psychiatric conditions including in patients suffering from depression (Agelink et al., 2001; Voss et al., 2006; Boettger et al., 2008) and schizophrenia (Mujica-Parodi et al., 2005; Zahn and Pickar, 2005; Boettger et al., 2006; Bär et al., 2008a; Peupelmann et al., 2009). Acute psychotic

episodes in patients suffering from schizophrenia seem to be associated with decreased parasympathetic modulation (Okada et al., 2003; Toichi et al., 1999; Bär et al., 2005; Bär et al., 2007a; Bär et al., 2007b). Moreover an increased sympathetic modulation, associated with psychotic stress, has been evidenced in non-medicated patients with schizophrenia which is likely to increase the stress on the heart due to reduced parasympathetic tone (Dinan, 2004; Bär et al., 2007c). Furthermore, autonomic imbalance has been shown in first degree relatives of patients suffering from schizophrenia, suggesting a genetic link (Castro et al., 2009; Bär et al., 2009). Although the underlying mechanisms have not been investigated yet, a lack of activation in the medial prefrontal cortex in schizophrenia might affect the inhibitory control over amygdala-autonomic function (Williams et al., 2007), which can subsequently lead to an exacerbation of arousal responses (Williams et al., 2004; Bär et al., 2007a).

The investigation of different divisions of the ANS might be one approach to better comprehend changes of autonomic regulation in the disease. This has been shown in a recent study by Bob et al. (2007).

Abbreviations: ANOVA, analysis of variance; ANS, autonomic nervous system; ANS score, autonomic symptom score; ApEn, approximate entropy; EDA, electrodermal activity; EGG, cutaneous electrogastronomy; GMA, gastric myoelectrical activity; MANOVA, multivariate analysis of variance; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; ICDP, instability coefficient of dominant power; QTvi, QT variability index.

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The authors demonstrated that electrodermal activity (EDA) can be used as a measure of central nervous system and autonomic activity indicating possible chaotic neural processes in schizophrenia. Furthermore autonomic function has been assessed in the pupil (Lidsky et al., 1971; Rubin and Barry, 1976). However, the impact of medication was not satisfactorily excluded in these earlier studies. Bär et al. presented evidence that central regulation of pupil and heart is significantly altered in schizophrenia (Bär et al., 2008b) in addition to the breathing pattern (Peupelmann et al., 2009).

To further understand the dysfunction of other branches of the ANS in schizophrenia, we have investigated the gastric myoelectrical activity (GMA) in unmedicated patients by means of cutaneous electrogastrography (EGG), which is a non-invasive method for recording GMA. It had previously been demonstrated that stress has an inhibitory effect on postprandial GMA and this may involve both vagal and sympathetic pathways (Yin et al., 2004). Autonomic function within the enteric nervous system in patients with major depression has been recently investigated by EGG and an increased sympathetic modulation was suggested as a possible factor (Ruhland et al., 2008).

In addition, for the first time, we have calculated the non-linear measure approximate entropy (ApEn) from recorded EGG data to examine the regularity of the obtained signal. We have applied a technique previously described by Pincus (1991, 2006). In addition, we have assessed the psychopathology to better understand the influence of the disease using the scales for the assessment of positive (SAPS) and negative symptoms (SANS) and correlated values with measures of EGG. In addition, we have applied an autonomic symptom score (ANS score) as previously published (Ruhland et al., 2008) to examine the interrelation of clinical symptoms and EGG parameters in patients. We hypothesised that indicators of sympathetic activity such as tachygastria might be increased and correlate with positive symptoms as previously shown for heart rate variability (Bär et al., 2005). Thus, EGG was performed before and after test meal ingestion in 26 patients suffering from schizophrenia and 26 matched controls. ApEn was calculated from the obtained signal in addition to standardized measures to examine the regularity and complexity.

2. Methods

2.1. Subjects

Twenty-six patients suffering from paranoid schizophrenia and 26 healthy matched controls (see Table 1) were included in this study. Control subjects were recruited from hospital staff and medical students. A careful interview and clinical investigation was performed for all participants to exclude any potential psychiatric or other disease (apart from schizophrenia in patients). No psychotropic or other interfering medication was allowed (patients had to be unmedicated at least 8 weeks prior to the investigation). All participants were seen by a gastroenterologist (M.H.) to exclude any potential disease. Diagnosis of paranoid schizophrenia was established by a staff psychiatrist when patients fulfilled DSM-IV criteria (diagnostic and statistical manual of mental disorders) as assessed by the Structured Clinical Interview for DSM-IV (First, 1997). First episode patients were followed-up for 6 months to assure the correct diagnosis. Psychotic symptoms were quantified using SAPS and SANS scales (Andreasen et al., 1995) as well as the autonomic symptom score (ANS score; Ruhland et al., 2008). We obtained an ANS score, which includes the following symptoms: feeling of fullness, heartburn, nausea, vomiting, dry mouth, diminished appetite, constipation, diarrhoea, 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). All participants gave written informed consent to a protocol approved by

Table 1
Clinical and demographic data of participants.

	Controls	Patients
<i>Participants</i>	26	26
(Male/female)	(12/14)	(12/14)
Age (years) \pm SD	37.50 \pm 15.35	38.12 \pm 14.86
Body mass index \pm SD	23.54 \pm 3.67	24.00 \pm 3.90
<i>Education</i>		
Primary	n = 12	n = 15
Secondary	n = 14	n = 11
<i>Smoker/non-smoker</i>	n = 5/21	n = 8/18
\leq 5 cigarettes/day	n = 0	n = 2
5 – 10 cigarettes/day	n = 0	n = 1
> 10 cigarettes/day	n = 2	n = 5
First episode of psychosis	–	n = 10
Duration of illness (years, min–max)	–	8.96 (0–38)
Age of onset in male/female	–	22.35 \pm 4.9/33.6 \pm 6.9
SAPS \pm SD	n.a.	46.88 \pm 13.72
SANS \pm SD	n.a.	43.96 \pm 12.97
<i>ANS score</i>		
Sweating \pm SD	0	1.13 \pm 0.24
Tachycardia \pm SD	0	0.78 \pm 0.21
Total ANS score \pm SD	1.2 \pm 0.36	6.3 \pm 0.82

SAPS: scale for the assessment of positive symptoms, SANS: scale for the assessment of negative symptoms, ANS score: autonomic symptom score, SD: standard deviation.

the Ethics Committee of the Friedrich-Schiller-University, Jena, Germany.

2.2. Experimental task and procedure of EGG recordings

Patients were studied in the morning after an overnight fast. The EGG (EGG device; Medtronic, Minneapolis, USA) was recorded for 30 min in fasting state and thereafter for another 30 min during standard meal digestion (200 ml Clinutren®, 300 kcal, Vevey, Switzerland). All four electrodes were positioned to follow the antral axis of the stomach. The best results were obtained from channel 3, because it is positioned above the gastric pacemaker (Chen et al., 1994). Gastric slow wave is a measure for coupling of two EGG channels. In this paper, we calculated the slow wave parameter by coupling the channel one, placed over the fundus region and channel three positioned above the gastric pacemaker. Channel four was placed over the antrum region.

2.3. Data acquisition and preprocessing

EGG electrodes transmit the activity of the gastric pacemaker which is located in the corpus of the stomach (Chen et al., 1995). The power spectra of gastric myoelectrical activity were determined by using the adaptive running spectral analysis method. The normal frequency of the gastric signal is about 0.05 Hz. However, sudden changes of its frequency have been observed and are generally considered to be related to gastric motility disorders. The signal of the pacemaker contains slow waves as well as spike 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, 1978; Chen et al., 1995). Gastric slow waves represent the dominant frequency obtained from spectral analyses corresponding with frequency of phasic gastric contractions (Chen et al., 1995). The percentage of single slow wave spectra was defined as the percent of time during which it was present

over the observation period (e.g., normogastria in %, 2.4–3.6 cycles per minute). Gastric dysrhythmias include bradygastria (0.5–2.4 cycle/min; vagal modulation) and tachygastria (3.7–9.0 cycle/min; sympathetic modulation). Furthermore, arrhythmia within the signal of the activity of the gastric pacemaker is associated with a lack of a dominant frequency (0.5–9.0 cycle/min; sympathetic modulation) (Chen et al., 1995; Qian et al., 2003).

The instability coefficient of dominant power (ICDP) is an indicator of the stability of gastric electrical peak and reflects changes in gastric slow waves.

2.4. Approximate entropy (ApEn)

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 (1991, 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 (Pincus, 2001). 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, $\mathbf{x}(i)$ and $\mathbf{x}(j)$ is defined as the maximum difference in their respective scalar components. Then the sequence $\mathbf{x}(1), \mathbf{x}(2), \dots, \mathbf{x}(N-m+1)$ is used to construct $\ln C_i^m(r) = \{\text{number of } \mathbf{x}(j) \text{ such that } d[\mathbf{x}(i), \mathbf{x}(j)] \leq r\} / (N-m+1)$ for each ' $i \leq N-m+1$ '.

The $C_i^m(r)$ 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, $\phi^m(r)$ is the average value of $\ln C_i^m(r)$, \ln being the natural logarithm.

The value of ' N ' is fixed, typically between 100–5000 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, 2001). In this study, 1000 data points were used (Yeragani et al., 2003).

2.5. Statistical analyses

For statistical analyses, SPSS for Windows (version 14.0) 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. Thereafter, we performed a MANOVA to examine the overall differences between patients with schizophrenia and control subjects before and after test meal ingestion. Follow-up univariate analyses of variance (ANOVAs) were performed for EGG data with patients versus controls as the grouping factor. We then performed a MANOVA for repeated measures (GROUP \times TIME) to investigate the differences between both groups in time (before and after test meal).

For descriptive analysis a post hoc t -test was performed and presented in Fig. 1.

Ratings of psychopathological scales (SANS, SAPS) and the ANS score were correlated with EGG parameters. In addition, ANS score items were compared between patients and controls using a t -test. We used a probability level of 0.05 for significance.

3. Results

Multivariate analysis revealed a significant difference between patients and controls for all EGG parameters including percentage of normogastria, tachygastria, bradygastria, arrhythmia, dominant power (ICDP), the parameter slow waves and ApEn [$F(37,14) = 7.37$; $p < 0.0001$]. The follow-up univariate ANOVA revealed a significant effect for normogastria ($F = 4.6$; $p < 0.03$) being decreased in patients (before test meal (mean \pm standard error of mean): controls = 71.2 ± 4.8 , patients = 61 ± 5.1 ; after test meal: controls = 71 ± 4.6 , patients = 54 ± 4.4), whereas no difference for bradygastria was observed (before test meal: controls = 8.8 ± 2.7 , patients = 7.7 ± 1.6 ; after test meal: controls = 8.3 ± 1.4 , patients = 9.1 ± 2.0).

In addition, a significant effect was seen for the sympathetic parameter tachygastria ($F = 14.6$; $p < 0.0003$; Fig. 1A). An increased amount of arrhythmia ($F = 7.14$; $p < 0.01$) pointed to an increased sympathetic modulation as well (before test meal: controls = 19.8 ± 4.0 , patients = 22.1 ± 3.9 ; after test meal: controls = 13.0 ± 2.9 , patients = 27.9 ± 3.6). Furthermore, a significant difference was observed for slow wave ($F = 6.05$; $p < 0.01$; Fig. 1B) indicating gastric dysmotility in our patients. Similarly, a significant difference for ICDP was found ($F = 9.46$; $p < 0.003$; Fig. 1C) revealing an increased amount of instability of the gastric electrical peak. The non-linear parameter ApEn indicated decreased regularity in the analyzed signal ($F = 14.5$; $p < 0.00003$; Fig. 1D).

The MANOVA for repeated measures (GROUP \times TIME) indicated an overall difference before and after the test meal ingestion between patients and controls [$F(44,7) = 5.6$; $p < 0.0001$] and specifically for the parameter arrhythmia [$F = 8.02$; $p < 0.007$] and ApEn [$F = 30.0$; $p < 0.0001$].

Comparisons of parameters of the ANS score by means of a t -test revealed that schizophrenic patients complained significantly more often about sweating ($p < 0.001$), tachycardia, ($p < 0.002$) and loss of appetite ($p < 0.008$).

3.1. Correlations

We found a significant correlation between the subscale for delusion of SAPS with tachygastria ($r = 0.4$; $p < 0.04$). Furthermore, we observed a significant correlation between tachygastria with the item abdominal cramps ($r = 0.445$; $p < 0.02$) and with the total ANS score ($r = 0.508$; $p < 0.01$) in patients.

4. Discussion

To the best of our knowledge, this is the first study to investigate changes of gastric myoelectrical activity in patients with schizophrenia. In accordance to our hypothesis, we observed a significantly increased amount of tachygastria in patients before and after test meal ingestion. This activity is thought to be associated with sympathetic modulation and arises due to external pacemaker activity located in the antrum of the stomach propagating retrograde to the corpus (Qian et al., 2003). Furthermore, the amount of arrhythmia did not decrease after test meal digestion. This points to an increased sympathetic modulation that is seen in patients with gastric motility disorders like delayed gastric emptying or diabetic gastroparesis (Koch, 2001). Interestingly, tachygastria correlated with the amount of delusions in our patients corroborating previous results (Bär et al., 2007a; Bär et al., 2007c). These data might suggest that severely psychotic patients, presenting with intense delusions, show an overall shift of autonomic balance towards sympathetic predominance. Similarly, a previous study has shown that the sympathetic parameter QT_{vi}, reflecting cardiac repolarization lability, correlated with the intensity of delusions (Bär et al., 2007c). Thus, these patients might be prone to develop an increased risk for cardiac arrhythmias and putatively for gastrointestinal dysfunction. In contrast to previous results, the

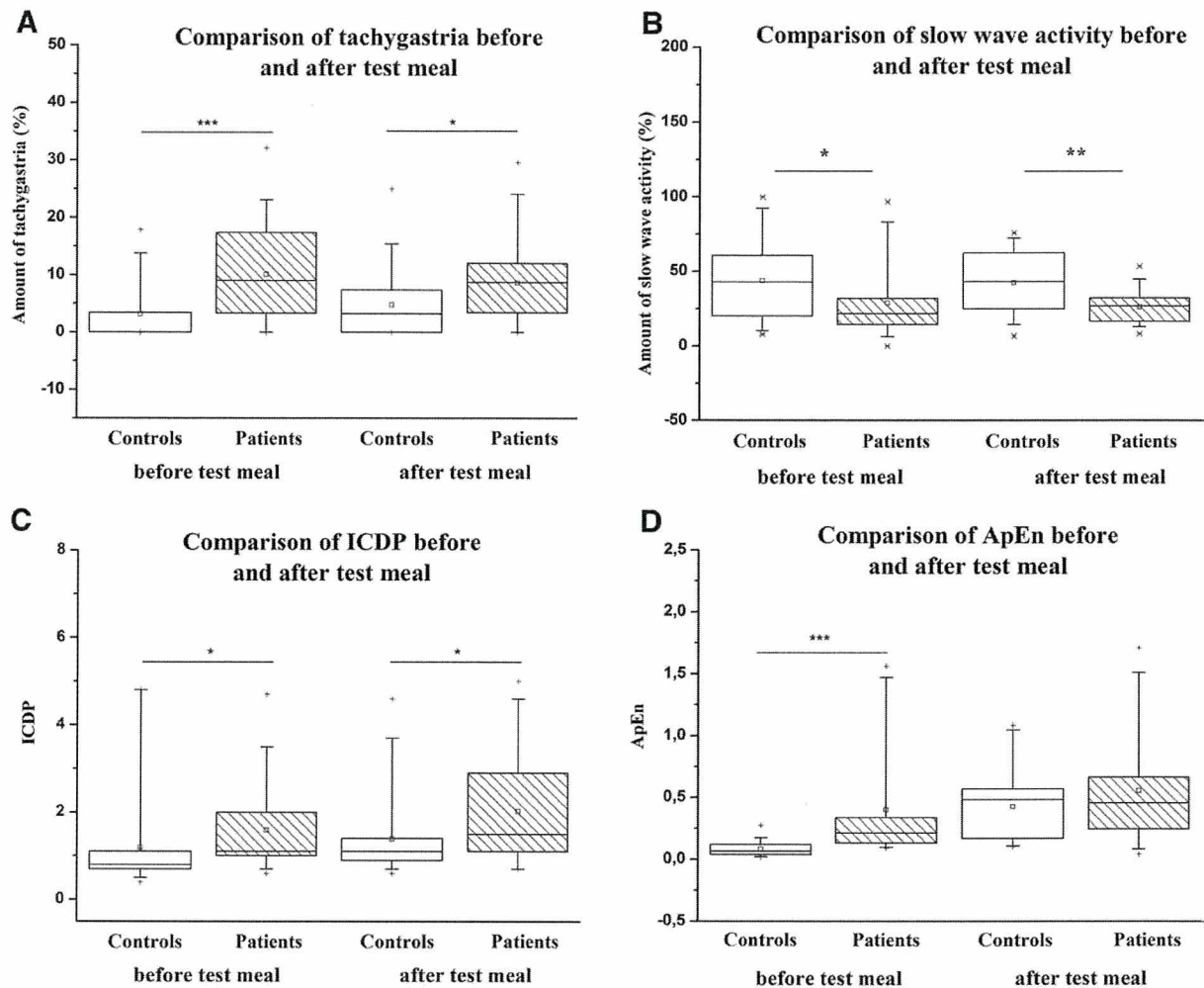


Fig. 1. Specific EGG – parameters before and after test meal ingestion are displayed in Fig. 1. The percentage of tachygastria (A) was significantly elevated before and after ingestion of the test meal suggesting increased sympathetic modulation in the enteric nervous system. Both parameters slow wave activity (B) and the instability coefficient of dominant power (C) were significantly altered before and after test meal ingestion indicating disturbed electrical propagation of the myoelectrical activity. The approximate entropy (ApEn; D) was significantly increased before test meal ingestion pointing to increased complexity. Data presented as scatter-plots; identical values are plotted non-overlapping; horizontal bars = mean. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

correlations to psychopathology are rather weak and the accuracy of measurement is different between EGG parameters and psychopathology and thus these findings need to be confirmed in larger populations. In addition, we have found few signs of reduced cardiac vagal modulation indicated by reduced normogastria in patients.

We have applied for the first time the non-linear measure approximate entropy (ApEn) to EGG data. We were able to show a significant difference between patients and controls. Based on numerous studies, ApEn correlates with “occult” changes of the signal often hidden for other methods. It identifies changes in underlying episodic behaviour not reflected in peak occurrences or amplitudes (Pincus, 1994; Pincus and Keefe, 1992). The significant increase of ApEn before and after test meal ingestion in our study might point to a disturbed myoelectrical activity within the stomach of patients. ApEn might not easily be attributed to sympathetic or parasympathetic modulation within the enteric nervous system. However, the introduction of ApEn into this new area shows again that non-linear measures can separate groups due to differences in complexity. Future pharmacological studies need to address the pathophysiological basis of this difference to gain more insight into the significance of this finding reported here. Nevertheless, gastric dysmotility was shown by the well-established parameter, slow wave and instability coefficient of dominant power in patients.

The observed pattern needs further clarification regarding three major directions. These findings underline the importance of systemic studies of autonomic dysfunction in schizophrenia to discern the interaction and influence of parasympathetic and/or sympathetic modulation in various autonomic divisions. The findings presented here should be added to studies on the cardiovascular system (Bär et al., 2005; Toichi et al., 1999), investigations of pupillary function (Bär et al., 2008a,b) and to the altered electrodermal activity (Bob et al., 2007) in schizophrenia.

Secondly, it raises the question of clinical gastrointestinal implications. Apart from an increased occurrence of ulcers in schizophrenic patients (Ozdemir et al., 2007) no other symptoms such as abdominal pain or constipation have been described in the disease. However, some items such as tachycardia or sweating were reported significantly more often from patients in our study. The generally low symptom rate might be caused by a lack of adequate introspection of patients (Jochum et al., 2006) in the acute stage or due to the known side effect of antipsychotics on enteric function (Pelizza et al., 2007; Raedler et al., 2007). The correlative analysis indicated a connection between gastrointestinal symptoms of patients and sympathetic modulation.

Therefore the third direction of future studies should elucidate the specific influence of new generation antipsychotics on gastric

pacemaker activity. The association of gastric dysmotility with the pathophysiology of the metabolic syndrome needs to be investigated in this context as well.

Our results are limited by the small study population. Furthermore, the specific explanatory power of EGG parameters is less well-established in comparison to sophisticated cardiac investigations. Although relatively young patients were investigated, the presented results are limited by the clinical exclusion of gastrointestinal diseases.

In conclusion, our findings suggest that gastric myoelectrical activity is altered in untreated patients suffering from acute schizophrenia. This result points towards a possible systemic autonomic imbalance in patients with schizophrenia that needs to be studied in respect to the neurobiology of the disease and clinical consequences for patients.

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