Neurocognitive processing of esophageal central sensitization in the insula and cingulate gyrus

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Lawal A, Kern M, Sanjeevi A, Antonik S, Mepani R, Rittmann T, Hussaini S, Hofmann C, Tatro L, Jesmanowicz A, Verber M, Shaker R. Neurocognitive processing of esophageal central sensitization in the insula and cingulate gyrus. Am J Physiol Gastrointest Liver Physiol 294: G787–G794, 2008. First published January 10, 2008; doi:10.1152/ajpgi.00421.2007.—The cingulate and insular cortices are parts of the limbic system that process and modulate gastrointestinal sensory signals. We hypothesized that sensitization of these two limbic area may operate in esophageal sensitization. Thus the objective of the study was to elucidate the neurocognitive processing in the cingulate and insular cortices to mechanical stimulation of the proximal esophagus following infusion of acid or phosphate buffer solution (PBS) into the esophagus. Twenty-six studies (14 to acid and 12 to PBS infusion) were performed in 20 healthy subjects (18–35 yr) using high-resolution (2.5 × 2.5 × 2.5 mm3 voxel size) functional MRI (fMRI). Paradigm-driven, 2-min fMRI scans were performed during randomly timed 15-s intervals of proximal esophageal barostatically controlled distensions and rest, before and after 30-min of distal esophageal acid or PBS perfusion (0.1 N HCl or 0.1 M PBS at 1 ml/min). Following distal esophageal acid infusion, at subliminal and liminal levels of proximal esophageal distensions, the number of activated voxels in both cingulate and insular cortices showed a significant increase compared with before acid infusion (P < 0.05). No statistically significant change in cortical activity was noted following PBS infusion. We conclude that 1) acid stimulation of the esophagus results in sensitization of the cingulate and insular cortices to subliminal and liminal nonpainful mechanical stimulations, and 2) these findings can have ramifications with regard to the mechanisms of some esophageal symptoms attributed to reflux disease.

reflux disease; esophageal distension; fMRI; hypersensitivity; esophageal acid stimulation

GASTROESOPHAGEAL REFLUX EVENTS result in both chemical and mechanical stimulation of the esophagus by acid and distention, respectively. It is conceivable that chemical stimulation of the distal esophagus results in sensitization of the proximal esophagus to the distention event through the process of central sensitization and facilitates the development of distention-related symptoms even in the absence of the chemical component of the refluxate.

Visceral hypersensitivity is thought to contribute to functional esophageal pain, and this is believed to be due to a complex interaction between peripheral and spinal nerves, higher cortical centers, descending inhibitory pathway, and psychological modulation triggered by the stimulus (14, 25). Various attempts have been made to elucidate the mechanisms of the exaggerated visceral sensitivity in humans using various neurophysiological and brain imaging techniques. The limbic system, which includes the insular, cingulate, amygdala, thalamus, hypothalamus, and prefrontal cortex has been reported to participate in the processing of esophageal afferent sensory inputs (3, 19, 22). In particular, the insula and cingulate have been shown to participate in the integration of autonomic, affective, cognitive, and motor responses to sensory signals originating from the upper and lower gastrointestinal tract (11).

Although sensitization to nonphysiological electrical stimulation of the esophagus in the insula and cingulate have been reported using cortical evoked potential (CEP) (35, 36), CEP lacks spatial resolution seen with functional MRI (fMRI). Electrical stimulation of the esophagus can cause discomfort or pain and trigger attention and emotional responses that can modulate neuronal processing. Conscious perception of stimuli results in a complex interaction between sensory and cognitive association areas of the cerebral cortex. Thus these findings reflect both the neural and neurocognitive components of the sensation (15, 28, 36, 37). With the recent recognition of cortical registration of subliminal gut stimulation (21, 38), it is now possible to study the neural circuitry of these areas without the influence of perception-related cognitive processes in humans. What is not known is whether this central sensitization of the cingulate and/or insular cortices encompasses the esophageal response to distention, a physiologically occurring stimulus induced by gastroesophageal reflux of gas, acidic, and nonacidic fluid. We hypothesized that distal esophageal acid exposure will lead to central sensitization of the insula and cingulate cortices to proximal esophageal distensions. The aim of the study is to objectively elucidate the neurocognitive processing (using fMRI) in the cingulate and insular cortices to mechanical stimulation of the proximal esophagus following infusion of acid or phosphate buffer solution (PBS) into the distal esophagus.

METHODS

Study Subjects

Subjects 18 to 35 yr old were recruited by advertisement and did not have a diagnosis of gastroesophageal reflux disease by interview as well as following a detailed health questionnaire and negative transnasal endoscopy. Twelve healthy volunteers (8 men and 4 women) participated in 14 studies involving intraesophageal acid
exposure (7 insular and 7 cingulate cortices). Two female subjects participated in both studies on 2 separate days 1–2 wk apart. An additional eight healthy subjects (6 women and 2 men) participated in 12 studies with intraesophageal PBS exposure (6 cingulate and 6 insular) and served as control. One male and three female subjects participated in both studies on 2 separate days 1–2 wk apart.

The Human Research Review Committee of the Medical College of Wisconsin approved the study, and all volunteers gave written, informed consent.

**Experimental Technique**

*Catheter assembly and determination of perception threshold.* The schematic representative of our experimental protocol is shown in Fig. 1. For determination of the sensation threshold (i.e., the liminal stimuli), we used a computer-controlled barostatic technique to deliver sustained distention pressures in the proximal esophagus. A catheter-affixed infinitely compliant polyethylene bag was passed transanally and positioned in the proximal third of the esophagus after determination of the upper border of the lower esophageal sphincter by manometry. The polyethylene bag was cylindrical with a length of 5 cm and a fully inflated diameter of 6 cm. The maximum bag volume was 57 ml. The barostat machine (G & J Electronic, custom biomedical system, Toronto, ON, Canada) was placed outside the MRI scanner and was connected to the bag by a 30-ft-long single-lumen tube (3-mm OD, 1.8-mm ID). The perception threshold for each individual subject was determined in the upright position by both the ascending method of limit and the forced-choice method (43). The barostat was programmed to deliver rapid phasic distention to a constant plateau pressure for 10 s. At each pressure step, the subjects were asked whether they “felt slight pressure under the sternum or not.” The balloon was completely deflated after each tested pressure. The distention pressure was phasically increased by a previously described method in 2- to 5-mmHg increments until perception was reported (43). This perception pressure was tested twice in each subject. This perception pressure was confirmed in each individual by the forced-choice method. Where there is discordance, the pressure perceived 75% of the test time for the forced choice was used as the perception threshold. All perception thresholds were performed 30 min before fMRI scanning. The maximum distension pressure is 10 mmHg above perception threshold.

*pH monitoring.* Intraesophageal pH was monitored via a two-site pH probe sensor [medical measurement system (MMS)] connected to a pH recorder (Digitrapper MKIII, Synectics Medical, Stockholm, Sweden; and MMS, Dover, NH). The pH sensors were standardized by use of standard solutions of pH 1 and 7 before the study. Acid or PBS infusion to the distal esophagus was at 5 cm above the upper border of a manometrically determined lower esophageal sphincter. The pH probe was transanally positioned in the esophagus with the distal and proximal pH sensors placed 3 and 13 cm above the lower esophageal sphincter, respectively, to accurately document acid exposure. The pH recorder was disconnected from the pH probe prior to placing the subjects in the MRI scanner. After the pre-acid/PBS distension protocol, subjects were removed from the MRI scanner and subsequently the pH recorder was connected to the pH probe outside the scanner room with the patient in the upright sitting position. Acid/PBS infusion was performed as described below. Analysis of the recorded data was performed by using the Medtronic polygram Net (Skovlunde, Denmark) and MMS software.

**Esophageal acid or PBS infusion, sensitization, and distention protocol.** Using a modified version of esophageal sensitization technique by acid by Sarkar et al. (37), we performed a range of proximal esophageal distentions prior to and following 30 min of distal esophageal acid (0.1 N HCl, pH 1) or 0.1 M PBS (pH 7.4) infusion at 1 ml/min via a Harvard pump (Harvard Apparatus). The preinfusion perception thresholds were determined 40 min before distension fMRI data acquisition. Postinfusion perception thresholds were determined 5 min after completion of infusion, and distension fMRI data were acquired 40 min after completion of infusion.

For testing cortical responses to proximal esophageal distention, we performed randomly timed 15 s of phasic proximal esophageal distention alternating with 25 s of no distention. The interval between distending stimuli was randomly varied to overcome potential anticipation of the distentions (Fig. 2). All subjects received nonpainful esophageal distensions with a range of distending pressures (2 to 5 mmHg incremental) until perception of pressure was felt. The pressures prior to perception were termed subliminal pressures, and the first perceived pressure using the forced choice method was regarded as liminal pressure. The lowest unperceived pressure (subliminal) tested was used for analysis and compared with the liminal pressure in each individual.

*fMRI scanning protocol.* Gradient echo planar magnetic resonance images were acquired using a 3.0-T GE Signa System (General Electric Medical Systems, Waukesha, WI) equipped with a custom three-axis head coil designed for rapid gradient field switching and a shielded transmit/receive head-cage radiofrequency coil. The magnetic resonance scanner and head coil were used to acquire a time course of echo planar images over the entire cingulate and insular cortex from its superior to the inferior margins. Eleven to 15 contiguous 2.5-mm-thick sagittal and axial slices of the cingulate and insula, respectively, were acquired depending on the extent of the cingulate and insular cortices on anatomical localization. One hundred twenty images were captured with an echo time of 41.6 ms and a repetition time of 1,200 ms. Echo planar images were 96 × 96 pixels over a 240-mm field of view (Fig. 3) yielding a voxel size of 2.5 × 2.5 × 2.5 mm³. High-resolution spoiled gradient recalled acquisition at steady-state images were also obtained consisting of whole brain 1.2-mm-thick slices. These high-resolution anatomical images were used for subsequent superimposition of cortical activity regions derived from the echo planar blood oxygenation level-dependent (BOLD) contrast image data. All MRI data were stereotaxically transformed to the Talairach-Tournoux coordinate system for comparison and display purposes (39).

*Image registration, movement correction, and data analysis.* All fMRI signal analysis was carried out with the Analysis of Functional Neuroimaging (AFNI) software (9). Subtle changes in head position during MRI scanning sessions was corrected using three-dimensional volume registration that corrects motions of a few millimeters and
Esophageal distention paradigm

\[
\begin{array}{cccccc}
R & R & D & D & D \\
0 & 10 & 25 & 50 & 65 & 90 & 105 & 145 s \\
0 & 15 & 30 & 55 & 70 & 95 & 110 & 145 s \\
0 & 5 & 20 & 45 & 60 & 85 & 100 & 145 s \\
0 & 20 & 35 & 60 & 75 & 100 & 115 & 145 s \\
0 & 12 & 27 & 52 & 67 & 92 & 107 & 145 s \\
\end{array}
\]

\(\text{D= Distention, R= rest}\)

Fig. 2. Shows randomization of esophageal distending stimuli thereby preventing anticipation of the stimuli.

rotations of a few degrees using first-order Taylor series at each point in the six motion parameters (3 shifts, 3 angles) and Fourier interpolation (9). Deconvolution (multiple regression) technique that computes the hemodynamic response function from the magnetic signal time series in each voxel was used to detect cortical regions that exhibit BOLD changes and tests whether the response function differs from the response associated with random Gaussian variation of the signal.

Behavioral test. Prior to catheter placement and MRI scanning, 14 subjects (6 acid and 8 PBS) were administered the Spielberger State and Trait Anxiety (STAI), Beck Anxiety Inventory (BAI), and MRI Fear Survey Schedule (MRI-FSS; 9 items) questionnaires and asked to give a rating of their anxiety level before and immediately after the study, asking them to report how they felt while in the MRI scanner. The Spielberger STAI-State anxiety 20-item test is a function of the stressors on an individual. Higher scores are seen in circumstances perceived as threatening irrespective of objective danger. It is low in nonstressful situations. The BAI is a 21-item self-report measure of anxiety severity that is descriptive of subjective, somatic, or panic-related symptoms of anxiety. MRI-FSS addresses specific features of MRI scanning environment (noise, confinement, and isolation) that may induce psychological distress such as anxiety and fear. All three instruments measure current state of anxiety and fear related to a stressor. Prior study has shown that the MRI-FSS was a better predictor of likely adverse psychological reactions in the MRI scan than other measures (18).

Statistical Analysis

Reproducibility of fMRI signal time series and cortical topography was tested by analysis of variance and regression analysis as indicated by AFNI. A composite fMRI activation data analysis was also performed. The significant level of threshold for the functional data was 0.05 and corrected for multiple comparison by Bonferroni’s correction. Statistical comparisons were performed with SigmaStat 2.03 statistical package (1997, SPSS, Chicago, IL). Average data are shown as means ± SE unless otherwise stated. We used paired t-test to compare the mean number of activated voxels induced by proximal esophageal distention prior to and after distal esophageal acid perfusion. A P value <0.05 was considered statistically significant.

RESULTS

There was wide variation in the perception threshold to balloon distention in the pre-acid infusion period among the study subjects. The perception threshold (liminal sensation) ranged from 5 to 30 mmHg (median 18 mmHg). In all subjects, 30 min of distal esophageal acid infusion resulted in predictable drop in distal intraesophageal pH to less than 4, with a corresponding pH above 6 in the proximal esophagus. Acid infusion in the distal esophagus resulted in mild burning sensation 25 min after onset of infusion in 7 of 12 subjects that resolved on cessation of infusion.

The median pre- and post-PBS subliminal pressure tested was 5 mmHg (5 ± 0). The median pre- and post-PBS liminal pressures tested was 20 mmHg (21 ± 5; range 10–30) and 18 mmHg (18 ± 5; range 10–25), respectively. The median pre-acid infusion subliminal and liminal pressures tested for all subjects were 5 mmHg (4.5 ± 0.5; range 2–10 mmHg) and 18 mmHg (17 ± 2; range 5–30 mmHg), respectively. Table 1 shows the perception threshold and subliminal distention pressures tested in each subject before and after distal esophageal acid exposure. The difference in pre- and post-acid perfusion perception pressures did not reach statistical significance.

In all subjects there was a significant increase in the number of activated voxels in both the cingulate gyrus and insular cortices in response to proximal esophageal subliminal (unperceived) and liminal (perceived) distentions following distal esophageal acid perfusion compared with pre-acid perfusion period (Figs. 4 and 5). The mean number of activated voxels induced by proximal esophageal distentions in the insula and cingulate gyrus was significantly larger postacid compared with preacid: 8 ± 2 vs. 22 ± 4; 11 ± 1 vs. 24 ± 5 (P < 0.05, cingulate gyrus). A similar phenomenon was observed for liminal stimulation in the cingulate gyrus and insula cortex: 20 ± 4 vs. 37 ± 6 (P < 0.05) and 22 ± 4 vs. 37 ± 3 (P < 0.05), respectively (Figs. 4 and 5).

Prior to distal esophageal acid infusion, the mean number of activated voxels induced by subliminal proximal distentions in both the insular cortex and cingulate gyrus was significantly lower than those induced by liminal proximal esophageal distension (subliminal vs. liminal, 8 ± 2 vs. 22 ± 4; P = 0.003 vs. 11 ± 1 vs. 20 ± 4; P = 0.02), respectively. This difference was also seen after distal acid infusion in the insular cortex (30 ± 3 vs. 37 ± 3; P = 0.01) and cingulate gyrus (24 ± 5 vs. 37 ± 6; P = 0.02) (Fig. 6).

The maximum percent signal intensity change to subliminal distensions in the cingulate gyrus before and after acid stimulation in the proximal esophagus was 2.1 ± 0.4 vs. 2.7 ± 0.5 (P = 0.007), respectively. During liminal distension the maximum percent signal intensity change was 3.9 ± 0.9 vs. 4.8 ± 1.0 (P = 0.03) before and after acid stimulation, respectively. In the insular cortex, the maximum percent signal intensity change to subliminal distensions before and after acid stimulation was 1.8 ± 0.3 vs. 2.3 ± 0.3 (P = 0.02), respectively. During liminal distension the maximum percent signal intensity change was 3.4 ± 0.6 vs. 4.9 ± 1.1 (P = 0.006) before and after acid stimulation, respectively. There was no significant difference in cortical activation before and after PBS infusion in the insula (subliminal: 1.3 ± 0.7 vs. 3.8 ± 1.7; P = 0.86; liminal: 12 ± 7 vs. 11 ± 4, P = 0.46) and cingulate (subliminal: 8 ± 5 vs. 9 ± 3, P = 0.91; liminal: 42 ± 11 vs. 33 ± 7, P = 0.79) cortices (Fig. 7).

Cerebral cortical composite activity in the cingulate and insular cortices induced by subliminal and liminal distending
stimuli prior to and following distal esophageal acid infusion are shown in Figs. 8 and 9. The corresponding composite Talairach coordinate of the voxels with the greatest fMRI signal increase is shown in Table 2. There were no significant differences in the BAI, STAI-state, and MRI-FSS scores in the acid or PBS groups before and after fMRI tests.

**Table 1. Tested liminal and subliminal pressure stimuli**

<table>
<thead>
<tr>
<th>Study Subject</th>
<th>Insular Cortex</th>
<th>Cingulate Gyrus</th>
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<tr>
<td></td>
<td>Subliminal, mmHg</td>
<td>Liminal, mmHg</td>
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<tr>
<td></td>
<td>Preacid</td>
<td>Postacid</td>
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<td>A</td>
<td>4</td>
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<td>B</td>
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Tested pressure was delivered to the proximal esophagus in each subject during subliminal and liminal distentions. *In these 2 subjects the same pressure was delivered before and after acid perfusion.

**DISCUSSION**

In this study we determined the effect of distal esophageal acid exposure on cingulate and insular activity in response to proximal esophageal distention. The study findings showed significant increase in fMRI activity volume in these areas.
brain regions in response to proximal esophageal distention following acid stimulation remote from the distention site, which was not seen during PBS infusion, indicating the development of acid-induced sensitization of the esophagus to mechanical distention. Furthermore, these findings indicate that there are central changes in response to acid sensitization that involve both the insula and cingulate cortices. This central sensitization is evident at the subliminal level, demonstrating the development of neural hypersensitivity to distention by chemical stimulation of the esophagus irrespective of perception and in the absence of noxious (painful) stimuli.

Although the mechanism of this sensitization was not the goal of this study, prior studies evaluating the cortical response to electrical perceived stimulation of the esophagus have shown involvement of NMDA receptors and implicated spinal pathways in this process (44). However, this enhanced neural sensitivity could have occurred in addition to the spinal cord, at the level of the brain stem (27) or cortical and subcortical processing areas. Furthermore, studies in rats have shown facilitation of spinal nociceptive tail-flick reflex in response to chemical or electrical stimulation of the anterior cingulate cortex (7), suggesting that both ascending and descending facilitation of sensory input can occur within the cingulate cortex. The increase in cortical activity seen here despite no significant decrease in perception threshold in the proximal esophagus after acid infusion may suggest vagal afferent augmentation or increased cortical processing within the insular and cingulate cortices rather than spinal mechanism. This sensitization may be a primer to more sustained spinal mechanism that eventually results in chronic visceral sensitivity. It is likely that vagal and/or spinal induced esophageal sensitization may be a continuum and may be important in chest...
pain perception in patients with gastroesophageal or non-erosive reflux disease and noncardiac chest pain. The increase in the number of activated voxels at the liminal level may simply reflect the carryover increase from subliminal neuronal-related activity or it may also include the effect of cognitive processes associated with perception. The design of the present study does not allow for addressing these issues. Furthermore, functional consequence of any change in neural function could not be addressed. It is conceivable that longer or chronic acid exposure in the distal esophagus may cause more pronounced level of hypersensitivity or desensitization, which could translate into functional consequence such as significant reduction or increase in perception threshold.

Animal study investigating the correlation of responses of vagal afferents and brain stem neurons after acute infusion of acid (0.1 N HCl) + pepsin (1 mg/ml) into the esophagus of cats showed that infusion of acid + pepsin into the esophagus produced a significant increase in ongoing resting firing of 31% of tested vagal afferent fibers. Their responses to graded esophageal distension did not change when tested 30 min after infusion. Pepsin or saline infusion did not change the resting firing and response to esophageal distension. Intraesophageal acid + pepsin infusion resulted in a decrease in threshold and increase in firing of excited brain stem neurons response to esophageal distensions. This sensitization of response after intraesophageal acid remained unaffected after cervical (C1–C2) spinal transection, indicating that sensitization of brain stem neurons was possibly initiated by increase spontaneous firing of the vagal afferent fibers to acid + pepsin but not to sensitized response of vagal distension-sensitive afferent fibers to esophageal distension and that spinal pathway does not contribute to sensitization of brain stem neurons (27).

Furthermore, studies in rats have documented long-lasting potentiation and enhanced sensory response within the anterior cingulate cortex after digit amputation (42) and following colonic distension in viscerally hypersensitive rats (16). Central neuroplastic changes within the cingulate cortex to acid sensitization following electrical stimulation of the esophagus.

Fig. 8. Three-dimensional representation of the composite cingulate cortical activity before and after esophageal sensitization for subliminal and liminal distending stimuli. As seen, the cingulate activity in response to subliminal stimuli representing neural activity alone prior to acid infusion (top left) and after sensitization by distal esophageal acid infusion (top right). This shows an increase in cingulate activity following sensitization. In the lower half is the response of the cingulate gyrus to liminal stimuli before and after sensitization. This also shows an increase in the areas of activation following sensitization.

Fig. 9. Three-dimensional representation of the composite insula cortical activity before and after esophageal sensitization for subliminal and liminal distending stimuli. Similar findings of an increase in the areas of activation were also seen in the insula in response to subliminal and liminal esophageal stimuli following sensitization by acid perfusion.
interrogate the neural activity in the gut-brain axis afferent/sensory pathway without the influence of stimulus-related cognitive process. In addition, since esophageal distention simulates the physiological stimuli occurring during gastro-esophageal reflux of gas and fluid, the findings of the present study demonstrate the influence of one component of the reflux event, i.e., acidity on cortical response to the other component of the refluxate, i.e., distention. It is conceivable that pathological acid exposure in the esophagus may sensitize esophageal mechanoreceptors to distention (mechanical) stimuli such that subsequent esophageal distensions induced by reflux events may lead to augmented sensory perception without the presence of acid. This exaggerated response to distention caused by acid exposure demonstrates the possibility of a dual effect of reflux events on esophageal symptom production when the otherwise innocuous distention aspect of reflux events could potentially reach symptomatic level without the need for further acid exposure.

Considering the findings of prior studies showing common cortical regions involved in the processing of esophageal distention, unperceived acid exposure, and heartburn (4, 22, 23), it is conceivable that these exaggerated sensory responses to distention may translate into a variety of symptom perceptions.

Visceral hypersensitivity is reported more commonly in patients with functional gastrointestinal disorders compared with healthy subjects, e.g., irritable bowel syndrome, functional dyspepsia, noncardiac chest pain, and functional heartburn (5, 8, 17, 26, 33, 34). Central sensitization has been postulated as one of the mechanisms for visceral hypersensitivity seen in these patients. This notion is further supported by studies of esophageal sensitization in healthy adult and patients with noncardiac chest pain (18, 20, 28). The findings of the present study corroborate these earlier reports (20, 37) and further define two of the subregions of the human cortex involved in registration and processing of esophageal sensitization, which may contribute to hypersensitivity seen in patients with functional bowel disorder.

The following are the limitations of our study. There was no significant reduction in threshold perception to proximal esophageal distension after acid or PBS infusion. This could be because sensory thresholds were tested 5 min after completion of infusion, which did not allow a lag time to demonstrate a decrease in perception threshold as previously reported by Sarkar et al. (37). Also we would have preferred to perform acid and PBS infusion in the same subjects on different days, but this was impossible since most subjects do not want to return to repeat the study because of the invasiveness and long time required to complete an fMRI study of this nature (minimum 3 h per study).

In conclusion, acid stimulation of the esophagus results in central sensitization to subliminal and liminal nonpainful mechanical stimulations.

This sensitization affects both neural as well as neurocognitive aspect of human esophageal viscerosensation registered in the cingulate and insular cortices. These findings can have ramifications with regard to the mechanisms of some esophageal symptoms attributed to reflux disease.
GRANTS
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