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Functional magnetic resonance imaging and functional dyspepsia: Predictive value questioned

Ressonância magnética funcional e dispepsias funcionais: Valor preditivo interrogado

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Gabriella Marques Sorpreso[1], Ethel Zimberg Chehter[2].

ABSTRACT

Functional dyspepsia is a challenging condition in gastroenterology, characterized by digestive symptoms without evidence of organic pathology. Conventional diagnostic methods have significant limitations in terms of sensitivity and specificity. This study aims to explore the potential of functional magnetic resonance imaging (fMRI) as an innovative diagnostic approach for functional dyspepsia, aiming to improve diagnostic accuracy and benefit patients. This integrative literature review, following PRISMA guidelines, investigated the use of fMRI in diagnosing functional dyspepsia. Sixteen articles were selected after rigorous screening, employing detailed descriptive analysis and narrative synthesis. As a result, it was noted that patients with functional dyspepsia exhibit changes in brain activity, especially in areas associated with sensory processing and emotional control, indicating dysfunction in these regions. It is concluded that fMRI has promising potential in diagnosing functional dyspepsia, complementing conventional methods. Although specific pathognomonic patterns have not been identified, the affected brain areas provide a basis for the application of fMRI, improving understanding of the condition and enabling more targeted therapies.

Keywords: Magnetic resonance imaging, Dyspepsia, Functional neuroimaging, Gastroenteropathies.

INTRODUCTION

DEFINITION

In a global context, while gastroenterology has advanced considerably in the area of imaging the gastrointestinal (GI) tract, focusing on morphology through endoscopy and abdominal radiography, "functional gastrointestinal disorders (GIFs)", responsible for non-specific abdominal symptoms without organic disease, initially remained in the background. However, given the growing public interest in patients' quality of life, DGIFs have gained

1 Lattes: 1757336867831272
Graduating in Medicine from the Faculty of Medicine of ABC
Email: gabriella.sorpreso@hotmail.com
[2] Lattes: 0972445363483141
Doctor in Medicine from the Faculty of Medicine of the University of São Paulo
Email: ethel.chehter@gmail.com

prominence, being disorders associated with physical and psychological stress prevalent in modern society (1)

The "Rome Foundation", a non-profit entity dedicated to advancing knowledge about functional and motor gastrointestinal disorders, was a pioneer in formalizing the definition of functional dyspepsia in gastroenterology. The inaugural edition, "Rome I", released in 1988, established diagnostic criteria, requiring the presence of pain or discomfort in the upper abdomen for at least 12 weeks in the year prior to diagnosis, with no identifiable organic cause, and the exclusion of other known gastrointestinal conditions.

In 1999, the criteria were updated in the "Rome II" edition. Notable modifications included extending the duration of symptoms to at least 12 consecutive weeks, adding the requirement that symptoms affect the patient's quality of life, and recognizing different patterns of symptoms, such as worsening after meals. These changes were intended to improve diagnostic accuracy and consistency in identifying functional dyspepsia.

Subsequently, the "Rome III" criteria, launched in 2006, introduced significant changes. Recognizing the heterogeneity of functional dyspepsia symptoms, they proposed subtypes, highlighting painful postprandial dyspepsia and epigastric dyspepsia. Furthermore, they emphasized greater specificity in the criteria, aiming to improve diagnostic accuracy and rejected the term "nervous dyspepsia", reflecting a more comprehensive and multifactorial understanding of functional dyspepsia. These modifications represent a more refined and nuanced approach to diagnosing these disorders over time.

More recently, in 2016, the Rome IV classification system brought notable updates in the understanding and diagnosis of functional dyspepsia, representing an evolution in the approach to these gastrointestinal disorders. The most current definition of functional dyspepsia, according to Rome IV, encompasses recurrent symptoms of pain or discomfort in the upper part of the abdomen, presenting specific characteristics, such as burning, stabbing pain or a sensation of pressure.

The new diagnostic criteria established by Rome IV include recurrent symptoms that occur with regular frequency, duration of symptoms for at least three months with onset occurring at least six months before diagnosis, and pain centered in the epigastric region.

These changes compared to previous editions reflect a more refined and specific approach, with the aim of improving diagnostic accuracy. The importance of Rome IV lies in its ability to provide clearer and more objective criteria for identifying functional dyspepsia, promoting uniformity in the diagnostic process and facilitating communication between health

professionals, improving the quality of care provided to patients facing these conditions. functional gastrointestinal challenges. Ultimately, Rome IV represents a significant advance in understanding and addressing functional dyspepsia in contemporary clinical practice, providing a better understanding of the prevalence and impact of this condition. (two)

EPIDEMIOLOGY

The ability to appropriately classify DF patients is key not only to facilitate diagnosis and treatment, but also to research its etiology. The global prevalence of functional dyspepsia (FD) varies significantly between different populations, being influenced by the definition used in research. When defined as "pain in the upper abdomen", the prevalence ranges between 7% and 34.2%, while a broader definition of "upper gastrointestinal symptoms" results in a range of 23% to 45%. Furthermore, the application of different Rome criteria across studies impacts prevalence estimates, making it challenging to determine the true epidemiological value of FD, excluding organic diseases. (3)

Global Prevalence and Regional Variations

In a systematic review involving more than 100 population studies and more than 312,000 participants, the pooled prevalence of uninvestigated dyspepsia was approximately 21%. However, regional analysis reveals notable variations. Most studies were conducted in Northern Europe and Southeast Asia, with the lowest prevalence recorded in Central America (7.0%) and the highest in South America (37.7%) (4)

Diagnostic Criteria and Duration of Symptoms

The prevalence of FD is sensitive to the diagnostic criteria used. When the Rome III criteria are applied, a lower prevalence is observed, while a broader definition results in higher rates. Furthermore, the duration of symptoms is a relevant factor; the prevalence is higher when symptoms persist for a minimum period of one month (5)

Data Collection Method

Data collection methods also play a role in variation in prevalence. Notably, studies with face-to-face interviews have a higher prevalence (41.7%), highlighting the influence of the methodological approach in obtaining results (6)

Prevalence by Sex and Risk Factors

Analysis by gender reveals a slightly higher prevalence in women (25.3%) compared to men (21.9%) (5) . Risk factors associated with FD include smoking, use of non-steroidal anti-inflammatory drugs (NSAIDs), Helicobacter pylori infection and, notably, psychological disorders such as sexual, emotional and verbal abuse. (5)

Prevalence by Age

Functional dyspepsia has a notable prevalence in children, as evidenced by epidemiological studies. Comparing these data with the prevalence in adults, we can highlight significant differences.

In the pediatric group (<16 years) in a hospital in the Community of Madrid, the overall prevalence of FGIDs was 32.4%, with 16.4% in children under 4 years of age. Constipation (48.4%) and regurgitation (22.5%) were the most common disorders in this age group. Above 4 years of age, the prevalence was higher, reaching 40.3%, with emphasis on unspecified abdominal pain (29%) and functional dyspepsia (28.4%).

When comparing these data with epidemiological studies in adults, we observed that functional dyspepsia is more prevalent in this age group. In adults, the prevalence of functional dyspepsia varies widely, but studies report numbers around 10 to 25% of the global population. Prevalence tends to increase with age, affecting older adults more frequently. Therefore, possible explanations for the differences observed include the physiological immaturity of the gastrointestinal tract among children, different responses to stress and psychological pressures compared to adults, affecting the prevalence, as well as variations in the presentation of symptoms, impacting the identification and accurate diagnosis. of FGIDs. (7)

Regional Variations and Associated Comorbidities

Studies in both the West and East have documented the prevalence of FD with various definitions, with the Rome III criteria being the most used. Significant differences emerge in the clinical patterns of FD between Asians and white Caucasians, with a predominance of motility subtypes in the East (6)

Body mass index (BMI) is associated with FD, with white Caucasians generally having a higher BMI (6) . Socioeconomic factors also play a role, with FD associated with lower socioeconomic status in the West and higher status in the East (6)

Helicobacter pylori Infection and Economic Consequences

Helicobacter pylori infection plays a role in the etiology of FD, with eradication rates associated with greater improvement in symptoms in Asian patients compared to Westerners. Furthermore, the economic consequences of FD vary between the West and the East, reflecting differences in healthcare systems and patterns of medical care seeking (6).

Association with depression and anxiety

Epidemiological findings on the relationship between functional dyspepsia and mental disorders highlight a significantly higher prevalence of these in individuals with psychiatric conditions. Research indicates that patients with anxiety and depression have an increased likelihood of developing functional dyspepsia compared to the general population. Furthermore, a dose-dependent correlation is observed, where the severity of psychiatric symptoms is associated with a greater incidence and intensity of dyspepsia. Proposed mechanisms include the direct influence of stress on gastrointestinal function, changes in visceral pain perception, and neuroendocrine dysregulation. (8)

In summary, the epidemiology of FD is complex and variable, presenting significant regional differences, distinct clinical patterns, and associations with specific comorbidities. Comprehensive understanding of this condition is subject to careful consideration of the methods used, definitions adopted, and demographic characteristics of the populations studied. (3) (5) (6)

PATHOPHYSIOLOGY

Functional dyspepsia (FD) continues to defy clinical understanding due to its multifactorial etiology and the heterogeneity manifested in its symptoms. The aim is to examine the various hypotheses and causes associated with FD, highlighting the underlying complexity and emphasizing the relevance of neurophysiological changes in the brain-gut axis.

Gastrointestinal Sensorimotor Disorders

One of the initial hypotheses involves gastrointestinal sensorimotor disorders. Inadequate gastric accommodation to the volume, disproportionate distribution in the stomach and abnormalities in antral motility are observed. Sensory dysfunction, including reduced excitability of enteric nerves, highlights the complex interplay between motility and sensitivity in the context of SCD.

Immune Dysfunction

The presence of immunological disorders is an intriguing facet in the pathogenesis of FD. Mucosal inflammation, increased inflammatory cells, and duodenal eosinophilia are associated with specific symptoms. Immune activation can trigger tissue damage, influencing enteric nerve function and increasing epithelial permeability.

Changes in the Gastrointestinal Microbiota

Recent investigations explore changes in the gastrointestinal microbiota as a possible contributor to FD. Correlations between changes in duodenal mucosal bacterial load and symptoms during nutritional testing suggest a dynamic interplay between the microbiota and clinical presentation.

Gut-Brain Axis Dysfunction

An emerging hypothesis highlights dysfunction in the gut-brain axis as a key piece in the FD puzzle. Changes in the epithelial barrier, induced by immunological disorders and microbiota, can modulate gut-brain communication. Stress, playing a central role, influences gastrointestinal permeability and activates stress hormone pathways.

In summary, functional dyspepsia reveals itself to be a complex clinical entity, where the multiple hypotheses investigated outline an intricate web of interactions between physical, immunological factors, microbiota and, above all, the complexities of the brain-gut axis. In this context, neurophysiological changes emerge as a central piece in the puzzle of understanding SCD.

The interconnection between psychosocial factors and gastrointestinal manifestations highlights the pressing need for an integrated approach that considers all these facets. However, it is imperative to focus on the neurophysiological changes observed in the brain in the context of the brain-gut axis. Central pain processing, modulated by intestinal disorders, stands out as a critical component that not only contributes to symptoms but also paves the way for more accurate diagnostic strategies and innovative therapeutic approaches.

Therefore, the unanimous conclusion is that advancing the understanding and effective treatment of functional dyspepsia requires comprehensive consideration of the various hypotheses with a particular emphasis on investigating neurophysiological changes. Recognition of these constitutes an essential milestone to offer promising light for understanding and overcoming this challenging clinical condition. (9) (10) (11) (12)

DIAGNOSIS

The diagnosis of functional dyspepsia (FD) is a complex task, predominantly based on an exclusionary approach, with upper gastrointestinal endoscopy (EDA) playing a central role in eliminating organic conditions such as peptic ulcers, esophagitis and malignancies (doi: 10.3238/arztebl.2018.0222). Although the Rome III guidelines have advanced the distinction between FD and structural diseases, their limitations in terms of sensitivity and specificity highlight the need for a more refined assessment. (12)

Meal testing emerges as a valuable tool, revealing that food-related symptoms are a hallmark of FD. Nutritional testing, despite still lacking clinical validation, remains a promising investigative tool. Differentiating between FD and gastroparesis, both associated with slow gastric emptying, presents a considerable challenge, questioning the adequacy of the conventional definition of gastroparesis. The notable overlap with gastroesophageal reflux (GERD), especially in gastric accommodation failure, adds complexity to the diagnostic analysis. Attention to other functional gastrointestinal disorders (FGIDs) is essential, requiring a comprehensive assessment. (4)

The Rome IV Criteria establishes strict criteria, highlighting the persistence of symptoms, the exclusion of organic causes for EGD, and the non-association with stool irregularities, thus excluding irritable bowel syndrome. Diagnosis requires exclusion of enteric infections, comprehensive laboratory evaluations, and, when necessary, invasive procedures such as endoscopy and abdominal ultrasound. (13)

Obtaining a detailed clinical history is crucial, emphasizing typical symptoms and identifying possible etiological triggers, such as previous infections and psychological factors. Additionally, considerations of chronic non-gastrointestinal disorders, family history, and recent changes in lifestyle or medication use are essential elements for a comprehensive assessment (13).

The diagnosis of FD is undeniably challenging, based on the meticulous exclusion of organic conditions. EDA, although crucial, has limitations in terms of sensitivity and specificity. Meal testing, differentiation of gastroparesis, overlap with GERD, and consideration of other FGIDs not only add complexity to the assessment but also highlight the pressing lack of more accurate diagnostic methods.

The lack of assertive approaches results in late diagnoses, increasing the burden on patients and highlighting the importance of effective collaboration between specialties, including gastroenterology, psychology and nutrition, aiming to improve management and provide patients

with a holistic approach. Furthermore, the recent deeper understanding of FD as a brain-gut interaction disorder may mean the discovery of new, more accurate and effective diagnostic pathways, vital for significantly improving the quality of life of patients affected by FD (14)

That said, this work seeks to go beyond traditional diagnostic methods, exploring functional magnetic resonance imaging (MRI) as an innovative tool for diagnosing functional dyspepsia. FMR, known for its unique ability to map brain activity, emerges as a promising extension to the diagnostic arsenal. Then, the next section of this work explores in detail the principles, functions and characteristics of FMR, presenting it as a potential way to increase the efficiency of FD diagnosis and offer a more accurate and comprehensive approach to existing challenges.

FUNCTIONAL MAGNETIC RESONANCE AND FUNCTIONAL DYSPEPSIAS

Functional Magnetic Resonance Imaging (FMR) is a class of imaging methods developed to demonstrate regional and time-varying changes in brain metabolism. These metabolic changes may be consequent to task-induced changes in cognitive state or result from unregulated processes in the resting brain. Since its creation in 1990, the FMR has been widely used in studies in cognitive neurosciences, psychiatry/clinical psychology and pre-surgical planning, being mentioned in thousands of entries on PubMed. The popularity of FMR stems from its wide availability, non-invasive nature, relatively low cost, and good spatial resolution. Increasingly, FMR is used as a biomarker for diseases, monitoring therapies or studying pharmacological efficacy, making it an essential tool. (15)

MRI is based on magnetic resonance imaging, which in turn uses nuclear magnetic resonance with magnetic field gradients to create images with different types of contrast. The main basis for MRI is magnetic resonance imaging (MRI), which incorporates several types of contrast, such as T1 weighting, T2 weighting, susceptibility, flow, among others. To understand the contrast mechanism used in MRI, it is necessary to discuss brain metabolism. All neural signaling processes in the brain, including formation and propagation of action potentials, release of neurotransmitters, and production of adenosine triphosphate (ATP), require energy. When a brain region is activated by a cognitive task, there is an increase in local energy demand, resulting in an increase in cerebral oxygen metabolic rate (CMRO2). The hemodynamic response to this increase in neural activity is detected by MRI and generates two main results: increased local cerebral blood flow (CBF) and changes in blood oxygen concentration (BOLD contrast). (15)

The spatial resolution of FMR is limited mainly by the signal-to-noise ratio due to the need for rapid acquisition of temporal information. Compared to other functional imaging methods, such as Positron Emission Tomography (PET) and Near Infrared Spectroscopy (NIRS), MRI stands out for its relatively high spatial resolution. However, its temporal resolution is limited by the slow hemodynamic response, being surpassed by methods such as Electroencephalography (EEG) and Magnetoencephalography (MEG) in terms of capturing neural dynamics on a millisecond scale. (15)

After image acquisition, the temporal series data undergoes a pre-processing process, including motion correction, noise filtering and spatial smoothing. Statistical analysis of data uses general linear models, cross-correlation, and data-driven methods, resulting in brain activation maps. Although FMR has limitations, such as low temporal resolution, it remains a crucial tool for advancing our understanding of brain functioning, and its applications in predicting cognitive behavior and disease biomarkers promise to contribute significantly to future neuroscientific research. (15)

Furthermore, Functional Magnetic Resonance Imaging (FMR) not only provides a detailed view of changes in brain metabolism, but also stands out for the possibility of mapping the complex relationship between the brain and the intestine. The brain-gut axis, which involves bidirectional communication between these organs, can be investigated through FMR, offering valuable insights into how the brain and digestive system interact in different cognitive and emotional states.

Therefore, MRI is an essential tool for identifying changes in the brain-gut axis that deviate from the physiological pattern. Deviations in this axis, such as anomalous responses to stimuli or dysfunctions in neurogastrointestinal regulation, can be detected and analyzed by FMR. This information is crucial to better understanding the neural bases of functional gastrointestinal disorders, eating disorders, and stress-related conditions, contributing to significant advances in the field of neurogastroenterology.

In this way, the application of FMR is not limited only to the assessment of brain functions, but extends to exploring the interactions between the brain and the gut, providing a comprehensive understanding of the brain-gut axis and the possible changes that can impact digestive health. and mental. In this context, brain areas of significant importance stand out and whose study can reveal more about the pathophysiology of functional dyspepsia, in addition to being protagonists in the study of new diagnostic approaches:

Solitary Tract Nucleus (NTS)

Function: Center for integrating viscerosensory information. Receives vagal input from the gastrointestinal system.

Relevance: Greater connectivity of the NTS with cortical areas, such as the anterior insula, anterior cingulate cortex (ACC), supplementary premotor area (preSMA), and ventrolateral prefrontal cortices (vlPFC), suggests its involvement in the pathophysiology of functional dyspepsia (FD). Changes correlated with the average peristaltic propagation speed.

Insula

Function: Interoceptive processing and interoceptive attention. Receiving signals from the NTS.

Relevance: The anterior division of the insula shows greater connectivity with the NTS, indicating greater attention to uncomfortable gastric sensations.

Pre-Supplementary Motor Area (preSMA)

Function: Planning and executing movements, especially internally motivated actions.

Relevance: Coordination and processing of visceral afferents and abdominal muscle activity in uncomfortable situations, such as nausea.

Ventrolateral Prefrontal Cortexes (vlPFC)

Function: Motor inhibition and cognitive control, including retrieval and storage of working memory.

Relevance: Greater connectivity between NTS and vlPFC suggests their participation in cognitive and motor regulation in response to gastric stimuli, contributing to the pathophysiology of FD.

Anterior Cingulate Cortex (ACC)

Function: Involved in executive functions, emotional processing and pain regulation.

Relevance: Differential activities during food intake in patients with FD, suggesting greater visceral perception and possible cortical sensitization.

Cerebellum

Function: Motor coordinator and regulator of cognitive processes.

Relevance: Increased activity in patients with FD indicates possible cerebellar hyperactivity related to visceral perception and emotional regulation.

Medial Prefrontal Cortex (MPFC)

Function: Emotional processing, decision making and pain adjustment.

Relevance: Reduced gray matter density in the MPFC associated with structural changes in patients with FD, indicating impact on emotional and decision-making functions.

Thalamus

Function: Processing and retransmission of sensory stimuli.

Relevance: Differential activation in patients with FD suggests an altered response to gastric distension and implications for visceral perception.

Relationship with Functional Dyspepsia

Such brain areas highlighted by functional magnetic resonance imaging (fMRI) prove to be fundamental for understanding the pathophysiology of functional dyspepsia. The complex interaction between cortical processing, emotions and motor regulation of the gastrointestinal tract highlights the importance of thoroughly investigating the relationship between each region mentioned and the clinical manifestation of functional dyspepsia. (16) (17) (18) (19) (20) (21)

RMF AS A DIAGNOSTIC TOOL

Having listed the main neurofunctional manifestations of functional dyspepsia identifiable by fMRI, this literary review proposes the elucidation of patterns of alteration in these areas, emerging as a promising, accessible and non-invasive approach for the diagnosis of this condition.

Understanding the disturbances in communication between the NTS and associated cortical areas not only enriches our understanding of the neurobiological basis of functional dyspepsia, but also paves the way for the accurate use of functional MRI as a diagnostic tool, leaving behind the diagnosis of exclusion. The establishment of specific patterns of alteration in these neural circuits, confirmed by fMRI, not only validates the diagnosis of functional dyspepsia, but also provides valuable insights for targeted therapeutic strategies. Thus, detailed

research into these brain areas offers innovative perspectives for advancing diagnostic accuracy and, therefore, the clinical management of functional dyspepsia.

JUSTIFICATION

The intrinsic complexity of functional dyspepsia (FD) demands an improved diagnostic approach, considering the multifactorial and heterogeneous nature of these gastrointestinal disorders. Currently, the diagnosis of FD is predominantly carried out by an exclusionary approach, employing upper gastrointestinal endoscopy (EDA) to rule out organic conditions. However, the limitations of this strategy, highlighted by the Rome III guidelines, highlight the need for more precise and refined diagnostic methods.

The integrative review proposed in this context focuses on the use of functional magnetic resonance imaging (FMR), aiming to identify distinct patterns of neurophysiological changes associated with FDs. This approach would not only consolidate current knowledge about such changes, but would also support proposals for more assertive diagnostic methods. Reducing dependence on the exclusion of organic conditions through EDA would not only improve diagnostic accuracy, but also contribute to the efficiency of public resources by avoiding unnecessary invasive tests.

Furthermore, the review can alleviate the anguish of patients, who are often subjected to invasive examinations without detecting organic changes. The proposal of new therapeutic approaches, based on the elucidation of the neurophysiological mechanisms of FDs, represents an additional benefit. A deeper understanding of the interactions between physical, immunological factors, microbiota and the complexities of the brain-gut axis will enable a more targeted approach to treatments, favoring superior clinical results.

Ultimately, the review will not only contribute to the diagnostic accuracy of FDs, but will play a crucial role in optimizing healthcare resources, enhancing patients' quality of life, and promoting substantial advances in the understanding and management of these functional gastrointestinal challenges.

GOAL

The main objective of this dissertation is to conduct a comprehensive integrative review on neurophysiological changes in functional diseases of the gastrointestinal tract. Specifically, we intend to investigate the possibility of using functional magnetic resonance imaging (fMRI) as a diagnostic method in functional dyspepsia. By exploring the innovative application of fMRI,

this research aims to contribute to the expansion of knowledge in the area, offering valuable insights for the development of more accurate and effective diagnostic methods to combat functional dyspepsia.

MATERIALS AND METHOD

This study was developed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and in the end, it was classified within the category of Integrative Literature Review

SEARCH STRATEGIES

A comprehensive search was performed in the following two electronic databases on 06/02/2024 PubMed and Virtual Health Library of the Ministry of Health. The PubMed search terms were as follows: functional dyspepsia fMRI. After the electronic searches, we also examined the references of relevant reviews and included articles to find potential studies. In the end, 166 articles were selected.

INCLUSION AND EXCLUSION CRITERIA

Initially, 92 articles were selected by PubMed and 74 by VHL. After excluding duplicate studies (53), 113 articles were analyzed based on the title.

According to the title, those that met at least one of the following criteria were included: (1) include "MRI" in the title; (2) include “functional brain imaging” in the title; (3) include “functional dyspepsia” in the title; (4) include “functional gastrointestinal disorders” in the title. After this stage, 61 studies were excluded, leaving 52 studies.

According to reading the abstract, the 52 articles were analyzed and included according to the following criteria: (1) the study must have been carried out on humans; (2) all subjects were over 18 years old; (3) the study method used must be fMRI; (4) the term "acupuncture" was not mentioned in the abstract. 31 studies were included after applying the inclusion criteria.

Studies were subsequently excluded if they presented the following characteristics: (1) article in a language other than English or Portuguese; (2) the study method does not compare the control group with a group diagnosed with functional dyspepsia according to the ROMA criteria; (3) the article does not present clinical trial results; (4) study materials and methods were not specified, (5) article published before 2014; (6) the analysis compares pre- and postprandial individuals, (7) the analysis is about GABA concentration.

Finally, 16 articles were included in this integrative review. (16, 20, 22-34)

DATA EXTRACTION

Two authors independently screened the identified articles and then reviewed the full text to verify that the articles met the inclusion and exclusion criteria. Any disagreements or uncertainties were discussed in consultation and resolved by the third author. The following study information was acquired: (1) basic information (name of first author, year of publication, country of origin and type of study), (2) methodology (sample size of patients and HCs, sample age, criteria of patients' diagnosis and details of the neuroimaging method), and (3) difference in functional brain activity between patients with FD and HCs (based on the functional connectivity of the area of interest in the resting state).

DATA ANALYSIS

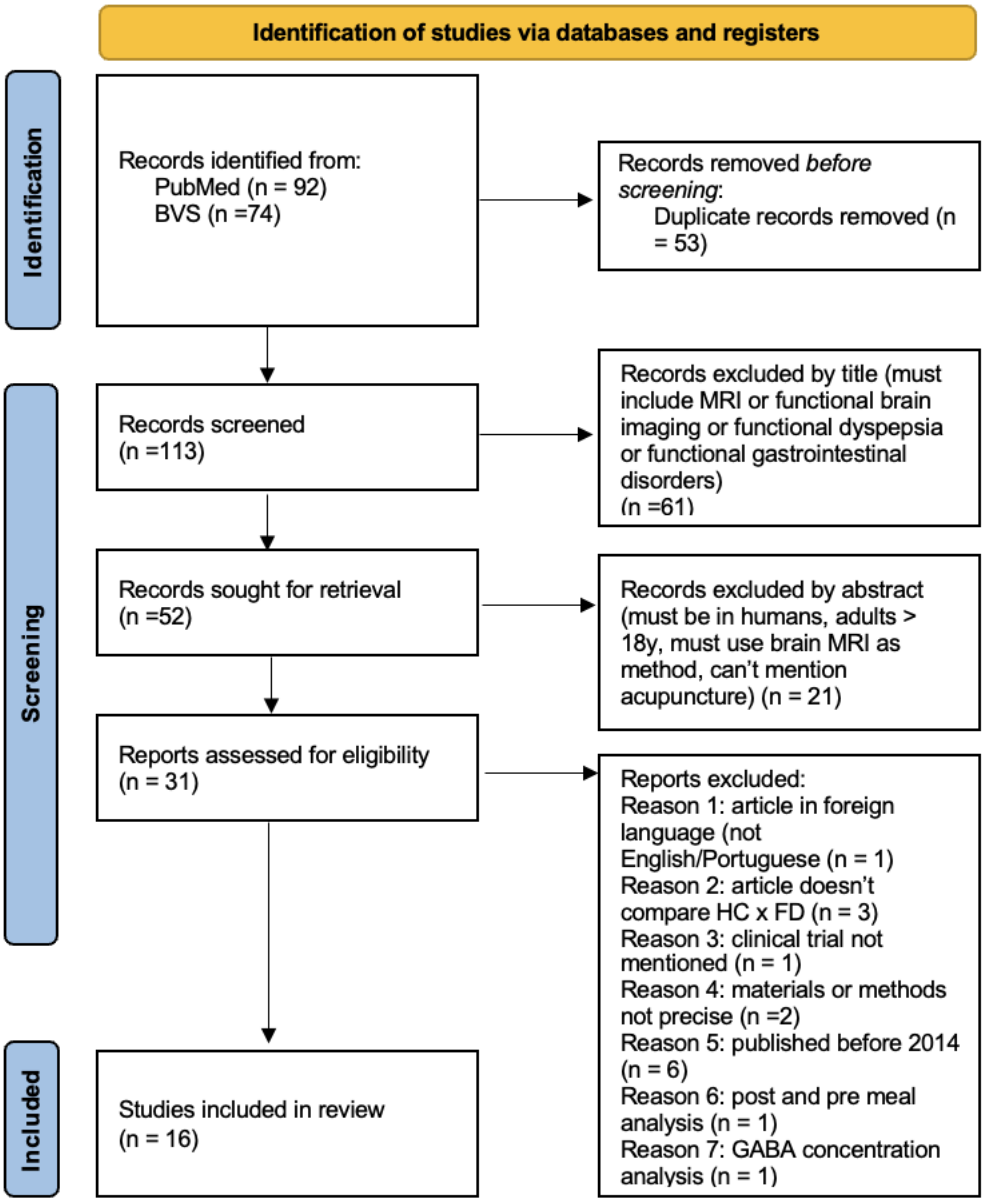
To analyze the data obtained in this integrative literature review, an approach was adopted that involved a detailed descriptive analysis of the results of the individual studies included. A narrative synthesis was used to identify common patterns and trends between studies, highlighting the main findings and characteristics of each study. During this process, key emerging themes, recurring patterns, and discrepancies in results between studies were identified and discussed. Furthermore, when reporting the results obtained, transparency about the limitations of the integrative review was advocated, recognizing the diversity of included studies in terms of study designs, study populations, interventions/exposures and outcome measures. This approach allowed us to offer a comprehensive and informed interpretation of the review results, providing valuable insights for future research and clinical practice.

RESULTS

CHARACTERISTICS OF INCLUDED STUDIES

A total of 166 articles were retrieved based on our search strategy, and 16 articles were finally qualified. The flowchart shows the procedure for retrieving and including studies (Figure 1). As a result, a total of 16 outcomes were included in the cross-sectional review to qualitatively investigate brain abnormalities among FD patients and HCs. These studies analyzed data from 984 SCD patients (335 males and 649 females) and 821 HCs (272 males and 549 females). Detailed information about the included studies is available in Table 1.

(Figure 1)


Identification of studies via databases and registers
Identification
Records identified from:
PubMed (n = 92)
BVS (n =74)
Records removed *before screening*:
Duplicate records removed (n = 53)
Screening
Records screened
(n =113)
Records excluded by title (must include MRI or functional brain imaging or functional dyspepsia or functional gastrointestinal disorders)
(n =61)
Records sought for retrieval
(n =52)
Records excluded by abstract (must be in humans, adults > 18y, must use brain MRI as method, can't mention acupuncture) (n = 21)
Reports assessed for eligibility
(n = 31)
Reports excluded:
Reason 1: article in foreign language (not English/Portuguese (n = 1)
Reason 2: article doesn't compare HC x FD (n = 3)
Reason 3: clinical trial not mentioned (n = 1)
Reason 4: materials or methods not precise (n =2)
Reason 5: published before 2014 (n = 6)
Reason 6: post and pre meal analysis (n = 1)
Reason 7: GABA concentration analysis (n = 1)
Included
Studies included in review
(n = 16)

(Table 1)

IT HURTS.	Year of publication	Country of origin	Article type	total HC	HC (F)	HC (M)	total FD	FD (F)	FD (M)	Age range	Diagnostic criteria
10.3389/fnmol.2022.1001557	2022	China	Original Research	98	78	20	109	90	19	18-25	Rome IV
10.14309/ctg.0000000000000004	2019	China	Journal Article	97	70	27	97	70	27	18-45	Rome III
10.3389/fnins.2023.1174287	2023	China	Systematic Review	202	118	84	260	147	113	20-53	Rome III
10.1111/nmo.14396.	2022	USA	AuthorManuscript	14	9	5	15	13	two	18-65	Rome IV
10.3389/fpsyt.2020.00461	2020	Poland	Journal Article	18	9	9	18	13	5	20-47	Rome III
10.5056/jnm17076	2018	China	Journal Article	10	5	5	28	17	11	20-65	Rome III
10.5056/jnm15118	2016	China	Journal Article	25	14	11	25	19	6	20-30	Rome III
10.1007/s11682-017-9705-z	2017	China/ USA	Journal Article	49	31	18	69	43	26	20-26	Rome III
10.1111/nmo.12311	2014	China	Journal Article	20	12	8	20	15	5	20-25	Rome III
10.1111/nmo.13345	2017	China	Journal Article	46	31	15	67	41	26	20-25	Rome III
10.1111/nmo.12372	2014	China	Journal Article	39	25	14	44	28	16	20-25	Rome III
10.1111/nmo.12560	2014	China	Journal Article	33	24	9	34	19	15	20-25	Rome III
10.1111/nmo.13060	2017	China	Journal Article	42	27	15	66	42	24	20-25	Rome III
10.1093/ajcn/nqy077	2018	Germany	Journal Article	14	9	5	12	7	5	40-55	Rome III
10.1177/0284185119883391	2019	China/ USA	Journal Article	22	13	9	31	13	18	24-60	Rome III
10.1093/cercor/bhab419	2022	China	Journal Article	92	74	18	89	72	17	18-25	Rome III

ABNORMAL BRAIN ACTIVITY IN PATIENTS WITH SCD

When comparing HCs with SCD patients, a variety of changes in brain activity associated with functional dyspepsia are observed. The most frequently mentioned areas with increased activity in the DF group include the left insula, precentral gyrus, anterior cingulate gyrus, left supplementary area, putamen, and thalamus. These results suggest that functional dyspepsia may be associated with dysfunction in specific areas of the brain, especially those involved in sensory and motor processing, as well as emotional control and pain regulation. However, it is important to highlight that the heterogeneity in findings between studies highlights the complexity of this condition. Detailed data on the changes documented in each study are available in Table 2. Those articles already cited by Mao et al were not duplicated in the table (n = 3).

(Table 2)

Article (DOI)	Right Insula	Left Insula	Pre-Central Giro	Anterior Cingulate Gyrus	Left Supplementary Area	Putamen	Thalamus
Mao et al. 10.3389/fnins.2023.1174287	↑	↑	↑	↑	↑	↑	↑
Zhang et al. 10.3389/fnmol.2022.1001557	-	-	-	-	-	-	↑
Zeng et al. 10.14309/ctg.0000000000000046	↑	-	↑	-	↑	↑	↓
Sclocco et al. 10.1111/nmo.14396	↑	↑	-	-	↑	-	-
Skrobisz et al. 10.3389/fpsyt.2020.00461	-	-	-	-	↑	-	-
Jiaofen Nan et al. 10.5056/jnm15118	-	↓	↑	-	-	↑	-
Liu et al. 10.1007/s11682-017-9705-z	-	↑	↑	↑	-	-	-
Nan et al. 10.1111/nmo.12311	↑	↑	-	-	↓	↓	↓
Liu et al. 10.1111/nmo.13345	↓	-	-	-	-	-	↑
Liu et al. 10.1111/nmo.12372	-	-	-	-	-	-	-
Nan et al. 10.1111/nmo.12560	-	-	-	-	-	-	-
Liu et al. 10.1111/nmo.13060	-	↑	-	-	-	↑	-
Yin et al. 10.1093/cercor/bhab419	-	-	-	-	-	-	-

DISCUSSION

It is possible to note the prevalence of studies on functional dyspepsia in China. This can be attributed to a number of factors, including characteristics of the Chinese diet that may precipitate symptoms associated with the condition. The traditional Chinese diet is often rich in fatty, fried and spicy foods, which are known to trigger gastrointestinal discomfort in some people. This relationship between the typical Chinese diet and the symptoms of functional dyspepsia may have sparked the interest of local researchers in further investigating the neurophysiological changes associated with the condition. However, it is important to highlight that data on the prevalence of functional dyspepsia in the East are scarce and contradictory, not necessarily suggesting a higher prevalence in this region compared to the West. Still, China, with its vast population and growing research infrastructure, offers a conducive environment for conducting studies in this area. The increase in research coming from China is likely due to growing academic interest, expanding research infrastructure, access to relevant study populations, and resources available for conducting scientific investigations. In addition to the factors mentioned above, another significant reason for the increasing prevalence of studies on functional dyspepsia in China is the growing investigation into the relationship between

intestinal microbiota and the manifestation of the condition. Studies have suggested that imbalance in the intestinal microbiota may be associated with the development of symptoms of functional dyspepsia, and the indiscriminate use of antibiotics in Chinese aquaculture may play a crucial role in this dynamic. China is one of the largest seafood producers in the world, and excessive use of antibiotics in aquaculture can contaminate aquatic products, which are a substantial part of the Chinese population's diet. This not only increases researchers' interest in the relationship between antibiotics, gut microbiota and functional dyspepsia, but also highlights the importance of addressing food safety and public health issues. However, accurate information about the use of antibiotics in water and their potential risks to the health of the population may be limited, which increases the urgency of research in this area to better understand the impacts on the gastrointestinal health of the Chinese population. This complex interaction between diet, intestinal microbiota, use of antibiotics in aquaculture and the manifestation of functional dyspepsia symptoms may, therefore, justify the growing interest of Chinese researchers in the subject. (35) (36)

Regarding the age of patients, although most of the studies selected by the review used patients aged between 20 and 30 years, there is no definitive correlation in the literature that suggests a greater prevalence of the condition in this age group. In fact, research, such as the study published in Wien Klin Wochenschr, indicates that functional dyspepsia symptoms may actually increase with age. This finding contradicts the idea that the condition is predominantly associated with young adults. Other factors may justify the choice of this age group in studies, including the availability of participants for research, the possibility of controlling important variables and the search for a population that can represent a relatively healthy group, thus minimizing the interference of comorbidities. Furthermore, practical considerations, such as ease of recruitment and willingness of participants to undergo examinations and procedures, may also influence the selection of this age group. Therefore, while the age of participants in functional dyspepsia studies may be mostly young, factors other than the prevalence of the condition in this age group must be considered when interpreting the results. (37)

Regarding the predominance of using the Rome III definition over Rome IV in many selected studies it can be attributed to several factors: The Rome III definition was released in 2006, while Rome IV was introduced in 2016, which means that there was a significant gap between the two versions. The lack of adoption of the newer definition may be a result of a lack of updating by healthcare professionals or researchers, who may be more familiar with the previous definition and choose to continue using it for the sake of consistency with previous

studies. Furthermore, there may be a preference to maintain continuity with existing literature, especially if previous studies have used the Rome III definition. However, it is important to highlight that the more up-to-date definition may offer a better understanding of the condition and its diagnostic criteria may reflect advances in understanding the pathophysiology and clinical practice. Therefore, future studies may benefit from adopting the Rome IV definition to ensure consistency and diagnostic accuracy.

With regard to the Functional Connectivity at Rest (CFR) MRI method adopted in the selected studies, its application stands out as a robust technique to investigate the neurophysiological changes associated with functional dyspepsia. This approach allows the analysis of the functional interaction between different brain regions while participants are at rest, without external stimuli or performing specific tasks. MRI CFR is based on the detection of spontaneous low-frequency fluctuations in the functional magnetic resonance imaging (fMRI) signal, which reflect the brain's intrinsic neuronal activity. By calculating the temporal correlation between time series from different brain regions, it is possible to map patterns of functional connectivity between these regions. This allows for a more detailed understanding of the neural networks underlying dyspeptic symptoms. It is worth mentioning that the studies conducted used techniques to minimize artifacts, such as head movement, ensuring the accuracy and reliability of the results obtained. Thus, MRI CFR emerges as an essential tool to investigate the neurophysiological bases of functional dyspepsia, providing valuable insights into the brain mechanisms involved in the pathogenesis and manifestation of symptoms. (38)

Regarding the aspects revealed by the analysis of changes recorded in fMRI, relationships were established that seek to rationalize the identified patterns, taking into account the function of each frequently affected brain area. This approach aims to contextualize the findings within current knowledge about neuroanatomy and neurophysiology, providing a deeper understanding of the mechanisms underlying functional dyspepsia. By identifying specific brain areas that demonstrate consistent changes in patients with functional dyspepsia, it is possible to speculate about the possible neural substrates involved in the genesis and manifestation of dyspeptic symptoms. This detailed analysis of brain activity patterns can provide valuable insights into the neural circuits and neurophysiological processes associated with the condition, thus contributing to a better understanding of its etiology and possible therapeutic targets.

The relationship between increased activity in the insular cortex and the painful symptoms present in functional dyspepsia can be understood in light of the different functions attributed to this brain region. The insular cortex acts as a broad cortical area where multimodal

inputs from different brain areas converge, playing crucial roles in the integration of multimodal information and the regulation of diverse physiological and emotional functions. In particular, parts of the insular cortex are recognized as the primary gustatory cortex, the thermosensory cortex, and the visceral sensory cortex. These functions include sensory perception of internal stimuli and maintenance of body homeostasis, establishing the insular cortex as the main interoceptive cortex. Furthermore, the strong interconnection between the insular cortex and the limbic system indicates an essential role in regulating emotions, including aversive and positive emotions. Thus, increased activity in the insular cortex may be related to pain perception and processing in functional dyspepsia, given its function as an integral part of nociceptive processing and emotional regulation. Clinical studies have consistently demonstrated activation of the insular cortex in response to noxious stimuli, correlating this activation with the perceived intensity of pain. Furthermore, the nociceptive specificity of insular activation is evidenced by studies that demonstrate changes in the connectivity and activity of the insular cortex in patients with chronic pain, indicating a central role of this region in the pathophysiology of chronic pain. Furthermore, the connectivity of the insular cortex with other pain-related brain regions plays a crucial role in the integration and processing of sensory information. The insular cortex receives multiple sensory inputs from different sources, including projections from the thalamus and primary and secondary sensory cortical areas, and also influences descending pain modulatory pathways, exerting pro-nociceptive effects. In summary, the connection of the insular cortex with other brain regions involved in pain processing and modulation highlights its importance in the pathophysiology of pain, providing a neurobiological basis for understanding the mechanisms underlying chronic pain and potentially identifying new therapeutic targets for the management of pain. pain associated with functional dyspepsia (39) .

The precentral gyrus plays a fundamental role in sensorimotor processing and modulation of autonomic responses, influenced by dysfunctions in the orbitofrontal cortex (OFC), associated with the discrimination of sensations and the production of avoidance behaviors. The anterior cingulate gyrus, part of the cingulate cortex (CC), plays a crucial role in integrating multimodal information, especially sensorimotor, emotional, and cognitive functions. Increased activation in these areas may reflect dysfunctions in pain modulation, emotional regulation, and visceral perception, contributing to the painful symptoms of functional dyspepsia. In turn, changes in the thalamus, a key structure in the transmission of sensory signals to the cerebral cortex, suggest dysfunctions in the visceral sensory pathway, influencing the perception of unpleasant or painful sensations. Therefore, increased activation of these brain areas may reflect an imbalance in pain

modulation and regulation of visceral responses in functional dyspepsia, contributing to the understanding of the mechanisms underlying this condition. (40-45) .

The changes described suggest concrete hypotheses about the symptoms of functional dyspepsia. Increased activation of these areas may contribute to the painful, sensory, and emotional symptoms characteristic of these conditions due to mechanisms of increased visceral sensory perception (precentral cortex), emotional dysregulation of pain, altered modulation of motor responses associated with gastrointestinal function (cingulate gyrus, anterior and supplementary area), exacerbated sensory processing (putamen) and amplification of unpleasant visceral sensations (thalamus). These hypotheses provide important insights into the mechanisms underlying functional dyspepsias.

CONCLUSION

The integrative review proposed in this context explored the neurophysiological changes associated with functional dyspepsia, focusing on the use of functional magnetic resonance imaging (fMRI) as a potential diagnostic method. Although distinct patterns of brain changes have been identified, especially in the areas of the precentral cortex, anterior cingulate gyrus, supplementary area, putamen and thalamus, no specific pathognomonic patterns of functional dyspepsia have been found. This finding highlights the complexity of the pathology, which involves several areas of the brain and is not limited to a single neurophysiological pattern.

Still, the identification of these areas of increased brain activity offers a promising perspective for the use of fMRI as an auxiliary tool in the diagnosis of functional dyspepsia. By mapping key sites of neurophysiological change, fMRI can complement conventional diagnostic methods by providing additional insights into the mechanisms underlying the condition. However, it is important to highlight that fMRI does not replace existing diagnostic methods such as upper gastrointestinal endoscopy (EDA), but can improve diagnostic accuracy and reduce dependence on ruling out organic conditions through EDA.

Furthermore, the elucidation of the main pathways involved in functional dyspepsia, evidenced by the integrative review, confirms the neurophysiological nature of the pathogenesis of these gastrointestinal disorders. The identification of affected brain areas and their specific functions paves the way for a deeper understanding of the mechanisms of pain, emotional regulation and sensory processing involved in the pathophysiology of functional dyspepsias.

Ultimately, although fMRI represents a promising tool for diagnosing and understanding functional dyspepsias, continued effort is needed to integrate these findings into more

comprehensive diagnostic and therapeutic approaches. The intrinsic complexity of these conditions demands a multidisciplinary approach, which takes into account not only the neurophysiological aspects, but also the physical, immunological and microbiota factors involved. Only in this way can we advance in the development of more accurate and effective diagnostic strategies, as well as targeted therapies that significantly improve the quality of life of patients with functional dyspepsia.

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