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Symptom perception in adults with chronic physical disease: A systematic review of insular impairments

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ABSTRACT

Background: To perform self-care, individuals with a chronic illness must be able to perceive bodily changes (ie., interoception) so they can respond to symptoms when they arise. Interoception is regulated by the insular cortex of the brain. Symptom perception is poor in various physical diseases, which may be associated with impairments in the insular cortex.

Objective: The purpose of this study was to explore whether patterns of insular impairment exist among adults with chronic physical diseases and to analyze the relationship with disease-related symptoms.

Methods: We identified studies that assessed the structure and/or activity of the insula through MRI and/or (f) MRI in adults with chronic physical diseases (vs. healthy controls) by searching five databases. Results are reported as a narrative synthesis.

Results: Fifty studies were conducted to investigate the structure or activity of the insula among adults with diabetes, cancer, heart failure, or chronic pulmonary disease. In 19 studies investigators found that patients with a chronic disease had lower/damaged insular volume/density/thickness than healthy controls or reduced insular blood flow. When insular activity was explored in 22 studies, most investigators reported higher insular activity and lower neural connectivity. Five studies explored the association between insular volume/activity and symptom severity: four reported a positive trend.

Conclusion: People with chronic physical diseases have lower insular grey matter volume/density/thickness and abnormal insular activity when compared to healthy people. Insular activity may be related to symptom severity. These results suggest that insular structure and/or activity may explain poor symptom perception.

Introduction

Self-care is described as a process of maintenance, monitoring, and management.[1,2] Specifically, self-care maintenance involves maintaining health and wellbeing, self-care monitoring involves the detection of signs and symptoms, while self-care management is the response to signs and symptoms. As an accurate perception of internal sensations is critical for effective self-care management, identifying barriers to accurate perception can facilitate effective self-care.[2] Impaired interoception is one such barrier. Thus, identifying impairments in interoception can support patient self-care and improve outcomes.

Interoception refers to the ability of the brain to perceive, elaborate, and respond to signals originating from within the body.[3,4] Interoception includes (a) the afferent interoceptive signals communicated to the brain from internal organs, (b) the neural encoding, representation, and integration of information concerning the bodily state, (c) the influence of afferent interoceptive signals on perceptions, cognitions, and behaviors, and (d) the conscious perception of interoceptive signals as physical sensations and feelings.[5] Interoception allows for the maintenance of internal stability through covert reflexes (e.g., autonomic reflexes), motivational drivers (e.g., hunger), and symptoms (e.g., sweating). As such, interoception may influence symptom detection,

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interpretation, and response. This process is vital for the management of chronic diseases and, if inhibited, may promote disease progression[6–9] by causing patients to ignore symptoms until an acute exacerbation is imminent. To date, interoception has been studied primarily in neurodivergent populations and much less frequently among people with chronic physical diseases.[8]

Broadly, the WHO defines chronic conditions as those having long duration, generally slow progression, and requiring some level of health care management across time.[10,11] This definition includes four categories: persistent communicable conditions (e.g., HIV), non-communicable chronic conditions (i.e., chronic physical diseases, e.g., cardiovascular diseases, cancer, diabetes), long-term mental disorders (e.g., depression, schizophrenia), and ongoing physical/structural impairments (e.g., blindness). As accurate perception of internal sensations is critical for detection and response to health changes, healthcare professionals must know how to support patients' interoceptive abilities and how to address barriers to accurate bodily perception that patients may face to eventually facilitate effective self-care and improve clinical outcomes.[2,12]

In addition to external sensory functions and autonomic regulation,[13] the insula (Fig. 1) is the brain substrate underpinning higher-order interoceptive processing of visceral information, including conscious perception of interoceptive signals.[5,14,15] The insula is a region of the cerebral cortex located deep within the lateral sulcus.[16] Interoceptive inputs (e.g., a pain signal) are first relayed to the posterior insula, which integrates these somatosensory, vestibular, and motor signals into objective representations.[17] Then, interoceptive information is projected to the anterior insula for re-representation and integration with exteroceptive and motivational information.[5] Indeed, the anterior insula, which is strongly connected with the limbic regions, integrates interoceptive information with emotional, cognitive, and motivational functions (e.g., connecting a pain signal with feelings of fear and readiness to act)[16,17] to support subjective feeling states[18] that inform emotion and motivate behavior.[5]

Brain conditions directly impact brain structure and function,[19,20] potentially including the insula. Yet, there is a paucity of evidence identifying insular impairment among chronic physical diseases that do not primarily affect the brain. For example, neuronal damage in the insular cortex has been identified in heart failure and is associated with distorted sympathetic control,[21] parasympathetic patterns during challenges, mood and anxiety regulation, as well as autonomic, pain, and neuropsychologic functions.[21–24] Identifying such alterations across chronic physical diseases may explain previously identified interoceptive impairment and, consequently, better characterize mechanisms underlying altered symptom perception in physical chronic diseases.[8] Indeed, symptom detection, interpretation, and response are critical for self-care intended to maintain physical functioning and mental well-being.[2]

To date, there has been no systematic review of studies that evaluated insular impairment among people with chronic physical diseases. Therefore, the purpose of this systematic review was to explore whether common patterns of insular impairments (i.e., quantified by Magnetic Resonance Imaging (MRI) or Functional Magnetic Resonance Imaging (fMRI)) (**Box**)[25–27] referenced against physiologic function in healthy adults) exist among adults with chronic physical diseases. While doing so, considering the relevance of interoception in the symptom experience,[8] particular attention was paid to analyzing the relationship between the insular cortex and the disease-related symptoms.

Identification of common patterns of insular impairment and their relationships to symptoms in patients with chronic physical diseases may enable healthcare professionals to anticipate and address barriers to accurate bodily perception among their patients. Such intervention may improve patients' unique needs for improved body awareness and symptom management and ultimately improve health outcomes.

Box
Description of MRI and fMRI of the brain

	What is it for?	How does it work?
Magnetic Resonance Imaging (MRI) of the brain	MRI provides a map of the brain showing its structure at the specific moment when the test is performed. This structural information can provide information, for example, on the dimensions, density, thickness, or locations of different parts of the brain.	The magnetic field from MRI interacts with the protons in our hydrogen atoms making them align in the same direction. A radio pulse is then emitted, turning protons to the side. As the radio frequency ceases, the protons relax and return to their normal state, which makes energy that is released and detected by the MRI machine. Based on this released energy, it is possible to determine how the brain tissue looks.
Functional Magnetic Resonance Imaging (fMRI) of the brain	fMRI provides a description of the brain's functionality. Specifically, fMRI provides information on the activity of certain brain areas and their connectivity among each of the areas.	When a certain area of the brain activates, it receives more oxygenated blood. Thus, as for MRI, in fMRI the energy emitted from the relaxation of protons is measured. But this time the calculations aim to determine how the amount of oxygenated blood flow changes. If there is more oxygenated blood in a certain part of the brain, it indicates that the brain area is more active (i.e., Blood-Oxygenation Level Dependent response).

Methods

Design

A systematic review with narrative synthesis[28,29] (without meta-analysis) was used to explore the presence of insular impairments among adults with a chronic physical disease compared to healthy subjects. This systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42023396669).

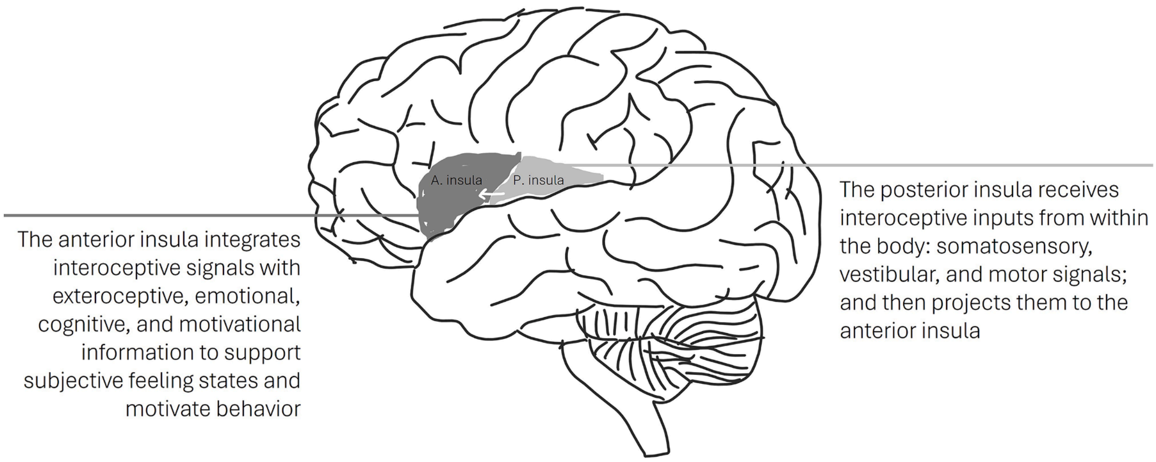

Fig. 1. The role of the insula in processing interoceptive signals.

Search methods

To identify all relevant published studies, we searched PubMed, Psychinfo, Embase, CINAHL, and Web of Science–Science Citation Index Expanded until 2023, without any limitations on the beginning date. The main search terms included: (insula OR insular cortex) AND (MRI OR fMRI OR magnetic resonance) AND (chronic). MeSH terms were used when possible. Terms referring to the main chronic diseases were also included (e.g., heart failure, diabetes, COPD, cancer). No language or time limits were used. Only adults (≥18 years old) were included. More details on the inclusion and exclusion criteria can be found in Table 1. More details on the search strategy can be found in Appendix I.

Table 1
Inclusion and exclusion criteria.

INCLUSION CRITERIA	All primary research investigating the structure and/or function of the insular cortex using Magnetic Resonance Imaging (MRI) or functional Magnetic Resonance Imaging (fMRI) of the brain including adults (≥ 18 years) (as children's brain is still maturing[33] and there are significant structural and functional differences between children and adults' cerebral cortex, including the insula[34]) including healthy controls investigating chronic physical diseases that do not primarily affect the brain, that have a physical etiology, and that represent an altered physical status (classified as *non-communicable chronic condition* by the World Health Organization. Examples are: heart failure, cancer, diabetes, chronic respiratory diseases[30,35])
EXCLUSION CRITERIA	Non-primary research (e.g., literature reviews) including case studies, protocols, and abstracts including minors (< 18 years old) including adults (≥ 18 years) without a chronic physical disease not including healthy controls investigating chronic conditions and mental disorders in the neuropsychiatric or neurodivergent domains (e.g., addictions), conditions primarily affecting the brain structures/functionalities (e.g., brain cancer – as they are already intrinsically expected to directly damage the brain), or conditions not related to an underlying non-communicable chronic physical disease (e.g., insomnia or pain as primary condition)

Search outcome

The initial search identified 1541 records. After removing 608 duplicates, 933 records underwent title and abstract screening by the first two authors. A total of 83 remaining records underwent full-text screening, with 50 studies included in this review (Fig. 2). Inter-rater reliability was 96% during the title and abstract screening and 90% during the full-text screening.

Quality appraisal

Regardless of data quality, all included studies underwent data extraction and synthesis. The methodological validity of the studies was assessed by two independent reviewers (GL and AM). As judging study quality is subjective, final grades were determined using the standard JBI critical appraisal instruments in JBI SUMARI.[30] Grades of the quality assessment are described in the results section.

Data abstraction

All identified citations were uploaded into EndNote X.9.3.3/2020,[31] and then Rayyan[32] to remove duplicates and conduct title and abstract screening. Then, the two reviewing authors independently screened the article titles and abstracts to identify those that preliminarily met the inclusion criteria. Articles were flagged by each reviewer as "include in full-text screening," "exclude," or "discuss further." At the end of this phase, the same two reviewers discussed and solved minor discrepancies. The same two reviewing authors screened the full texts of the remaining articles, adopting the same process (include/exclude/maybe) as the first phase. The data extraction process was documented using the PRISMA 2020 flow diagram[33] shown in Fig. 2. Inter-rater reliability (consistency between the two reviewers when including/excluding articles) is reported in the results. For each included study, data were extracted in JBI (Joanna Briggs Institute) SUMARI[28] using standardized JBI data extraction tools. Data extracted included the study design, country/setting, study aim(s), study methods, participant characteristics, and main results.

Synthesis

We expected all relevant studies to use a quantitative design, but since we included any study design and any population, we were unable

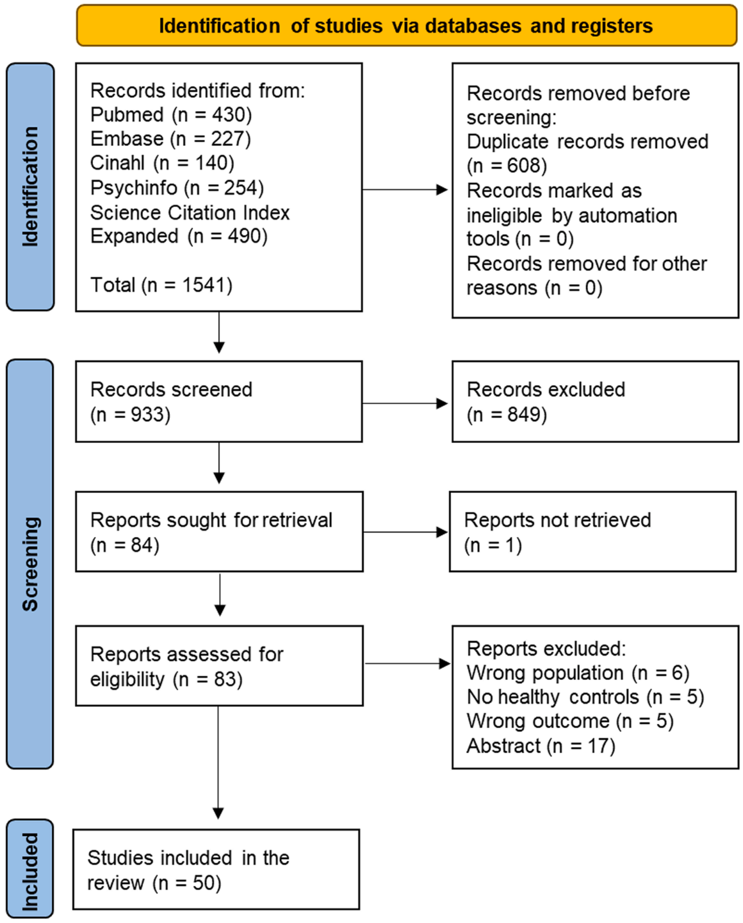

Fig. 2. Prisma flow diagram.

to conduct a meta-analysis. Instead, quantitative data were synthesized using a descriptive narrative approach, which summarizes the quantitative evidence extracted from the included studies in words. This approach is recommended for the synthesis of studies with heterogeneous measures or designs where statistical pooling is not possible.[28] To provide transparency in the process of how included data were synthesized, we clearly articulate the synthesis process throughout.

Results

Quality appraisal

The results of the quality appraisal are reported in Appendix II. The two independent reviewers assessed the overall quality of included studies as high (between 75% and 100% of the highest possible quality). Inter-rater reliability during the appraisal process was estimated at 93%.

To assess the accuracy of the synthesis findings, details on all the included studies and their findings are reported in Table 2. In addition, a detailed description of the quality appraisal for each included study is reported in Appendix II.

Participants

A total of 3978 individuals were studied in the 50 included studies. Patients had a mean age ranging from 21 to 84 years and were mainly male (56% of the studies). Diseases studied were diabetes mellitus (n = 27 studies), heart failure (n = 10 studies), cancer (n = 9 studies), and chronic respiratory diseases (n = 4 studies).

Characteristics of included studies

The included studies (Table 2) were conducted in China (n = 18, 36%), the United States (n = 16, 32%), Canada (n = 2, 4%), the Netherlands (n = 2, 4%), the United Kingdom (n = 2, 4%), Spain (n = 2, 4%), Turkey (n = 1, 2%), Denmark (n = 1, 2%), Germany (n = 1, 2%), Japan (n = 1, 2%), Norway (n = 1, 2%), Portugal (n = 1, 2%), and Taiwan (n = 1, 2%). One study (2%) did not declare the country. Thirty-two studies were cross-sectional, 11 were quasi-experimental, five were cohort studies, one was a randomized controlled trial, and one was a case-control study. Among all the retrieved records, 10 were in another language (one in Chinese, three in French, four in Japanese, one in Italian, and one in German). All these articles had an English title and abstract. All were excluded during the title and abstract screening phase because they did not meet the inclusion criteria.

Measures

Structural (e.g., thickness) and functional (e.g., activity and connectivity) impairments of the insular cortex were quantified through Structural and Functional Magnetic Resonance Imaging of the brain (Table 2).

Some studies also explored the association between insular

Table 2
Extracted data from included studies.

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
Boland et al., 2014 *Quasi-experimental study*	UK, Hospital	To explore the structure and activity of brain areas involved in pain processing in patients with cancer	- Structural and Functional MRI of the brain - Chronic Pain Acceptance Questionnaire - Pain Catastrophizing Scale	Patients (n = 12) with multiple myeloma and chemotherapy induced peripheral neuropathy (66.6% males, median age 63 years old, IR: 56–67). Control group (n = 12): healthy subjects (50% males, median age 53 years old, IR: 35–58)	Activity: no difference in the insular activation to pain stimuli between patients and controls. Measured symptoms, which were positively correlated with insular activation.
Bolo et al., 2011 *Quasi-experimental study*	USA, Academic medical center	Investigate effects of acute hypoglycemia on working memory and brain function in T1D	fMRI	Patients with type 1 diabetes (n=16): mean age 33.8 +/- 9.9; 50% male Control group (n=16): healthy subjects (mean age 31.3 +/- 10.0, 81% male)	Activity: Both groups during both hypo- and euglycemia demonstrated activation in the bilateral insula during the working memory task. During euglycemia, activation during the working memory task was similar when comparing activated brain volume (613 vs 498 cm^3). Activation during hypoglycemia was 80% larger in T1D than controls (431 vs 239 cm^3; p <0.05) Activation decreased with hypoglycemia relative to euglycemia in both groups, with less decrease observes in patients with diabetes vs controls (p<.05). Decrease in activation from euglycemia to hypoglycemia was greatest in the insula, whereas greatest area of decrease for controls was the cerebellum (p<.05). No symptoms assessed
Bolo et al., 2015 *Quasi-experimental study*	USA, Academic medical center	Investigate brain resting state network functional connectivity (FC) changes during hypoglycaemia in patients with type 1 diabetes mellitus (T1DM)	fMRI	T1DM patients (n=16): 30 +/-8 yrs., 63% males. Control group (n=10): healthy subjects (mean age 31 +/- 11 yrs., 80% males)	Activity (Connectivity): patients – left striatum and frontal lobe regions expressed higher FC with the hypothalamus network (containing the posterior insula) vs controls during euglycemia. (p<.01) During hypoglycemia, controls showed decreased FC of right anterior insula with cerebellum and basal ganglia network and temporal pole network vs patients (p<.03) During hypoglycemia in patients right anterior insula and medial frontal FC increased relative to euglycemia (p<.05) Correlation of Functional Connectivity changes with symptoms and A1C T1D: right insular cortex and medial frontal FC changes during hypoglycemia with Executive control network/ medial prefrontal lobe (including the anterior insula) were positively correlated with HbA1c (R62 = 0.733, p<.001) Symptom Scores: patients reported significantly greater symptoms of hypoglycemia

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
					at euglycemia and hypoglycemia conditions (EU, 4.8 points more, p<.003; HY, 10.7 points higher, p<.002).
Chechlacz et al., 2009 *Quasi-experimental study*	Germany, hospital	To investigate if patients with type 2 diabetes (T2DM) (compared to healthy controls) would show enhanced brain responses to pictures of foods and if these stronger activations would relate to scores for dietary adherence and to measures of potential difficulties in adherence	Structural and Functional magnetic resonance imaging of the brain	T2DM patients (n = 11) with (mean age 55.36 ± 14.94). Control group (n = 12): healthy subjects (mean age: 46.58 ± 15.58)	Activity: T2DM patients showed increased responses to pictured foods in the insula (compared to controls) (Increased activation to food within the insula positively correlated with external eating, dietary self-efficacy (r=0.8) and dietary self-care). No symptoms assessed
Chen et al., 2018 *Cohort study*	USA, hospital	To evaluate changes in brain grey matter density (GMD) before and after adjuvant chemotherapy in older women with breast cancer	Structural magnetic resonance imaging of the brain	Patients (n = 16) with stage I–III breast cancers receiving adjuvant chemotherapy (100% females, mean age 67 ± 5.39). Control group (n = 15): healthy subjects (100% females, mean age: 68.5 ± 5.69)	Structure: Patients showed significantly greater GMD reductions over time (from T1 to T2) in the right insula, compared to healthy controls (p<.05). (Patients showed significant GMD reduction over time (p<.05) from T1-before chemo to T2-after chemo). No symptoms assessed
Chen et al., 2022 *Analytical cross-sectional study*	China, hospital	a) To examine the differences of olfactory performance between type 2 diabetes mellitus (T2DM) patients and healthy subjects. b) To investigate the relationships between olfactory performance, brain structure, and cognitive function	Structural Magnetic Resonance Imaging of the brain Chinese Smell Identification Test, Montreal Cognitive Assessment	T2DM patients (n = 68) (71% males, mean age 47.71 ± 7.80). Control group (n = 68): healthy subjects (68% males, mean age 45.76 ± 7.57)	Structure: No differences in the cortical thickness of olfaction-related regions (including the insula) between patients and healthy controls. Positive correlations between Chinese Smell Identification Test scores and cortical thickness in the left insula (r = 0.303, P = .040) and right insula (r = 0.328, P = .030) in T2DM groups (and not in healthy controls). Cortical thickness in the left insula showed significant positive correlations with MoCA (r = 0.391, P = .010) in patients. No symptoms assessed
Croosu et al., 2022 *Analytical cross-sectional study*	Denmark, academic Hospital	Examine total and regional grey matter volume (GMV) in T1D with painful diabetic peripheral neuropathy (DPN), painless DPN, and no DPN	Structural MRI	T1DM patients with painful DPN (n=19): mean age 51.4 +/- 9.7, 53% females. T1DM patients with painless DPN (n=19): mean age 52.6 +/- 9.0, 53% males T1DM patients without DPN (n=18): mean age 50.6 +/- 9.1, 5% males. Control group (n=20): healthy subjects (mean age 51.5 +/- 9.2)	Structure: Total Gray matter volume significantly less in T1D w DPN with and without pain than HC (p=.024 and p=.019) Lower GMV was observed in T1D w/ Pain DPN compared to HC in insula (P<.05) T1D w/ DPN vs HC: Lower GMV in left insula in T1D (p<.018) T1D w/o DPN vs HC: Lower GMV in insula (p<.004). No symptoms assessed
Frokjær et al., 2013 *Analytical cross-sectional study*	Norway, University Hospital	Assess the brain microstructure in areas involved in visceral sensory processing in patients with Diabetes Mellitus (DM) (either type 1 or type 2) with gastrointestinal symptoms	MRI	DM patients (n=26): mean age 45.8 (25–67) yrs., 73% females; among which 81% T1DM and 19% T2DM. Control group (n=23): healthy subjects (mean age 43.8 (21–56) yrs., 35% male)	Structure: Apparent Diffusion Coefficient (diffusivity of water): No differences between patients and control Fractional anisotropy (FA) (i.e., organization of fibers): Patients had reduced FA values (reduced microstructural tissue organization) compared to controls in the anterior white matter (F=4.1, p <0.05), anterior gray matter (F=4.6, P<.05), and posterior gray

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
					matter (F=9.9, P=.002) of the insula. No differences observed between groups in the mid-insula gray or white matter or posterior insula white matter (p>.05). Negative association between anterior insular white matter FA and gastroparesis Cardinal Symptom Index bloating score (r = -0.47 p=.001) (More microstructural changes = more symptoms)
He et al., 2022 *Analytical cross-sectional study*	China, Academic Hospital	Investigate alterations in whole-brain grey matter density in early type 2 diabetes mellitus (T2DM) patients with cognitive impairment (CI)	MRI	T2DM patients with CI (n=36): mean age 54.17 +/- 9.89 yrs., 61% male. T2DM patients without CI (n=34): mean age 52.39 +/- 10.55 yrs. 56% male. Control group (n=30): healthy subjects (mean age 53.44 +/- 10.21 yrs., 53% male	<u>Structure:</u> Density of the left insular lob was greatly reduced in T2D-CI compared with T2D w/o CI (t-value: 3.890 p<.001). No symptoms assessed
Herigstad et al., 2015 *Analytical cross-sectional study*	UK, hospital	To investigate if differences in brain activation to dyspnea-related environmental cues between patients and healthy subjects may reflect differences in salience of these cues and changes in the cognitive-affective state.	- fMRI of the brain (with dyspnea-related word cues) - VAS (how breathless and anxious word cues make patients feel) - St. George's Respiratory Questionnaire - Medical Research Council dyspnea scale - Dyspnea-12 questionnaire - Catastrophizing about Asthma Scale - Pain Vigilance and Awareness Questionnaire	Patients (n = 41) with Chronic Obstructive Pulmonary Disease (63% females, mean age: 68.0 ± 8.2). Control group (n = 40): healthy subjects (60% females, mean age: 69.1 ± 8.1)	<u>Activity</u>: Dyspnea-related word cues activated the left anterior insula much stronger in patients than in controls (p<.05). Symptoms were assessed and, in patients, dyspnea ratings were correlated with activation in the left-side anterior insula, a structure associated with interoception.
Hirabayashi et al., 2022 *Analytical cross-sectional study*	Japan	To examine the association between diabetes and gray matter atrophy patterns.	- Structural MRI scans of the brain and Voxel-based morphometry to measure regional gray matter volumes and intracranial volumes	Patients (n = 272) with either type 1 or type 2 diabetes (57% males, mean age: 74 ± 6). Control group (n = 917): healthy subjects (61% females, mean age: 74 ± 7)	<u>Structure</u>: Patients had significantly lower mean values of grey matter volume/intracranial volume in some brain regions including the insula than healthy subjects. A longer duration of diabetes was significantly associated with lower mean values of gray matter volumes and intracranial volume in the same brain regions. No symptoms assessed
Hu et al., 2020 *Cohort study*	China, hospital	To investigate chemotherapy-related variations in the intrinsic static and dynamic functional connectivity of the executive control network	Resting state Structural and fMRI of the brain	Patients (n = 18) with lung cancer (72% males, mean age: 59.72 ± 9.04). Control group (n = 21): healthy subjects (62% males, mean age: 58.57 ± 9.61)	<u>Activity (Connectivity)</u>: At baseline (before chemotherapy), patients showed significantly decreased dynamic functional connectivity between the right dorsolateral prefrontal cortex and left insula compared to controls. (This decreased connectivity in patients was negatively associated with the cognitive scores (r =-0.548, p =0.028)). No symptoms assessed
Huang et al., 2016 *Analytical cross-sectional study*	China, hospital	To explore mild cognitive dysfunction and/or spatial working memory impairment in patients with primary onset middle-age type 2 diabetes mellitus (T2DM)	- fMRI of the brain (while performing the n-back test to find activation intensity of cognition related areas) - Montreal cognitive assessment - Wechsler Memory Scale	T2DM patients (n = 18): 67% females, mean age: 43.33 ± 6.41). Control group (n = 18): healthy subjects (67% females, mean age: 43.17 ± 6.48)	<u>Activity</u>: Patients showed lower activation intensity in the right insula compared to controls (→ lower activation in such cognition-related area even under the memory loads). No symptoms assessed

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
Hwang et al., 2018 *Quasi-experimental study*	–	General aim: to distinguish the defects in the central nervous system leading to hypoglycemia unawareness. Specific aim: To determine how individuals with type 1 diabetes mellitus respond to hypoglycemia	- Functional MRI brain scanning - Two-step hyperinsulinemic euglycemic-hypoglycemic clamp technique	Patients (n = 29) with type-1 diabetes mellitus, among which n = 16 hypoglycaemia-aware patients (69% females, mean age: 30 ± 8) and n = 13 hypoglycaemia-unaware patients (54% females, mean age: 40 ± 12). Control group (n = 13): healthy subjects (54% females, mean age: 33 ± 11)	Activity: In healthy controls, mild hypoglycaemia altered (diminished) insular activity (meaning that the insula is responsive to changes in circulating glucose levels), whereas in patients it showed no insula changes. No symptoms assessed
Jorge et al., 2022 *Quasi-experimental study*	Portugal, hospital	To test if type-1 diabetes mellitus (T1DM) presents an overactivation of brain regions related to cognitive impulsivity, decision making, reward and saliency processing (which directly relates to interoception)	- Functional MRI of the brain - Glycosylated hemoglobin - Balloon Analogue Risk Task (cognitive impulsivity)	T1DM patients (n = 25): 56% females, mean age: 38.72 ± 10.38. Control group (n = 25): healthy subjects (60% females, mean age: 35.08 ± 8.77)	Activity: Patients showed larger activation in the (bilateral) insula compared to controls (in decision making) ($p<.05$). Activity in the saliency network (ACC, insula), which monitors interoceptive states, was related to metabolic trajectories: dopaminergic reward and saliency (interoceptive and error monitoring) circuits (insula, ACC) were linked to impaired metabolic trajectories and cognitive impulsivity in T1DM.
Kumar et al., 2011 *Analytical cross-sectional study*	USA, Academic Medical Center	Assess whole-brain axial and radial diffusivity to provide a more complete description of affected tissue	MRI	HF patients (n = 16): (age 55.16 +/- 7.8 years, 75% males) Control group (n=26): healthy subjects (mean age 49.76 +/- 10.8 years, 65% male)	Structure: - Increased axial diffusivity (loss of axonal integrity) near the anterior insula in patients. - Increased Axial Diffusivity and radial diffusivity in the left anterior and mid insula in patients. No symptoms assessed
Li et al., 2020 *Analytical cross-sectional study*	China, hospital	To investigate intrinsic functional hubs and their connectivity and how they contribute to cognitive deficits in Chronic Obstructive Pulmonary Disease (COPD) patients	- Structural and Functional MRI of the brain - Arterial blood gas analysis - Mini Mental State Assessment - Montreal Cognitive Assessment - Spirometry	COPD patients (n = 19) with (74% males, mean age: 62.7 ± 5.9). Control group (n= 20): healthy subjects (75% males, mean age: 60.8 ± 6.3)	Activity (Connectivity): Patients showed significantly decreased functional connectivity between the right insula and the supplementary motor area. No symptoms assessed
Li et al., 2018 *Quasi-experimental study*	China, hospital	To explore the changes in brain activity in response to thermal stimuli in patients with type 2 diabetes mellitus (T2DM)	Structural and Functional MRI of the brain (with and without thermal stimuli)	T2DM patients (n = 21) among which n = 8 with diabetic peripheral neuropathy (50% males, mean age: 55 ± 7.9) and n = 13 without diabetic peripheral neuropathy (54% males, mean age: 55.8 ± 11.9). Control group (n = 15): healthy subjects (60% females, mean age: 56.1 ± 7.4)	Activity: In response to temperature stimuli, patients with diabetic peripheral neuropathy showed stronger activation in the right insula compared to healthy controls and diabetic patients without neuropathy. No symptoms assessed
Liu et al., 2022 *Analytical cross-sectional study*	China, hospital	To explore the functional changes of the brain and associated cognitive impairment in non-small cell lung cancer patients	- Resting-state Structural and Functional brain MRI - Mini Mental State Examination - Montreal Cognitive Assessment - Functional Assessment of Cancer Therapy-Cognitive Function	Patients (n = 49) with non-small cell lung cancer (80% males, mean age: 60.35 ± 8.58). Control group (n = 61): healthy subjects (69% males, mean age: 58.38 ± 6.17)	Activity: Compared to controls, patients showed increased Regional Homogeneity values in the bilateral insula ($p<.05$) No symptoms assessed
Liu et al., 2019 *Analytical cross-sectional study*	China, hospital	To investigate regional homogeneity in type-2 diabetes patients, their first-degree relatives, and healthy subjects	- Resting-state Structural and Functional brain MRI - Mini Mental State Examination - Montreal Cognitive Assessment - Clock Drawing Test - Rey–Osterrieth Complex Figure Test - Instrumental Activities of Daily Living scale	Patients (n = 26) with type-2 diabetes (62% females, mean age: 51.9 ± 10.7) First-degree patients' relatives (n = 26) (58% females, mean age: 48.1 ± 10.1). Control group (n = 26): healthy subjects (58% females, mean age: 48.2 ± 6.7)	Activity: Patients showed decreased regional homogeneity in the left insula compared to healthy subjects. No symptoms assessed

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
			- Prospective and Retrospective Memory Questionnaire - Comprehensive Assessment of Prospective Memory		
Luo et al., 2022 *Analytical cross-sectional study*	China, Academic Hospital,	Investigate alterations in cerebral blood flow (CBF) and its connectivity patters of neural regions (olfactory) in type 2 diabetes mellitus (T2DM) patients	fMRI	T2DM patients (n=69): mean age 46.4 +/- 8.2 yrs., 72% males. Control group (n=63): healthy subjects (mean age 45.1 +/- 7.7 yrs. 68% males)	Structure: CBF in right insula significantly lower in patients (p<.05). Patients with antidiabetic drug therapy had significantly lower CBF in right insula than non-drug therapy patients (p<.05) Disease duration negatively correlated with CBF changes in right insula (r = -0.262, p = .033). CBF of right insula negatively correlated with max blood glucose (*r* = -0.451, *p*= .021) Nonspecific symptoms: Self-rated depression: T2DM 6.2 +/- 3.5 vs 4.5 +/- 3.8, p<.009) Self-rated anxiety: T2DM 34.5 +/- 6.5 vs 32.3 +/- 5.3, p<.039)
McDonald et al., 2022 *Cohort study*	USA, University	To examine the effects of antiestrogen hormonal therapy on brain imaging metrics in breast cancer	- Structural and Functional MRI of the brain - Neuro psychological Assessment Battery - Wide Range Achievement Test-4 Word Reading subtest - Center for Epidemiologic Studies Depression Scale - State-Trait Anxiety Inventory - N-back task (verbal working memory)	Patients (n = 29) with breast cancer treated with hormonal therapy (100% females, mean age: 67.7 ± 4.8). Control group (n = 29): healthy subjects (100% females, mean age: 66.8 ± 3.9)	Structure: Reduced insular cortex volume in patients vs controls (p<.05). No symptoms assessed
Ogren et al., 2012 *Analytical cross-sectional study*	USA, Cardiomyopathy Center	To assess the temporal patterns of neural response in a priori defined brain autonomic control areas to the Valsalva maneuver	- Structural and functional MRI of the brain	Patients (n = 16) with advanced heart failure (69% males, mean age: 54.4±8.1). Control group (n = 33): healthy subjects (70% males, mean age: 52.3±7.7)	Activity: - Left Insula: patients showed initial activation signal decrease similar to controls, and after 6s returned to baseline while control values declined and remained decreased (p < .05) - When comparing responses to Valsalva manoeuvre in patients versus controls, there are more significant differences in response between patients and controls in left insula than in right insula. Meaning that the left insular response looks more abnormal in HF patients than the right insular response (p < .05) No symptoms assessed
Peng J. et al., 2016 *Analytical cross-sectional study*	China, Hospital	To investigate whether global spontaneous brain activity changes in type 2 diabetes mellitus (T2DM) patients and these changes vary according to the degree of microangiopathy.	Structural and Functional MRI of the brain	T2DM patients with microangiopathy (n = 26, 54% females, mean age: 57.6 ± 9.3), and without microangiopathy (n = 22, 55% females, mean age: 58.8 ± 7.9). Control group (n = 28): healthy subjects (57% females, mean age: 56.2 ± 6.9)	Activity: - Voxel-Based Morphometry analysis: No significant difference between patients and controls - Increased Regional Homogeneity in the insula in patients compared to controls (p<.05, AlphaSim corrected). No symptoms assessed
Rosenkranz et al., 2012 *Quasi-experimental study*	USA, University	Determine if activity in the anterior cingulate gyrus and insula is associated with systematic alterations in lung function and inflammatory mediators.	fMRI	Asthma patients (n=18); mean age: 22.53 yrs., 62% females. Control group (n=10): healthy subjects (mean age: 23.2 yrs., 40% male)	Activity: Following antigen exposure, asthma patients with late phase response to stimuli showed significantly increased anterior insular

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
					reactivity to asthma-related words compared to their response to negative or neutral words when compared with non-late phase group (p=.02) and control group (p=.005). Following antigen exposure, patients with no late phase response to antigen showed increased ventral posterior activity to negative words during antigen test compared to L-phase response (Asthma related words: p.089), Neutral words: p =0.003) and Control (p= .009; Neutral: p= .003). No symptoms assessed
Roy et al., 2020 *Analytical cross-sectional study*	USA, Outpatient Diabetes Center of Academic Hospital	Examine regional brain gray matter volume (GMV) in type 2 diabetes mellitus (T2DM) compared to HC and assess association with depression and anxiety symptoms	MRI	T2DM patients (n=34): mean age 56.8 +/- 7.1, 66% females. Control group (n=88): healthy subjects (mean age 54.4 +/- 5.1 yrs. 52% male)	Structure: Significantly reduced GMV in bilateral anterior insula in patients (p<.01) Anxiety scores had negative correlation with anterior and posterior insula GMV in patients. Depression scores had a negative correlation with GMV of the anterior insula in patients. Nonspecific symptoms: Patients had significantly higher anxiety (p=.003) and depression (p=.001)
Scherling C. et al., 2011 *Analytical cross-sectional study*	Canada, Regional Cancer Centre	To examine functional neural processing in breast cancer patients (prior to chemotherapy commencement) completing a visuospatial working memory task	Structural and Functional MRI of the brain during visuospatial working memory task (2-back test)	Patients (n = 23) with breast cancer (100% females, mean age: 51 ± 8.5 years). Control group (n = 23): healthy subjects (100% females, mean age: 49 ± 9 years)	Activity: - Patients showed increased activity in the Left insula (Z= 4.12, p < .001) when accounting for depression - Patients showed significantly less (p < .05) activation in the right insula compared to controls during the test. No symptoms assessed
Simo et al., 2015 *Analytical cross-sectional study*	Spain, Lung cancer unit and Radiation Oncology department of an academic medical center	Assess differences in brain structure between small-cell lung cancer (C+) following chemotherapy, non-small-cell lung cancer (C-) before chemotherapy, and Healthy controls	MRI	Cancer patients post chemotherapy (n=28): mean age 59.2±5.5 yrs, 79% male Cancer patients before chemotherapy (n=20): mean age 60.3±6.3 yrs, 90% male Control group (n=20): healthy subjects (mean age 62.3±8.0 yrs, 90% male)	Structure: Patients with lung cancer (C+, C-) had significantly decreased grey matter density in the left insula. C+ showed a significant decrease in grey matter density in the right insula compared to HC. No symptoms assessed
Simo et al., 2016 *Analytical cross-sectional study*	Spain, Lung cancer unit and Radiation Oncology department of an academic medical center	Describe long-term cognitive toxic effects, together with relationship to Grey Matter and White Matter microstructural changes, in small cell lung cancer (SCLC) treated with prophylactic cranial irradiation	MRI	SCLC patients (n=11): mean age 68 [57–77], 91% male. Control group (n = 11): healthy subjects (mean age 65 [53–74], 91% male)	Structure: - patients showed reduced grey matter density in the right insula (p<.05) - No significant differences in grey/white matter in the insula. Nonspecific symptoms: patients showed no difference in Beck Depression score (Fisher exact test, p>.015)
Song X. et al., 2018 *Analytical cross-sectional study*	USA, Cardiomyopathy Center	To evaluate neural responses to the Valsalva manoeuvre and to assess regional brain structural changes in heart failure (HF)	- Structural and Blood oxygen level-dependent Functional MRI of the brain - Diffusion tensor imaging-based mean diffusivity	HF patients (n = 29): 76% males, mean age: 54.2 ± 8.0). Control group (n = 35): healthy subjects (63% males, mean age: 51.2 ± 5.9)	Activity: - Right Insula showed less extensive signal increase in response to Valsalva maneuver in patients (p<.050) - Patients has lower neural response to valsava

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
					maneuver in left anterior insula Structure: - Patients showed increased values of mean diffusivity in posterior insular cortices + decreased neural response to Valsalva in left anterior insula ($p<.050$) - Higher mean diffusivity values significantly correlated with lower activation in insular cortices ($p<.05$) No symptoms assessed
Song et al., 2019 *Quasi-experimental study*	USA, Academic Medical Center	Evaluate insular and cerebellar functional connectivity (FC) with other neural regions before, during, and after a Valsalva challenge in heart failure (HF) patients	fMRI	HF patients (n=29): mean age 54.2 +/- 8; 76% males. Control group (n=35): healthy subjects (mean age 51.2 +/- 5.9, 63% males)	Activity (Connectivity) In patients: During baseline and challenge, patients had increased FC between bilateral insula and putamen-thalamus ($p<.05$) During recovery, left insula showed higher FC with bilateral thalamus and globus pallidus, and lower FC with left posterior insula in ($p<.05$) During recovery, left cerebellum showed impaired negative FC with bilateral insula. ($p<.05$) At baseline, R cerebellum showed impaired FC with right insula ($p<.05$) At recovery, R cerebellum showed decreased negative FC with bilateral insula during recovery ($p<.05$) No symptoms assessed
Sun D.M. et al., 2017 *Analytical cross-sectional study*	China, Hospital	- To investigate the neural basis of decision making at the initial onset stage of type 2 diabetes mellitus. - To explore the link between functional magnetic resonance imaging of the brain information and Iowa Gambling Task performance and clinical data	Structural And Functional MRI of the brain	Patients (n = 18) with type 2 diabetes mellitus (50% males, mean age: 42.89 ± 7.01). Control group (n = 18): healthy subjects (50% males, mean age: 40.33 ± 4.14)	Activity: Abnormally elevated activations in the insula of patients (Left insula T = 3.78, R insula T = 4.55, $p < .05$) compared to controls. No symptoms assessed
Taskiran Sag et al., 2019 *Analytical cross-sectional study*	Turkey, Outpatients	To test functional connectivity patterns in resting-state networks	fMRI	Diabetic patients with painful neuropathy (n = 10) 50% female; mean age 50.1±6 Patients with hereditary neuropathy (n = 10, 50% female; mean age 37.8±14) Diabetic patients without painful neuropathy (n = 7, 57% female, mean age 51 ±6.3). Control group (n = 18): healthy subjects, 50% female, mean age 48.1±7.2	Activity (Connectivity): All groups compared to healthy controls: higher connectivity between right and left insula; and between left insula and right cingulate. Hereditary neuropathy patients also reported higher connectivity between left insula and left anterior cingulate cortex; and inversely correlated activity between left insula and left inferior parietal lobule. No symptoms assessed
Ten Kulve J.S. et al., 2015 *Quasi experimental study*	Netherlands, University Medical Center	- To assess the physiological role of GLP-1 (Glucagon-like peptide 1) in the central regulation of food intake in obese patients with type 2 diabetes and healthy individuals	- Structural and Functional MRI of the brain - Pre-post infusion of GLP 1 or placebo	Patients (n = 20) with obesity and type 2 diabetes mellitus (55% males, mean age: 59.5 ± 0.9). Control group (n = 20): healthy subjects (50% males, mean age: 56.3 ± 1.4)	Activity: - Placebo in fasted condition: patients showed increased activation of bilateral insula (right: p = .02, left: p=.04) in response to food pictures and in left insula (p = .04) in response to high-energy food pictures compared to controls -Placebo in post-prandial

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
					condition: Reducing effect of meal intake on central nervous system activation in response to viewing food pictures was observed in bilateral insula of obese T2DM patients (right p=.04, left p=.05) and in the left insula (p = .04) - GLP-1 blockade: Reducing effect of meal intake on central nervous system activation in bilateral insula (right p=.04, left p=.05) and in the left insula (p = .08) was largely prevented by GLP-1 Blockade in obese T2D patients No symptoms assessed
Ten Kulve J.S. et al., 2016 *Randomized controlled trial*	Netherlands, University Medical Center	To investigate whether modulation of the central nervous system responses to palatable food consumption may be a mechanism by which Glucagon-like Peptide 1 contributes to the central regulation of feeding	Structural and Functional MRI of the brain to assess activation of brain areas in response to chocolate milk receipt at baseline and pre-post treatment with 2 medications (liraglutide vs insulin glargine)	Patients (n = 20) with obesity and type 2 diabetes mellitus (55% males, mean age: 59.5 ± 0.9) . Control group (n = 20): healthy subjects (50% males, mean age: 56.3 ± 1.4)	Activity: - Compared to controls, patients showed less activation of right insula (p = .04) in response to chocolate milk receipt as well as a tasteless solution. - after ten days of treatment with liraglutide, compared with insulin glargine, the central nervous system activation to chocolate milk compared with baseline was increased in right insula (p = .032) in patients - Correlation analysis between CNS activation of the right insula after 10 days on treatment and difference in weight changes over 12 weeks between treatments revealed significant positive relationship. (r = 0.5, p = .03) No symptoms assessed
Tseng M. et al., 2013 *Analytical cross-sectional study*	Taiwan, Hospital	To explore how the patterns and degree of activations to noxious stimuli in patients with type 2 diabetes mellitus (T2DM) with nerve degeneration-induced chronic neuropathic pain differ from those in healthy subjects	- Structural and Functional MRI of the brain - 0–10 numeric scale to assess pain intensity	T2DM patients (n = 22) with painful neuropathy (n = 11, 64% females, mean age 51.1 ± 9.1) or painless neuropathy (n = 11, 55% males, mean age 51.3 ± 10.6). Control group (n = 11): healthy subjects (64% females, mean age 50±16.6)	Activity: Patients with painful neuropathy showed greater signal change within the insula in response to hot stimulation compared to healthy (p=.023) and painless neuropathy (p= .013) groups
Wang et al., 2022 *Analytical cross-sectional study*	China, Department of Endocrinology, Shaanxi Provincial People's Hospital,	Investigate functional connectivity (FC) between right dorsal anterior insula and the central executive network and default-mode network in type 2-diabetes mellitus (T2DM)	fMRI	T2DM patients (n=44): mean age 55.18 ± 6.25, 70% males Control group (n=41): healthy subjects (66% males, mean age 54.41 ± 4.96)	Activity (Connectivity): Significantly decreased FC in T2DM between the right anterior insula and right inferior frontal gyrus (T-value = -4.409, p<.05), right middle frontal gyrus (T-value = -5.122, p<.05), right precuneus/posterior cingulate cortex (T-value = -4.325, p<.05), bilateral medial prefrontal cortex (T-value = -4.443, p<.05), left angular gyrus (T-value = -4.453, p < .05), right angular gyrus (T-value = -4.372, p <0.05). No symptoms assessed
Woo et al., 2003 *Analytical cross-sectional study*	USA, Academic Medical Center	Evaluate neural damage in heart failure patients (HF)	Structural brain MRI	HF patients (n = 9): mean age 51 +/- 10; 67% men; all NYHA class III-IV Control group (n=27): heathy	Structure: - Total Gray Matter Volume: No differences after correcting for age and gender (Controls had greater GMV

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
				subjects (mean age 46 +/- 12; 81% males)	prior to this correction) - Regional Gray Matter Volume: HF showed significant loss of grey matter in left and right insular cortex. Loss was larger on right side but spanned the entire insular region (all p <0.005). Anterior-dorsal portion of left insula demonstrated significant GMV loss as well (p<.005) No symptoms assessed
Woo et al., 2005 *Quasi-experimental study*	USA, Academic Medical Center	Determine if functional responses in brain to autonomic challenge would differ from normal and if differences would appear in areas of previously demonstrated grey matter loss in heart failure (HF)	Functional MRI during 54-s baseline and during 90-s forehead cold-presser challenge	HF patients (n = 6): mean age 49±12; 100% male) who exhibited grey matter loss in our earlier study. Control group (n=16): healthy subjects (mean age 48 +/- 11 years; all male)	<u>Activity:</u> Neural Signal Responses to challenge: Right anterior insula bordering the frontal cortex showed rising signals in HF over HCs and declining in left insular cortex below HCs (p<.005) No symptoms assessed
Woo M.A. et al., 2007 *Analytical cross-sectional study*	USA, tertiary heart failure referral center	To determine if the Valsalva manoeuvre, an autonomic nervous system challenge, would show abnormal responses in ANS regulatory areas of the brain in heart failure (HF)	Functional MRI of the brain to assess responses to Valsalva manoeuvre	HF patients (n = 5): 60% male, mean age: 50 ± 10. Control group (n =14): healthy subjects (100% males, mean age: 47 ± 11)	<u>Activity</u>: Right anterior insula in patients showed an inverted response to Valsalva maneuver: signals in patients declined during Valsalva and increased during recovery, contrarily to controls (p<.05) No symptoms assessed
Woo et al., 2009 *Analytical cross-sectional study*	USA, Academic Medical Center	Evaluate the extent of brain injury across the brain in heart failure (HF) patients	MRI	HF patients (n = 13): mean age 54.6 ± 8.3 years; 69% male). Control group (n=49): healthy subjects (mean age 50.6 ± 7.3 years, 59% male)	<u>Structure:</u> Voxel-based-relaxometry: Anterior and posterior insula demonstrated significant injury (p<.005). Significantly greater T2-relaxation values in HF for left anterior insula (p < .001), left posterior insula (p < .001), right anterior insula (p < .001). No symptoms assessed
Woo et al., 2014 *Analytical cross-sectional study*	USA, Academic Medical Center	Evaluate the metabolite patterns in bilateral anterior insula in heart failure (HF) to indicate the extent of neuronal and glial injury in HF.	MRI	HF patients (n = 11): mean age 51.6 ± 8.38 years; 63% males. Control group (n=53): healthy subjects (mean age 46.8.1 ± 8.13 years, 60% male)	<u>Structure:</u> - Left Insula: Significantly greater Cho/Cr ratio in HF than controls (p = .02) (= greater glial injury) - Right Insula: Significantly lower NAA/Cr ratio in patients vs controls (p = .04) (= neuronal loss/disfunction) <u>Nonspecific symptoms:</u> - Greater anxiety scores in HF (p = .027) - Greater depression scores in HF (p=.05)
Woo et al., 2015 *Analytical cross-sectional study*	USA, Academic Medical Center	Determine if structural changes in the brain observed in heart failure (HF) result from acute or chronic processes.	MRI	HF patients (n = 16): mean age 55.16 +/- 7.8 years, 75% males. Control group (n=26): healthy subjects (mean age 49.76 +/- 10.8 years, 65% males)	<u>Structure:</u> - Global Mean Diffusivity values: greater in patients than controls (p = .038) - Greater regional brain mean diffusivity in left Insula (p = .001) and right insula: (p = .004) in patients than controls. No symptoms assessed
Yang S.Q. et al., 2016 *Analytical cross-sectional study*	China, Hospital	To evaluate the functional connectivity patterns (integrity, network, connectivity) within the default mode network, the dorsal attention network, the control network, the salience network and the sensorimotor network in patients with type 2 diabetes mellitus (T2DM)	Structural and Functional MRI of the brain	T2DM patients with normal cognition (n =19, 63% females, mean age 59.53 ± 6.17) and impaired cognition (n =19, 74% females, mean age 61.95 ± 5.93). Control group (n = 19): healthy subjects (58% females, mean age: 60.21 ± 5.35)	<u>Activity (Connectivity)</u>: Significantly decreased connectivity strength of the right insula was observed in patients with diabetes and impaired cognition compared to healthy controls (p < .05). No symptoms assessed

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
Zhang D. et al., 2019 *Analytical cross-sectional study*	China, Hospital	To find the neuroimaging endophenotypes of type 2 diabetes and investigate the role of inherent neurological disorders in the pathogenesis and deterioration of type 2 diabetes mellitus (T2DM)	Structural and Functional MRI of the brain	T2DM patients (n = 26): 62% females, mean age 51.9 ± 10.7. Patients' siblings (n = 26): 58% females, mean age 48.1 ± 10.1. Control group (n = 26): healthy subjects (58% females, mean age: 48.2 ± 6.7)	Structure: Compared to healthy controls, patients showed grey matter volume of bilateral insular cortex with significant atrophy and the left insular presented significantly decreased cerebral blood flow (p <0.05). Siblings: Compared with healthy controls, significant atrophy of the left insular cortex was observed (p<.05) No symptoms assessed
Zhang D.S., et. al., 2020 *Analytical cross-sectional study*	China, Hospital	To explore the neural mechanisms of brain impairment in type 2 diabetes mellitus	Structural and Functional MRI of the brain	Patients (n = 38) with type 2 diabetes mellitus (79% males, mean age: 55.71 ± 6.32). Control group (n = 33): healthy subjects (79% males, mean age: 54.01 ± 4.99)	Activity (Connectivity): patients (vs controls) showed lower functional connectivity between left insula and right posterior cerebellum (t = -5.04). Functional connections between right insula and left medial frontal gyrus (t = -4.20) and left supplementary motor (t = -5.98) were significantly lower in patients vs controls. All p <0.05 No symptoms assessed
Zhang H.Y. et al., 2012 *Case-control study*	China, Hospital	Investigate brain structural damage in chronic obstructive pulmonary disease (COPD)	Structural MRI of the brain	Patients (n =25) with COPD (84% males; mean age: 69.2 ± 8.1). Control group (n = 25): healthy subjects (84% males, mean age: 67.96 ± 8.0)	Structure: Patients showed reduced grey matter density in the bilateral anterior insula: right insula (t =5.15, p <0.05), and left insula (t= 4.48, p <0.05) No symptoms assessed
Zhang Y. et al., 2021 *Cohort study*	China, Hospital	Investigate whether and how regional neurovascular coupling changes in patients with type 2 diabetes mellitus longitudinally and whether these changes also exist in matched controls without diabetes	- Resting state Functional MRI of the brain - Self-rating Anxiety Scale and Self-Rating Depressive Scale measuring symptoms of anxiety and depression - Mini mental state examination - Auditory Verbal Learning Test to assess short- and long-term memory	Patients (n = 27) with type 2 diabetes mellitus (59% males, mean age: 55.03 ± 7.63). Control group (n = 36): healthy subjects (63% males, mean age: 52.25 ± 6.94)	Activity (Connectivity): - Patients showed significant longitudinal changes in mReHo:mCBF (=standardized Regional Homogeneity to Cerebral Blood Flow ratio) in left insula (p <0.05) while healthy controls did not show significant changes over time (F = 8.082, p = .006) - No significant differences in left insula mReHo:mCBF at baseline, but there was significantly lower mReHo: mCBF at 5-year follow-up (t=3.069, p=.003) Nonspecific symptoms: No significant between group-differences were observed in anxiety or depression
Zunini R. et al., 2013 *Cohort study*	Canada, Regional Cancer Centre	Investigate the possible side-effects of chemotherapy on brain function.	fMRI of the brain during a verbal recall task (before and after chemotherapy)	Patients (n = 21) with breast cancer (100% females, mean age: 50.62 ± 8.37) . Control group (n = 21): healthy subjects (100% females, mean age: 49.67 ± 8.75)	Activity: - The left insula in patients was significantly more active pre-chemotherapy compared to post-chemotherapy (p<.01). The right insula showed a similar trend (p = .06) - Between group differences at T2 (controls vs pts post-chemotherapy): patients showed less activation in the right insula (p < .05) and a trend in the left insula (p=.06) during the verbal recall task. No symptoms assessed
Zhang et al., 2023 *Analytical*	China, Radiology Department of Henan	To explore spontaneous brain activity in patients with type 2 diabetes mellitus (T2DM) and	Resting state fMRI	T2DM patients (n = 52, 60% females, mean age 53.9 ± 9.5).	Activity (connectivity): Patients showed: - decreased ReHo values in

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Table 2 (*continued*)

Study	Country, setting	Aim/s	Methods	Participants' characteristics	Main Results
cross-sectional study	Provincial People's Hospital	to determine the relationship between brain changes and cognitive dysfunction.		Control group (n = 52): healthy subjects (56% males, mean age 53.0 ± 7.7)	the insula - positive association between fasting glucose and neural activity in left insula. Strong relationship between higher blood sugar and abnormalities in the surrounding areas of the insula = vulnerable target in the brain for T2DM. Decreased neural activity in the surrounding areas of the insula may act as an early biomarker of its potential contribution to cognitive decline in DM. No symptoms assessed.

impairments and symptoms. To do so, they adopted a battery of instruments depending on the condition of interest. More details on the instruments are reported in Table 2.

Main results

The included studies explored either the structure (e.g., cortical thickness or grey matter volume) or the function (i.e., functional condition, such as neural responses) of the insular cortex. Only one study assessed both.[34] Figs. 3 and 4 show the structure and function of the insular cortex across and within chronic diseases. To provide a structured synthesis of the study findings, results are presented as follows: (a) structure of the insular cortex; (b) function of the insular cortex; and (c) relationship between the insular cortex and symptoms.

Structure of the insular cortex

Nineteen studies (38%) explored the structural condition of the insula. These studies revealed that patients with chronic disease had lower insular grey matter volume/density/thickness compared to healthy controls,[35–45] damaged insular tissue,[21,34,46–49] and reduced cerebral blood flow.[50] Hirabayashi et al.[36] also found that disease duration was negatively associated with insular grey matter volume; insular grey matter was lower in patients with a longer duration. Only one study[51] found no difference between patients and healthy controls in insular grey matter volume/thickness.

Function of the insular cortex

Thirty-two studies (64%) explored the functional condition of the insula. Specifically, among them, 22 explored insular activity (e.g., activation of external stimuli), and 10 explored functional connectivity (i.e., interaction) between the insular cortex and other regions of the brain.

Among the 22 studies exploring insular activity, 10[52–62] found higher insular activity and reactivity to external stimuli in patients with a

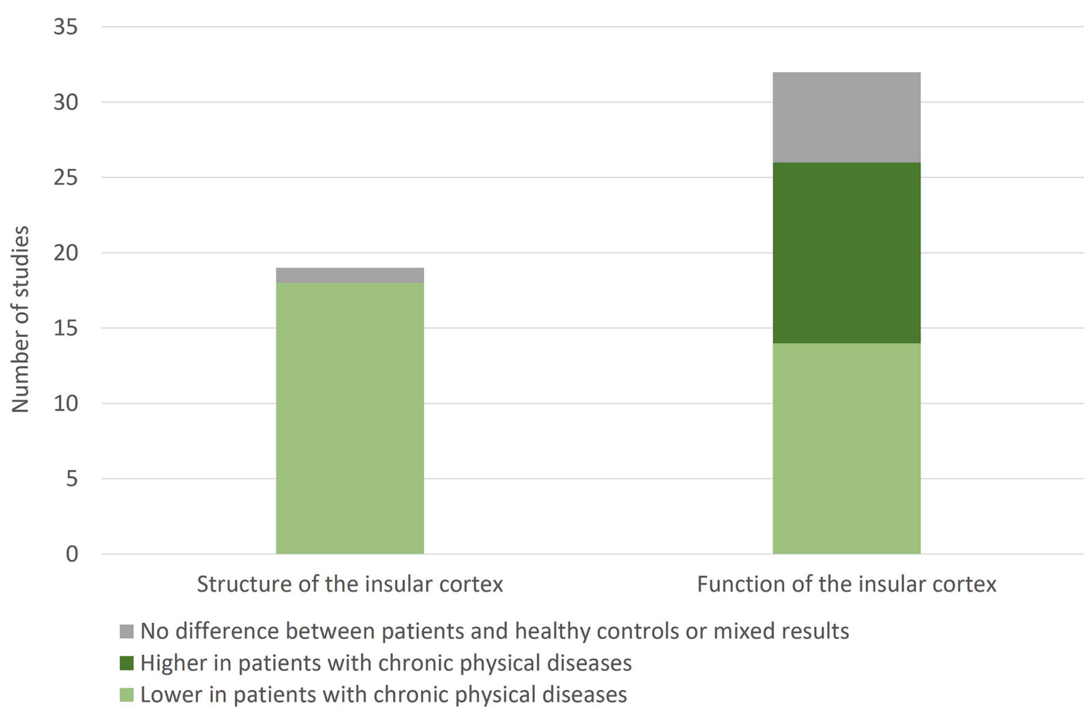

Fig. 3. Structure and function of the insular cortex across chronic physical diseases. Note: One study assessed both insular structure and function. *Structure* refers to the grey matter status (e.g., volume, density, thickness). Thus, *lower structure* = lower insular grey matter volume/density/thickness/blood flow in patients vs healthy controls.

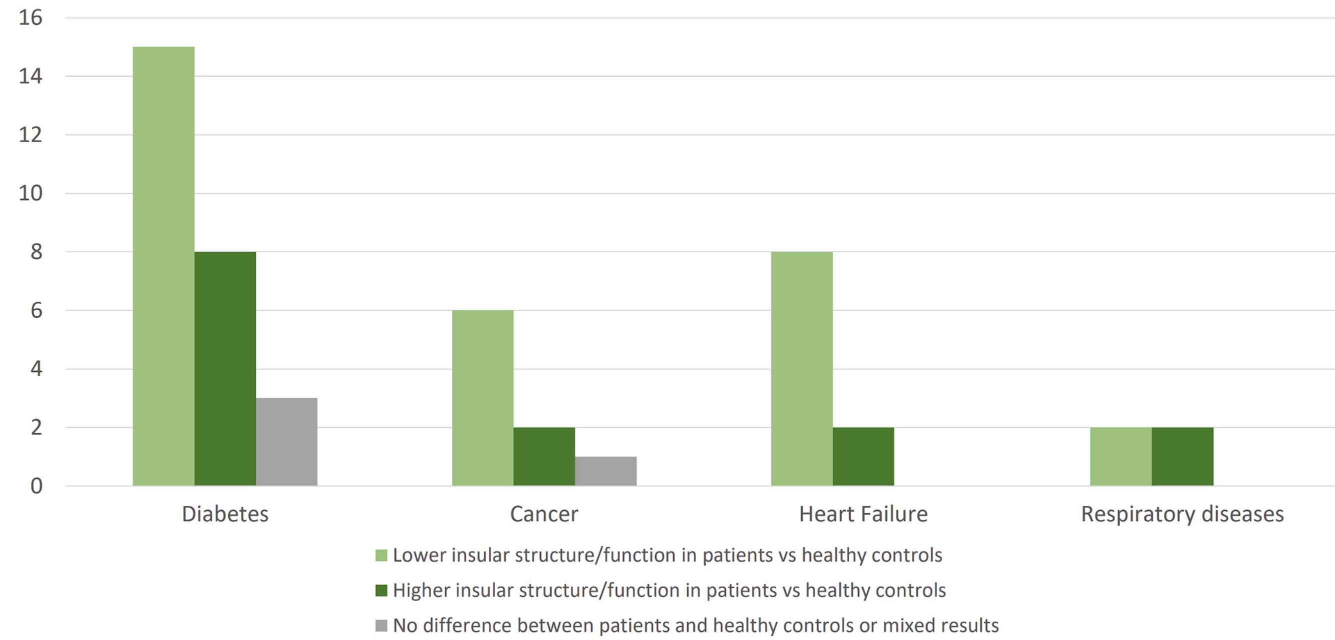

Fig. 4. Structure and function of the insular cortex for each chronic physical disease. Note: One study assessed both insular structure and function. "Structure" refers to the grey matter status (e.g., volume, density, thickness, blood flow). Thus, *lower structure* = lower insular grey matter volume/density/thickness/blood flow in patients vs healthy controls.

chronic disease compared to healthy controls. Among them, Jorge et al.[54] also reported that the saliency circuits (which monitor interoceptive states and determine behavioral responses to stimuli and include the insular cortex and the anterior cingulate cortex) were associated with impaired metabolic trajectories and cognitive impulsivity in patients with type-1 diabetes mellitus. In contrast, six studies[34,63–66] found lower insular activity/reactivity in patients compared to healthy controls. Among them, Zunini et al.[65] found that insular activity in cancer patients significantly dropped after receiving chemotherapy. One study[67] found no difference in the activity/reactivity of the insular cortex between patients and healthy controls.

Other studies reported mixed results. Scherling et al.[68] found higher activity in the left but lower activity in the right insula in patients vs. healthy controls. Woo et al.[69] found inverted activation in the insular cortex in patients vs. healthy controls; patients had lower insular activation during the stimulus and increased insular activation afterward during recovery, while healthy controls showed the opposite trend. In addition, Woo et al.[22] also found that patients showed higher activation in the anterior insula but lower activation in the left insula compared to healthy subjects. Ten Kulve et al. conducted two studies[70,71] and found that patients had different insular activation depending on the way the stimulus was provided (i.e., compared to healthy controls, patients showed higher insular activation to food pictures but less insular activation to food ingestion).

Among the ten studies that explored functional connectivity in the insular network, two[72,73] found higher functional connectivity in patients compared to healthy controls (i.e., the insular cortex was highly connected and co-active with other brain regions), and eight[74–81] found lower functional connectivity in the insular cortex network in patients compared to healthy controls. More details on the regions of the brain as they interact with the insular cortex can be found in Table 2.

Relationship between the insular cortex and symptoms

Only five studies (10%) explored the relationship between the insular structure/function and disease-related symptoms. Four (80%)[53,60,67,81] found a positive association between insular activity and symptom severity, and one found a negative association between insular grey matter volume and symptom severity.[49]

Discussion

We found that people with chronic disease had lower insular grey matter volume/density/thickness compared to healthy people without chronic disease. Additionally, people with a chronic disease had abnormal insular activity (i.e., either higher or lower) compared to healthy controls. This means that the insula is overreacting or underreacting to stimuli; either way, insular activity seems to be altered in those with a chronic disease. The way abnormal insular activity is linked to symptoms remains unclear and needs further investigation.

As the primary substrate responsible for higher order interoceptive processing,[14] lower insular grey matter volume/density/thickness may indicate lower interoceptive potential in people with a chronic disease. As some authors noted,[82] lower insular activation in patients may indicate a deficit in interoceptive processing and an inappropriate homeostatic response to stimuli.[34] Some investigators reported higher insular activation in patients. As previous evidence has shown, this finding might be explained by the fact that the right anterior insula mediates awareness of interoceptive information,[18] and the grey matter volume in this region negatively correlates with interoceptive accuracy.[18,83] Enhanced activity in the anterior insula during anticipation of negative stimuli has been described in subjects with anxiety[84] and in response to uncertainty in patients with a chronic disease.[85] Furthermore, higher activation in the insular cortex seems to be associated with an urgency-trait personality profile and to predict more risky decisions.[59,86] In light of this, our findings on abnormal insular activity in people with a chronic disease may indicate abnormal processing of interoceptive stimuli.

We found that most studies that explored symptoms found a positive association between insular structure/activity and symptom severity: an overactive insula might lead to a distorted or exaggerated perception of bodily sensations or increased awareness of subtle symptoms. The insula receives and integrates information about all sorts of bodily sensations and states, such as blood pressure and oxygenation, gastrointestinal motility, heartbeat timing and strength, hunger, nausea, etc. Additionally, the insula engages in top-down control of autonomic functions regulating physiologic process such as heart rate, blood pressure, and gastric motility.[87] When the insular cortex is damaged (as seen in patients with a chronic disease), insular lesions do not alter sensory perception thresholds but, instead, affect the recognition and valence given to sensory input, as well as the promotion of emotion regulation.[87] This suggests that when a stimulus arises in the body, it will most likely reach the insula both in healthy people and those with a chronic disease. However, in chronic illness, it may be caused by an altered valence (e.g., an over-active insula may overestimate bodily signals). This might explain the observed positive association between insular structure/activity and perceived symptom severity in those with a chronic disease. Furthermore, the insula estimates the valence, magnitude, and probability of expected outcomes while taking bodily signals (cognitive functions, bodily feelings, emotions) into account. For this reason, it has a crucial role in decision-making.[87,88] Thus, when the insula is altered, impairments in decision-making about symptoms may also be observed. However, it is difficult to draw conclusions based on only five studies. While the insular cortex has been identified as having a key role in processing symptoms in chronic disease,[89,90] further evidence is required to understand its relationship with symptom perception in chronic conditions.

The results of this review suggest that people with a chronic disease may have lower insular volume compared to healthy subjects, while findings on insular activity remain mixed and inconsistent. None of the studies included in this review assessed the association between insular structure/activity and interoceptive levels. However, we previously concluded that people with a chronic condition have lower interoceptive accuracy and that their interoceptive sensibility levels are negatively associated with symptom burden.[8] Thus, the results of this review help to better explain impaired interoceptive abilities in chronic illness. Future research is warranted to further explore whether there is a direct association between insular grey matter volume/activity and interoceptive abilities and how this might link to the symptom experience.

Some studies reported strategies able to improve interoceptive abilities. Examples include meditation, yoga, breathing exercises, and physical exercises.[91–93] Some techniques, such as yoga[94] and working memory training,[95] have been shown to increase dopaminergic tone and induce growth in paralimbic structures, including the insula. Several studies also found that physical exercise [96–98] enhances physiologic arousal by manipulating the inputs entering the interoceptive network, which appears to optimize the integration of sensory stimuli with later responses. Mindfulness and other forms of meditation produce neuroplasticity effects by modulating the insular size and activity, eventually resulting in improved interoception.[92] Mindfulness approaches may improve interoceptive awareness by cultivating attention to bodily sensations that are sustained. Mindfulness engages neural networks involved in interoception, executive function, and emotion regulation. Slow breathing is thought to activate cardiopulmonary baroreceptors, leading to reflex reductions in sympathetic nerve activity, resulting in lowered blood pressure. Such interventions implemented to address interoceptive functioning have effectively improved clinical outcomes, including cardiovascular symptoms, pain, and psychological symptoms.[91] In light of the evidence suggesting that interoceptive functioning may be improved by various interventions, healthcare professionals may consider encouraging such interventions to improve interoceptive functioning, body awareness, and symptom management in their patients with chronic disease.

Limitations

To the best of our knowledge, this is the first systematic review analyzing how the insular cortex is impaired in chronic physical diseases. The results of this systematic review may help explain previously identified interoceptive impairments and characterize a mechanism underlying altered symptom perception in chronic physical diseases. However, the review has some limitations. Most of the studies (54%) included patients with diabetes mellitus, and only four (8%) included patients with chronic respiratory diseases. Additionally, chronic conditions primarily affecting the brain (e.g., brain tumors, stroke) were excluded due an inability to distinguish between damage to the brain and insular dysfunction. These factors may reduce the generalizability of these results. Finally, due to the heterogeneity of study designs and outcomes being measured, we were unable to perform a meta-analysis.

Conclusion

People with chronic physical diseases such as diabetes, cancer, heart failure, and chronic pulmonary disease have lower insular grey matter volume/density/thickness and abnormal insular activity (i.e., either higher or lower) compared to healthy people. Although few studies explored the relationship between insular activity and symptom severity, there appears to be a positive trend that may be attributed to distorted perception of bodily sensations. The results of this review provide information that can be used to help explain a phenomenon frequently encountered in clinical practice – poor symptom perception. Future research is warranted to investigate the association between insular grey matter volume/activity and interoceptive abilities and how this relationship influences symptom perception and response.

List of abbreviations

- MRI = Magnetic Resonance Imaging
- fMRI = functional Magnetic Resonance Imaging
- WHO = World Health Organization
- PROSPERO = International Prospective Register of Systematic Reviews
- JBI = Joanna Briggs Institute

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CRediT authorship contribution statement

Giulia Locatelli: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Austin Matus:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chin-Yen Lin:** Writing – review & editing. **Ercole Vellone:** Writing – review & editing, Supervision, Conceptualization. **Barbara Riegel:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2024.11.004.

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