Allostatic interoception in frontotemporal dementia: a scoping review protocol

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Abstract

Frontotemporal dementia (FTD) encompasses a spectrum of disorders characterized by distinct behavioral, cognitive, and motor symptoms. Deficits in interoception and allostasis have garnered attention, considering the involvement of the allostatic-interoceptive network in FTD, their contribution to canonical social cognitive and affective deficits, and the identification of whole-body biomarkers related to autonomic and allostatic processes. Traditionally, interoception has been defined as the perception of visceral signals, yet contemporary understandings broaden this to encompass both the representation and regulation of the physiological state across bodily tissues. Consequently, interoceptive deficits in FTD extend beyond classical viscerosensory paradigms to include pain, temperature, autonomic, metabolic, immune, and neuroendocrine phenomena. Allostasis involves the prospective regulation of energy balance, as well as the anticipation and adaptive response to homeostatic challenges. These repeated challenges result in physiological consequences measurable by markers of allostatic load, spanning various bodily systems. Despite emerging evidence highlighting dysfunction in interoception and allostasis in FTD, the literature remains fragmented, lacking cohesive reviews addressing the diverse mechanisms comprehensively. Thus, this scoping review examines the reciprocal interaction between brain and bodily physiology (interoception) and the physiological responses to environmental demands (allostatic load) in FTD. Following the principles outlined in the PRISMA statement, we will systematically search and screen quantitative primary research studies on patients with FTD, utilizing interoceptive or allostatic metrics. By synthesizing the existing literature, we aim to identify active research areas, delineate primary deficits across physiological systems, uncover syndrome-specific patterns of dysfunction, and identify the most promising and understudied domains in this field.

Keywords

Interoception; Allostasis; Autonomic Nervous System; Frontotemporal Dementia; Frontotemporal Lobar Degeneration.

1. Introduction

Frontotemporal dementia (FTD) is a spectrum of neurodegenerative diseases characterized by frontal and temporal lobe degeneration due to accumulation of various abnormal proteins, a pathological process termed frontotemporal lobar degeneration (FTLD). Clinically, FTD may manifest with a combination of behavioral, cognitive, and/or motor symptoms, categorized into different syndromes based on the main presenting features: behavioral symptoms are prominent in behavioral variant FTD (bvFTD); language deficits predominate in primary progressive aphasia (PPA); a combination of behavioral and semantic dysfunction is seen in right temporal variant FTD (rtvFTD); while motor symptoms are cardinal features of progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). Recently, attention has turned towards interoception and allostasis as additional dimensions of symptomatic and pathophysiologic relevance in FTD, across the various syndromes particularly in bvFTD (Migeot, Duran-Aniotz, Signorelli, Piguet, & Ibáñez, 2022).

Interoception refers to the integrated interpretation of both internal and external stimuli to construct a physiological representation of the state of the body, encompassing conscious and unconscious elements (Berntson & Khalsa, 2021). The current understanding of interoception goes beyond Sherrington's original concept of visceral sensory signaling (Sherrington, 1906) to include a comprehensive representation of the physiological condition of all tissues of the body, including the skin and skeletal muscle (Craig, 2002; Khalsa et al., 2018; Crucianelli & Ehrsson, 2023). Interoceptive information includes mechanical, chemical/metabolic, humoral, as well as pain and temperature modalities (Berntson & Khalsa, 2021). This interpretation of interoception is based both on its physiological, homeostatic role (Desmedt, Luminet, Maurage, & Corneille, 2023) and on the functional and neuroanatomical organization of interoceptive pathways, which predominantly consist of thinly myelinated or unmyelinated fibers ascending through lamina I spinothalamic pathways and vagal/cranial afferents and ultimately converging within the allostatic-interoceptive network (AIN) (Chen et al., 2021; Craig, 2002). The AIN encompasses a wide range of cortical areas, including prefrontal, orbitofrontal, cingulate, insular, and somatosensory cortex, as well as subcortical structures such as the amygdala, hippocampus, thalamus, hypothalamus, parabrachial nucleus and nucleus of the solitary tract (Chen et al., 2021; Kleckner et al., 2017). Furthermore, the AIN is involved in processing afferent interoceptive signals and regulating internal states (Chen et al., 2021; Kleckner et al., 2017). Indeed, current theories of interoception challenge the traditional dichotomy between afferent "interoceptive" and efferent "autonomic" systems, instead

viewing them as a unified system and highlighting the bidirectional nature of brain-body interactions (Barrett & Simmons, 2015; Chen et al., 2021; Ibanez & Northoff, 2024; Kleckner et al., 2017; Quigley, Kanoski, Grill, Barrett, & Tsakiris, 2021). Interoceptive predictive coding and active inference models are representative of such theories and postulate that the brain stores an internal model of the body based on past experiences (Barrett, 2017; Barrett & Simmons, 2015; Petzschner, Garfinkel, Paulus, Koch, & Khalsa, 2021). This model is used to issue predictions about the occurrence and causes of interoceptive inputs representing the current physiological state of the body. Simultaneously, it operates as interoceptive regulatory/control signals, aiming to align the current body state with predicted or preferred states when there's a discrepancy between predictions and sensory input (termed prediction error) in a perception-action loop (Pezzulo, Parr, & Friston, 2024). Another consequence of running an internal predictive model is that interoceptive control shifts from being solely reactive to enabling anticipation and adaptive responding to homeostatic perturbations as well as prospectively regulating energy balance – allostasis (Migeot et al., 2022; Quigley et al., 2021; Sennesh et al., 2022).

The rationale for studying interoception and allostasis in FTD is readily apparent from the considerable overlap between the AIN and the brain areas predominantly affected in FTD syndromes (Peet, Spina, Mundada, & La Joie, 2021; Schroeter, Raczka, Neumann, & Yves von Cramon, 2007). Furthermore, as a domain-general network, the AIN plays a crucial role in emotional processing and social cognition (Adolfi et al., 2017; Kleckner et al., 2017; Van den Stock & Kumfor, 2019), which are key dimensions underlying behavioral deficits in FTD (Kumfor & Piguet, 2012; Magno, Canu, Agosta, & Filippi, 2022; Magno, Canu, Filippi, & Agosta, 2022). Thus, interoception and allostasis offer the potential to identify novel, objective, and cross-cultural biomarkers associated with canonical behavioral manifestations in FTD.

Traditionally, interoception has been investigated with self-report measures, performance-based tasks, and assessment of neural signatures of interoceptive processes (Suksasilp & Garfinkel, 2022). These paradigms have been applied in FTD, for example providing evidence of reduced interoceptive accuracy and awareness in heartbeat detection tasks (Abrevaya et al., 2020; García-Cordero et al., 2016; Hazelton, Devenney, et al., 2023; Hazelton, Fittipaldi, et al., 2023; Marshall et al., 2017), and abnormal modulation of heart-evoked potentials using EEG (Abrevaya et al., 2020; Birba et al., 2022; Salamone et al., 2021). Nevertheless, in addition to these traditional interoceptive paradigms and by contemporary understandings of interoception, other clinical and experimental findings could be interpreted as indicative of interoceptive dysfunction in FTD. First, there is self-report and experimental data on noci- and

thermoceptive abnormalities (Carlino et al., 2010; Fletcher et al., 2015). Second, somatic symptoms relating to the abnormal interpretation of bodily sensations are frequently reported (Erkoyun et al., 2020; Gan, Lin, Samimi, & Mendez, 2016; Waldö, Santillo, Gustafson, Englund, & Passant, 2014). Third, other common symptoms in FTD can be construed as having an interoceptive component, e.g. abnormalities in eating behavior can be related to atypical regulation of energy metabolism or impaired perception of satiety cues (Ahmed et al., 2016, 2017). Fourth, clinical symptoms of dysautonomia are frequent in FTD (Ahmed et al., 2015), alongside experimental evidence of resting-state and task-related autonomic changes (e.g., Guo et al., 2016; Marshall et al., 2018; Sturm et al., 2018; Hua et al., 2020, 2023). Finally, systemic (blood-based) immune, metabolic, and endocrine/neuroendocrine markers are an area of active study in FTD (Katisko et al., 2020; Phan et al., 2020; Woolley et al., 2014). It is important to highlight that several of these biological and physiological markers are indicators of allostatic load. Indeed, these markers represent the physiological consequences of the individual's lifetime exposure to homeostatic perturbations and environmental demands relating to adverse health outcomes (Guidi, Lucente, Sonino, & Fava, 2021; McCrory et al., 2023; Migeot et al., 2022). Of note, interoceptive-allostatic overload has been proposed as a pathophysiological mechanism in FTD (Migeot et al., 2022; Migeot & Ibáñez, 2023).

Despite abundant evidence regarding different interpretations of interoception, autonomic function, and allostasis in FTD, the current literature fails to provide a thorough investigation that combines these aspects cohesively. A preliminary search of PubMed, Cochrane Database of Systematic Reviews, PROSPERO, and Open Science Framework for systematic or scoping reviews on interoception and allostasis in FTD was conducted in February 2024, and no current or underway reviews on the topic were identified. Accordingly, a scoping review is required to identify the types of available evidence, assessing how research is currently conducted, and identifying knowledge gaps in this field (Munn et al., 2018).

Therefore, this scoping review aims to synthesize the dispersed evidence about the reciprocal interactions between brain and bodily physiology (interoception) and the physiological consequences of repeated homeostatic challenges (allostasis and allostatic load) in FTD. This encompasses various domains, including visceral, pain, temperature, affective touch and taste sensations, immune responses, metabolic functions, endocrine processes, and the regulation and dysfunction of autonomic responses. Our goal is to present a coherent narrative and interpretation to fill this gap in the existing literature.

1.1. Review questions

1. What is the evidence for interoceptive and allostatic dysfunction in FTD?
    a. Which physiological systems have been primarily investigated, and what assessments and measures have been employed?
        i) Peripheral physiological measures
        ii) Biochemical (plasma) markers
        iii) Neural markers
        iv) Performance-based tasks
        v) Self-report/clinical measures
    b. What are the main findings across FTD syndromes?
    c. What are the demographic and clinical characteristics of the reported FTD population across and within syndromes?
    d. Are there syndrome-specific patterns of interoceptive and allostatic dysfunction in FTD?
    e. What areas of interoception and allostasis are currently understudied in FTD?

2. Methods

We followed the Joanna Briggs Institute guidelines for developing the scoping review protocol (Aromataris & Munn, 2020), aligning with the PRISMA extension for scoping reviews reporting guidelines (Tricco et al., 2018).

2.1. Eligibility criteria

2.1.1. Participants

We will include studies that report at least one human participant group of the FTD spectrum, namely bvFTD, PPA, PSP, CBS/CBD and rtvFTD. For PPA, we will include participants with semantic variant PPA (svPPA), non-fluent/agrammatic variant PPA (nfvPPA) or primary progressive apraxia of speech (PPAOS). Logopenic variant of PPA (lvPPA) can be included if negative for Alzheimer's Disease (AD) biomarkers because AD is the major underlying etiology for this syndrome (Mesulam et al., 2014). For CBS, biomarker negativity will not be mandatory since FTLD represents the majority of neuropathological diagnoses (Koga, Josephs, Aiba, Yoshida, & Dickson, 2022). Pre-symptomatic carriers of FTLD mutations may be included. Motor neuron disorders can be included only if clinically accompanied by FTD.

Animal or in vitro studies will be excluded. Current clinical criteria for each syndrome will be considered as a diagnostic category.

2.1.2. Concept

We will include studies that report at least one metric of interoception and/or allostatic load. For interoception, we will use a physiology-based definition (Craig, 2002; Desmedt et al., 2023), using the following criteria: 1) both afferent/sensory or efferent/regulatory signals relating to the physiological state of any bodily tissue; 2) having a primarily homeostatic role; 3) with neural signaling mainly through unmyelinated or poorly myelinated fibers (Aδ or C fibers); 4) and predominantly projecting to/from the AIN. While acknowledging that this conceptualization is not without limitations (Desmedt et al., 2023), this definition was chosen as we are particularly interested in bidirectional interoceptive modalities that have predominant central representation in the brain areas most affected in FTD. Based on this definition, we will include studies reporting on visceral, autonomic, pain, temperature, affective touch and taste modalities. Olfaction, proprioception or vestibular function will not be included as interoceptive modalities in this scoping review.

For allostatic load, we will include any cardiovascular, metabolic, neuroendocrine, immune or anthropometric markers that represent physiological "wear and tear" through repeated homeostatic challenges, associated with poor health outcomes (Juster, McEwen, & Lupien, 2010; McCrory et al., 2023). This definition will allow us to capture other, non-neural, pathways of brain-body interaction, including humoral, immune or metabolic signals.

For any of these metrics we will include different types of assessments, including self-report, clinical assessment, performance-based tasks, and biological or physiological markers (including blood-based, anthropometric, neuroimaging and electrophysiological markers at rest or during tasks). Notably, since we are interested in brain-body interactions, we will not include: immune/inflammatory or metabolic biomarkers exclusively studied in the central nervous system (e.g., cerebrospinal fluid); biomarkers specific to neuroinflammation (e.g., GFAP) or nervous system autoimmunity (e.g., NMDA, AQP4, Hu) whether in cerebrospinal fluid (CSF) or blood; biomarkers of neurodegeneration (e.g., NfL) or pathological biomarkers (e.g., amyloid, tau) whether in CSF or blood.

2.1.3. Context

As we will be focusing on a clinical population, our study will encompass reports concerning FTD patients across various healthcare contexts, while excluding samples from community settings.

2.1.4. Types of evidence source

We will include quantitative primary research studies, covering both experimental and observational designs with the exception of case reports. Case series may be included. Reviews (including systematic reviews and meta-analyses), books/book chapters, commentaries, editorials, and letters will be excluded from our analysis. We will include reports written in languages understood by at least two members of the reviewing team (CC, FC, JLH), limiting the languages to English, Portuguese, and Spanish.

2.2. Search strategy

The search strategy will be developed in PubMed, Web of Science Core Collection, and EBSCO (Psychology and Behavioral Sciences Collection, APA PsycArticles, and PsycInfo) databases. We will not include any time or language constraints during the search stage. For interoception, we used general search terms related to major physiological systems or common assessment methodologies for interoception/autonomic function. Given the huge repertoire of possible markers of allostatic load, we used both general search terms for allostasis and a set of parameters that was most consistently used to define allostatic load according to a recent meta-analysis (McCrory et al., 2023). The complete search strategy and preliminary search results are reported on Table 1. Additionally, we will screen the grey literature for relevant studies using the ProQuest database. Furthermore, the reference lists of major reviews addressing any interoceptive and autonomic modalities or allostasis in dementia will be searched for additional reports. Finally, authors from the included records will be invited to send any additional studies meeting the eligibility criteria.

2.3. Source of evidence selection

Search results will be loaded into Endnote®. Duplicates will be removed by FC. After duplicate removal, the remaining references will be loaded into Rayyan® (Ouzzani, Hammady, Fedorowicz & Elmagarmid et al., 2016) and the above-mentioned eligibility criteria will be used for screening. Title/abstract will be reviewed by FC and JLH, using a standardized

screening procedure (Figure 1). Conflicts will be resolved by discussion between reviewers and, if it is not possible to reach consensus, a third element (CC) will help decide inclusion or exclusion. After title/abstract screening, articles selected for full-text analysis will be reviewed by FC and JLH following the same screening procedure (Figure 1) and methods for conflict resolution. Additional reports retrieved from reference searching in the full-text analysis may be included at this point, via discussion between reviewers and application of eligibility criteria. At each stage, the number of and the reasons for exclusion will be noted.

2.4. Data extraction

Data will be extracted by FC and loaded into a Microsoft Excel® spreadsheet.

For each reference, the following variables will be extracted:

1. Reference data: first author, publication year, DOI.
2. Population data: specification of FTD group(s) and, if present, control group(s).
    a. Demographic data: *n,* age (mean ± SD), sex (% males/females).
    b. Clinical data: disease duration (mean years ± SD); specification of cognitive performance measure used (e.g., Montreal Cognitive Assessment) and score; specification of disease severity measure used (e.g., Clinical Dementia Rating, Frontotemporal Dementia Rating Scale) and score; presence of general medical comorbidities or whether these were used as exclusion criteria (e.g., exclusion of patients with cardiac disease in a heartbeat detection study).
3. Interoception/allostasis data:
    a. Categorization of interoceptive or allostatic measure: peripheral physiological measures, including electrophysiological (e.g., heart rate, skin conductance response) or biometric indices (e.g., body mass index); biochemical (plasma) markers, such as metabolic/endocrine (e.g., cholesterol) or immune/inflammatory (e.g., cytokines); neural markers, including neurophysiological measures (e.g., EEG) and functional or structural neuroimaging (e.g., MRI, PET); performance-based tasks, i.e., behavioral measures in interoceptive/allostatic tasks (e.g., heartbeat detection accuracy); self-report/clinical measures, including self-report (questionnaires and scales), and symptoms or signs of interoceptive-allostatic dysfunction based on clinical assessment.

b. Categorization of interoceptive/allostatic system: cardiovascular, respiratory, gastrointestinal, genitourinary, metabolic/endocrine, immune/inflammatory, skin, pupil, pain/temperature/affective touch, taste, multi-system.
c. Specification of interoceptive or allostatic metric used.
d. Summary of main results.

Variables of interest including participant group, physiological system, and assessment will be attributed dummy variables to facilitate categorization and pooling of data. Missing values will be appropriately coded and reported in the analysis.

2.5. Analysis of the evidence and presentation of the results

A PRISMA flow diagram (Tricco et al., 2018) will be used to document the review procedure, exclusions and exclusion reasons.

In order to answer the review questions 1.a) and b), the reference data will be organized hierarchically according to the type of measure/assessment and physiological system, across FTD syndromes (Table 2). A narrative description of the number and characteristics of reports per type of measure/assessment and physiological system will be performed. We selected this approach to synthesize and present the results because we recognize that numerous reports utilize a specific paradigm to study various FTD syndromes simultaneously. Consequently, reporting primarily by syndrome might reduce the effectiveness of synthesis.

To address the review question 1.c), demographic and clinical data for each FTD syndrome and control groups from the different references will be synthesized quantitatively and presented in tabular form (Table 3).

We will examine the results to identify specific patterns of interoceptive or allostatic dysfunction unique to FTD syndromes, addressing question 1.d). These patterns may be summarized either narratively or in a tabular format, depending on the quantity and complexity of the data within each disease group, a matter that remains uncertain for the authors at this stage.

Finally, we will use this evidence to pinpoint areas or topics lacking sufficient data, potentially guiding future studies or research directions.

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Tables

Table 1. Search strategy and preliminary search results (February 2024).

Search terms	Search results		
	PubMed	Web of Science	EBSCO
Interoception/Allostasis (Title/Abstract) Interocept* OR Viscer* OR Body OR Bodily OR Somatic OR Allostas* OR Autonomic OR Sympathetic OR Parasympathetic OR Psychophysio* OR Pupil* OR Skin* OR Electrodermal OR Cardi* OR Heart* OR "Blood pressure" OR Respirat* OR "Peak expiratory" OR Breath* OR Gastr* OR Stomach* OR Oesoph* OR Esoph* OR Intestin* OR Gut OR Urin* OR Creatinine OR Cystatin-C OR Genit* OR Sexual OR Fatigue OR Thirst* OR Hunger OR Satiet* OR Itch OR Pain OR Nocice* OR Thermoregulation OR Temperature OR "Affective touch" OR "C-tactile" OR Taste OR Gustation OR Metabolic OR Endocrine OR Neuroendocrine OR Lipoprotein OR Cholesterol OR Triglyceride OR Glucose OR Glycated hemoglobin OR A1c OR Anthropometric OR Body Mass Index OR Waist* OR Cortisol OR Dehydroepiandrosterone OR Immun* OR Inflammatory OR Cytokine OR "C-reactive protein"	11,555,159	16,179,788	1,156,367
Frontotemporal dementia (Title/Abstract) "Frontotemporal dementia" OR "Frontotemporal lobar degeneration" OR "behavioral variant" OR "behavioural variant" OR "right temporal variant" OR "behavioral semantic variant" OR "behavioural semantic variant" OR "Primary Progressive Aphasia" OR "semantic variant" OR "non-fluent variant" OR "agrammatic variant" OR "logopenic variant" OR "primary progressive apraxia of speech" OR "Semantic dementia" OR "Progressive Supranuclear Palsy" OR "Richardson*" OR "Corticobasal degeneration" OR "Corticobasal syndrome"	21,168	38,345	11,702
Combined	5,370	9,159	2,574

Table 2. Presentation of main results. FTD: frontotemporal dementia.

Type of Measure	**System**	**Measure**	**FTD group(s)**	**Control group(s)**	**Main results**	**Reference**
Peripheral physiology						
Biochemical (plasma)						
Neural						
Performance-based tasks						
Self-report/Clinical						

Table 3. Presentation of clinical and demographic data of participant groups. DD: disease duration: DS: disease severity. F: female; FTD: frontotemporal dementia. M: male.

Participant group	***N* reports**	***N***	**M/F**	**Age ± SD (years)**	**DD ± SD (years)**	**DS metric**	**Score**	**Cognition metric**	**Score**
FTD									
Controls									

Figures

Figure 1. Standardized screening procedure. FTD: frontotemporal dementia.