

We thank the reviewers for their comments and suggestions on the manuscript. We apologize for the delay in our response, which was in part due to the closure of the PCI Registered Reports submission platform over the summer. Below, we address the points raised by the reviewers:

1. Disaggregation of biological and behavioral markers of interoception (reviewers 1 and 2).
2. Conceptual clarification of interoception, including the modalities it covers, whether it includes somatosensory information from bones and muscles, and the distinction between interoception and allostasis (reviewers 1 and 2).
3. Definition of allostatic load and overload (reviewer 1).
4. Identification of additional references through analysis of papers citing studies included in the review (reviewer 2).
5. Assessment of the role of sex and disease severity on allostatic-interoceptive dysfunction in FTD (reviewer 2).

### **Disaggregation of biological and behavioral markers of interoception**

We acknowledge the reviewers' observations that physiological and behavioral markers of interoceptive and allostatic dysfunction are distinct phenomena and require separate analysis. Initially, we addressed this by categorizing interoceptive/allostatic markers into: i) Peripheral physiological measures; ii) Biochemical (plasma) markers; iii) Neural markers; iv) Performance-based tasks; and v) Self-report/clinical measures. To further clarify these distinctions, we have refined our categorization to include two levels of description:

- i) Interoceptive-allostatic system/biological markers: representing interoceptors, afferent signals, central neural representations, efferent/regulatory signals, effectors and their respective transduction pathways. This category includes peripheral physiology, biochemical (plasma) and neural (brain) markers;
- ii) Interoceptive experience/behavioral markers: representing the detection, interpretation and attention to interoceptive signals as well as beliefs about and metacognitive evaluation of interoceptive experience. This category includes performance-based tasks, self-report measures and clinical report of interoceptive symptoms.

This has been updated throughout the manuscript.

### **Conceptual clarification of interoception**

The reviewers' comments on the definition of interoception resonate with our ongoing discussions and the existing controversies in the field regarding the distinctions between interoception, proprioception, and exteroception. We acknowledge the necessity for improved conceptual clarity and thank the reviewers for bringing up this important point. To address this, we have taken several steps.

Firstly, we have included a general overview of contemporary definitions of interoception, emphasizing the major controversies surrounding its boundaries and providing examples of modalities where consensus has been challenging to establish. We recognize that our interpretation of interoception, like others, has limitations and remains subject to ongoing debate.

Secondly, we have simplified and clarified our definition of interoception while also defining exteroception and proprioception. We have underscored the distinctions between these modalities in accordance with our conceptual framework. In essence, we define as interoceptive any modality where the perceptual process reflects the physiological state of the body, irrespective of organ location (including the skin and skeletal muscle) or receptor types. This contrasts with exteroception, where perception relates to features of the external environment, and with proprioception (including vestibular function), where perception pertains to body position and movement in space. This approach aligns with computational theories of interoception, as highlighted in a review by Toussaint and colleagues (Toussaint, Heinzle, & Stephan, 2024) published subsequent to our original manuscript. To be consistent with our refined definition, we have excluded taste and affective touch from our conceptualization of interoception (as well as vision, hearing, touch, olfaction, proprioception, and vestibular function). We emphasize that our definition is not without limitations and is partly context-dependent, serving practical purposes for the conduct of our review. Our search terms and results have been updated accordingly.

Regarding the specific query from reviewer 1 about somatosensory information from skeletal muscle, inclusion under our definition depends on the type of information and the perceptual process involved. For example, nociceptive information from bone or skeletal muscle representing the physiological condition of the tissue would be considered interoceptive (e.g. muscle pain associated with increased lactate levels during physical exertion), whereas information from Golgi tendon organs involved in representing the position of specific body parts and associated with movement would not.

Lastly, we address the distinction between allostasis and interoception. Consistent with our broader argument of integrating afferent and efferent information, this distinction becomes blurred. Given that interoception encompasses both the sensory/afferent and regulatory/efferent signals, it not only supports allostasis but also incorporates homeostatic and allostatic regulatory signals. Conversely, the proactive generation of responses to anticipated homeostatic challenges (i.e., allostasis) depends on predictive capabilities facilitated by an internal model of the body, based on past representations and sensory aspects of interoception. This perspective aligns with computational models such as predictive coding and active inference, where predictive signals are crucial for both the perceptual aspects of interoception and for generating visceromotor responses to real or anticipated deviations in homeostasis. Importantly, there is partial overlap in the types of measures used for interoception and allostasis, indicating that the physiological or biochemical signals representing the body's current state may also reflect the effects of recurrent homeostatic challenges on bodily systems. Therefore, instead of adopting a dichotomous categorization of interoception versus allostasis,

we advocate for integrating these concepts and organizing information according to physiological systems and types of assessment.

### **Definition of allostatic load and overload**

We appreciate the reviewer's suggestions regarding the definition of allostatic load. The conceptual framework proposed by Buller-Peralta (Buller-Peralta et al., 2024), which delineates primary mediators of the stress response and their downstream effects on physiological systems, has been instrumental in clarifying this concept. Additionally, we have briefly introduced the mechanisms contributing to high allostatic load and its pathophysiological consequences (termed allostatic overload, now included in our text) as established by McEwen (McEwen, 2006).

Regarding the challenging question of which measures constitute markers of allostatic load, we currently lack a precise definition. Recognizing this limitation and the broad scope of our scoping review, we have chosen not to restrict our analysis to specific markers of allostatic load. Instead, we accept markers related to cardiovascular, neuroendocrine, metabolic, anthropometric, or inflammatory processes that reflect systemic effects (excluding those exclusively present in the central nervous system). Selected markers of allostatic load are often used in combination (i.e., composite measures or indices of allostatic load) to predict adverse health outcomes in general populations (Juster, McEwen, & Lupien, 2010; Seeman, 1997). Our study, however, is focused on frontotemporal dementia, a specific clinical population characterized by an adverse health outcome (i.e., neurodegenerative processes). Therefore, we believe that taking this broad approach to markers of systemic effects is more sensible than to look for a specific set of markers of allostatic load originally studied in the general population. Future studies may need to address the specificity of markers identified in this review for frontotemporal dementia, as suggested by the reviewer. For the practical purposes of conducting our scoping review, in addition to the general terms of allostasis and allostatic load, we have utilized a set of markers frequently associated with allostatic load identified in a meta-analysis of the literature (McCrory et al., 2023).

### **Identification of additional papers**

We acknowledge the suggestion and have included it in our search strategy.

### **Role of sex and disease severity**

We thank the reviewer for the suggestions regarding additional variables of interest in our analysis. We had previously considered these questions to be highly relevant and have therefore included information on sex distributions (including both the number and percentage of males and females), disease duration, and severity. This includes both general dementia severity

ratings and cognitive scales that reflect the extent of cognitive deterioration. These details are provided in section 2.4 (Data Extraction), bullet 2, and are summarized in Table 3.

## References

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