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Intrinsic timescales and predictive allostatic interoception in brain health and disease

Agustin Ibanez[a,b,c,g,*,1], Georg Northoff[d,e,f,**,1]

[a] Global Brain Health Institute (GBHI), University of California San Francisco (UCSF), CA, USA
[b] Latin American Brain Health (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile
[c] Cognitive Neuroscience Center (CNC), Universidad de San Andrés, Buenos Aires, Argentina
[d] Mental Health Center, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China
[e] Center for Cognition and Brain Disorders, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, People's Republic of China
[f] Mind, Brain Imaging and Neuroethics, Institute of Mental Health Research, University of Ottawa, Ottawa, Canada
[g] Trinity College Dublin, Dublin, Ireland

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ABSTRACT

The cognitive neuroscience of brain diseases faces challenges in understanding the complex relationship between brain structure and function, the heterogeneity of brain phenotypes, and the lack of dimensional and transnosological explanations. This perspective offers a framework combining the predictive coding theory of allostatic interoceptive overload (PAIO) and the intrinsic neural timescales (INT) theory to provide a more dynamic understanding of brain health in psychiatry and neurology. PAIO integrates allostasis and interoception to assess the interaction between internal patterns and environmental stressors, while INT shows that different brain regions operate on different intrinsic timescales. The allostatic overload can be understood as a failure of INT, which involves a breakdown of proper temporal integration and segregation. This can lead to dimensional disbalances between exteroceptive/interoceptive inputs across brain and whole-body levels (cardiometabolic, cardiovascular, inflammatory, immune). This approach offers new insights, presenting novel perspectives on brain spatiotemporal hierarchies and interactions. By integrating these theories, the paper opens innovative paths for studying brain health dynamics, which can inform future research in brain health and disease.

1. Introduction

Despite significant advances in the cognitive neuroscience of brain health and disease, several challenges persist (Ibanez, 2022; Luppi et al., 2022a; Ibanez and Zimmer, 2023; Westlin et al., 2023). The field primarily features specific models and independent empirical studies instead of unified theories, posing four major challenges. One significant barrier is the complex relationship between brain structure and function (Genon et al., 2018), especially considering the spatiotemporal interactions among multiple signals (Deco et al., 2021; Luppi et al., 2022a; Kringelbach et al., 2023). The links between cognition and brain mechanisms are often weak and inconsistently understood, lacking direct one-to-one correlations (Ibanez et al., 2023). How hierarchy in spatiotemporal dynamics shapes the non-linear associations between observed structures and function is poorly understood (Deco et al., 2021; Kringelbach et al., 2023). Another challenge is the heterogeneity of brain phenotypes associated with different brain diseases (Anttila et al., 2018; Greene et al., 2022), which makes it challenging to fully understand the underlying mechanisms of each condition. Brain diseases lead to varied and overlapping symptoms and complex mechanisms, making it hard to develop integrative theories (Anttila et al., 2018; Feczko et al., 2019; Ibanez and Zimmer, 2023). This diversity calls for urgent, personalized multimodal approaches and more effective treatments for brain diseases. The heterogeneity of physiopathological mechanisms associated with different brain diseases is also a significant challenge (Kim et al., 2019; Daniels et al., 2020; Wilson et al., 2023), making it

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Abbreviations: ACW, Autocorrelation window; AIN, Allostatic interoceptive network; HEP, Heart evoked potential; INT, Intrinsic neural timescales; PAIO, Predictive coding theory of allostatic interoceptive overload.

* Correspondence to: Latin American Brain Health (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile.

** Corresponding author at: Mental Health Center, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China.

E-mail addresses: agustin.ibanez@gbhi.org (A. Ibanez), Georg.Northoff@theroyal.ca (G. Northoff).

[1] These authors contributed equally to this work

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difficult to develop more integrative theories of underlying mechanisms. For instance, psychiatric and neurological diseases are often assessed as distinct fields (Ibanez and Zimmer, 2023), despite the growing evidence of common physiopathological pathways (Tripathi et al., 2020; Petzschner et al., 2021a; Quigley et al., 2021b; Bohr et al., 2022; Jungilligens et al., 2022). In consequence, research on psychiatric and neurological diseases is fragmented, focusing on symptoms or pathology instead of underlying mechanisms (Ibanez et al., 2023). These challenges require more integrative approaches considering the common theorization across brain diseases.

In this work, we present a synergetic approach that has started addressing some of these limitations to improve our understanding of brain health and disease, combining findings from psychiatric and neurological diseases and considering common underlying mechanisms. The predictive coding theory of allostatic interoceptive overload (PAIO) (Kleckner et al., 2017a; Schulkin and Sterling, 2019a; Petzschner et al., 2021a; Quigley et al., 2021b; Migeot et al., 2022b) and the intrinsic neural timescales (INT) theory (Golesorkhi et al., 2021c; Wolff et al., 2022a), provide integrative and synergetic explanations. PAIO considers the complex interactions between different brain regions and the predictive interplay between top-down inferences and bottom-up errors. The INT theory proposes that different brain regions operate on a hierarchy of intrinsic timescales, defined by each region's average time constant of the neural dynamics. By combining these theories, a more dynamic approach to understanding brain function and dysfunction could be developed, especially in neurological and psychiatric disorders where disturbances in both allostatic interoceptive coding and temporal dynamics have been observed. However, both theories, despite of their commonalities, have not yet been integrated. The work proposes an integrative framework that combines the timescales of INT with the predictive coding framework of PAIO to provide a more comprehensive understanding of brain function and disease. The paper further discusses the application of this framework in understanding psychiatric and neurological disorders, linking allostasis, interoception, cognition, and intrinsic neural timescales, as well as the importance of spatiotemporal hierarchies and synergetic interactions in these disorders. This new integrative framework can contribute to overcoming some of the limitations and challenges of traditional approaches and provide a more effective framework for understanding brain health and disease.

2. Predictive coding theory of allostatic interoceptive overload

The PAIO (Sterling, 2014; Kleckner et al., 2017b; Schulkin and Sterling, 2019b; Petzschner et al., 2021b; Quigley et al., 2021a; Migeot et al., 2022a; Nord and Garfinkel, 2022) integrates the concepts of allostasis and interoception to understand the complex interactions between internal organismic or whole-body patterns and environmental stressors that affect brain health. Allostasis refers to the body's continuous regulation of different parameters to adapt to environmental demands before they become urgent (Karatsoreos and McEwen, 2011; McEwen, 2012; McEwen et al., 2015; McEwen and Akil, 2020). In predictive coding terms, allostasis is the continual process by which the brain anticipates the needs of the body and attempts to meet those needs before they arise (Schulkin and Sterling, 2019a). Allostasis happens independently whether environmental demands are urgent or not (Kleckner et al., 2017a; Daniels et al., 2020; Westlin et al., 2023). Interoception involves the brain's continuous, dynamic modeling of the sensory states of the body (Quigley et al., 2021b). Interoceptive processing is critical for such predictions as it provides information on body states and regulation required to adaptively perform different actions (Tsakiris and Critchley, 2016; Baez et al., 2017; Ibáñez et al., 2017; Ibanez and AM, 2018; Ibanez et al., 2018; Ibáñez, 2018; Ibanez and Schulte, 2020). Predictive coding principles describe the relationships between the levels involved in prediction inferences and prediction errors (Barrett et al., 2016b; Kocagoncu et al., 2021; Migeot et al., 2022a).

Different approaches such as predictive coding, active inference, belief propagation, or Bayesian predictions, provide different theoretical frameworks. Here we focus on PAIO as detailed below. In this predictive processing framework, interoception involves current (ascending viscerosensory signals) and past (interoceptive predictions) states (Ibanez et al., 2023). Interoception is modeled by the brain to regulate and coordinate the systems and tissues of the body. Allostatic and interoceptive processes are deeply intertwined and jointly contribute to facing environmental demands by performing internal regulatory functions (Sterling, 2014; Kleckner et al., 2017b; Schulkin and Sterling, 2019b; Petzschner et al., 2021b; Quigley et al., 2021a; Migeot et al., 2022a; Nord and Garfinkel, 2022). Interoception is in the service of allostasis (which involves visceromotor regulation) in the same way that somatosensation is in the service of skeletomotor regulation (Kleckner et al., 2017a). The interoceptive prediction inputs that help to create interoception represents a common currency of the visceromotor control signals that implement allostasis (Barrett and Simmons, 2015). Thus, integrating allostasis and interoception processes into a single model is instrumental in characterizing the interaction between biological and environmental factors in brain health and disease. Such integrated models offer potential advantages compared with compartmentalized models of cognition (Ibanez, 2022). These focus on understanding the mediators of adaptation to changing environments and can be instantiated across several biological levels, thus being suitable for coupling with, extending, and strengthening predefined neurocognitive models (Karatsoreos and McEwen, 2011; McEwen, 2012; Migeot et al., 2022a). This is possible by integrating internal processes with bodily and environmental dimensions (Fig. 1A).

2.1. The allostatic interoceptive system

Bottom-up signals from exteroception, interoception, and cognition involve synergetic dynamics (Deco et al., 2021; Luppi et al., 2022b) instantiated hierarchically by the allostatic interoceptive network (Kleckner et al., 2017b; Alvarez et al., 2022; Birba et al., 2022b). In contrast, top-down inferences about the external environment and the visceromotor signals come from the prefrontal cortex, different portions of the anterior-mid cingulate cortex, agranular insula, orbitofrontal cortex, and dorsal amygdala. These regions modulate their activity through within-level interactions and generate predictions regarding the activity of other levels. They send visceromotor and interoceptive predictions to the relay regions (thalamus, and hypothalamus). Sensory predictions are efferent inputs resembling the visceromotor control signals that impact allostasis (Kleckner et al., 2017c). These processes integrate predictions from the top areas and prediction errors from peripheral regions to generate their corresponding predictions and feedback. The types of predictions and errors correspond to environmental, visceromotor, interoceptive, and cognitive communication (Kleckner et al., 2017b; Alvarez et al., 2022; Birba et al., 2022b). Finally, the periphery, comprising organs (heart, gut), as well as autonomic, neuroendocrine, and immune systems, receives signals and communicates errors to relay regions, thus closing the loops through action. Although some models assume a hierarchical distinction between interoceptive (i.e., top-down) and autonomic (i.e., bottom-up) pathways, in our approach, these are conceptualized as bilateral interactions providing no single unidirectional current of information but multiple dynamics.

The AIN has been characterized at multiple levels and related mechanisms. Neuroimaging evidence has characterized the AIN through tract-tracing and functional connectivity techniques (Kleckner et al., 2017b). The heart-evoked potential (HEP), an electroencephalographical measurement of brain-heart communication, has been linked to interoception and allostatic markers at a cardiocerebral and autonomic level (Couto et al., 2015; Yoris et al., 2017; Fittipaldi et al., 2020; Coll et al., 2021; Birba et al., 2022b; Legaz et al., 2022). Convergent electroencephalography (Pollatos et al., 2005; Birba et al., 2022b; Legaz et al., 2022) and neuroimaging studies associate the HEP source with critical AIN brain hubs, and the HEP has been linked to socioemotional

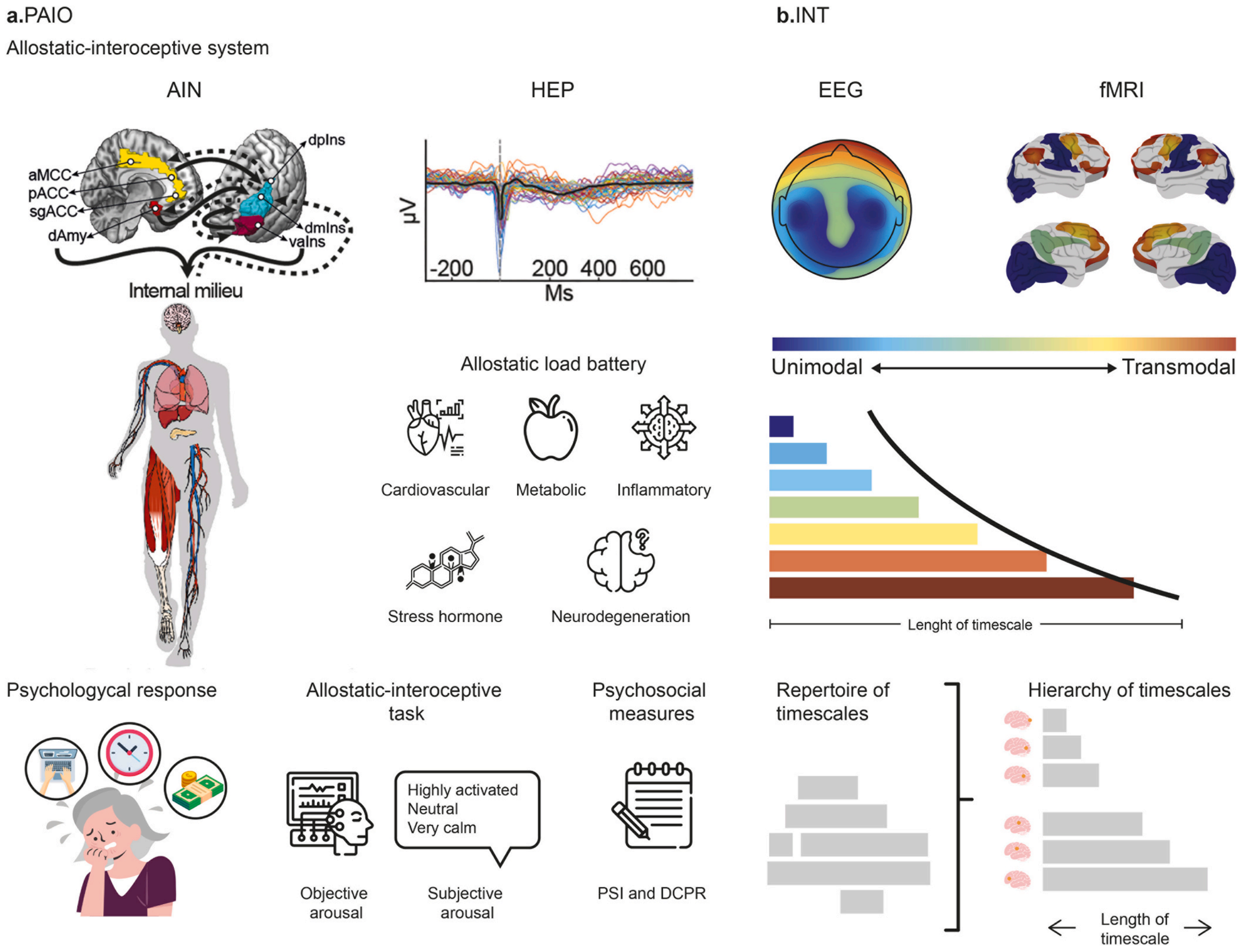


Fig. 1. Current integrative frameworks of brain health and spatiotemporal dynamics. A. Predictive coding theory of allostatic interoceptive overload. B. Intrinsic neural timescales (INT) theory. Multimodal allostatic load measures can be identified at different levels. The allostatic–interoceptive system (a) relies on the allostatic–interoceptive network (AIN), whose main hubs include the anterior mid-cingulate cortex (aMCC), pregenual anterior cingulate cortex (pACC), subgenual anterior cingulate cortex (sgACC), dorsal amygdala (dAmy), agranular insula (vaIns), dorsal mid-insula (dmIns), and dorsal posterior insula (dpIns). Specifically, the limbic cortices send prediction signals (unbroken magenta lines) and receive prediction error signals (dashed magenta lines) from the internal milieu. (b). At the cerebral level, the structure of the AIN hubs can be assessed by the voxel-based morphometry (VBM) technique and its functional connectivity by resting-state functional magnetic resonance imaging (rsfMRI) technique. The cardiocerebral level can be evaluated via the heartbeat-evoked potential (HEP) modulation. Moreover, the cardiovascular, metabolic, inflammatory, stress hormone and neurodegenerative biomarkers can assess the peripheral level, constituting an allostatic load battery. Finally, the psychological level can be evaluated by the allostatic–interoceptive task and psychosocial measures such as the psychosocial index (PSI) and the diagnostic criteria for psychosomatic research (DCPR). Modified with authorization from (19).

processes (Couto et al., 2015; Fittipaldi et al., 2020; Salamone et al., 2020). Multiple blood biomarkers indexing physiological imbalances triggered by allostatic processes, including cardiovascular (Seeman et al., 2008; Zeki Al Hazzouri et al., 2021), metabolic (Seeman et al., 2008; Soysal et al., 2020), inflammatory (Cagnin et al., 2004; Sjögren et al., 2004; Yaffe et al., 2004; Rentzos et al., 2006; Dik et al., 2007; Seeman et al., 2008; Zhang, 2015; Bright et al., 2019; Duran-Aniotz et al., 2021), the stress hormone (Woolley et al., 2014), and neurodegenerative parameters (Rohrer et al., 2016; Rojas et al., 2016; Takada et al., 2016; Yuan et al., 2017; Donker Kaat et al., 2018; Steinacker et al., 2018; Duran-Aniotz et al., 2021), have been linked to characterizing multiple diseases related with allostatic overload. At a psychological level, behavioral tasks employing psychophysiological measurements evaluate the allostatic interoceptive functional dynamics (Kleckner et al., 2017b), and clinical psychosocial metrics are used to assess dysregulated responses to environmental demands (Piolanti et al., 2016; Fava et al., 2017). Thus, the model allows the integration of peripheral, autonomic, cardiocerebral, and cerebral correlates with behavioral responses to environmental needs representing a more complex appraisal of brain health.

Allostatic interoceptive predictive coding models complement standard allostasis models of disease and offer a more specific assessment of brain-body-world interactions. Environmental stressors and pathophysiological pathways, integrated within a synergistic framework, reveal complex health impacts. The exposome (Vermeulen et al., 2020), which includes varied lifelong physical and social stressors, intersects with pathways like inflammation and DNA damage, affecting metabolic, cardiovascular, and brain diseases. Socioeconomic disparities exacerbate these effects, triggering cognitive and behavioral deficits in disadvantaged groups (Tawakol et al., 2017; Ribeiro et al., 2018; Ribeiro et al., 2019; Tawakol et al., 2019; Misiak et al., 2022). This negative exposome interaction leads to allostatic overload, a cumulative stress response (Kleckner et al., 2017c; Salamone et al., 2021b; Birba et al., 2022a; De Felice et al., 2022b; Migeot et al., 2022b; Migeot et al., 2023; Migeot and Ibáñez, 2023). Imbalances in cardiovascular (Seeman et al., 2008; Zeki Al Hazzouri et al., 2021), metabolic (Seeman et al., 2008;

Soysal et al., 2020), inflammatory (Cagnin et al., 2004; Sjögren et al., 2004; Yaffe et al., 2004; Rentzos et al., 2006; Dik et al., 2007; Seeman et al., 2008; Zhang, 2015; Bright et al., 2019; Duran-Aniotz et al., 2021), stress hormone (Woolley et al., 2014), and neurodegenerative factors (Rohrer et al., 2016; Rojas et al., 2016; Takada et al., 2016; Yuan et al., 2017; Donker Kaat et al., 2018; Steinacker et al., 2018; Duran-Aniotz et al., 2021) are associated with psychiatric and neurological conditions. Similarly, different social and socioeconomic adversities could induce dysregulated responses to environmental demands, such as inhibitory control deficits linked to early-life poverty, accelerated cognitive decline, and socio-emotional difficulties in individuals from low socioeconomic status (Tawakol et al., 2017; Ribeiro et al., 2018; Ribeiro et al., 2019; Tawakol et al., 2019; Misiak et al., 2022).

2.2. *Advantages and disadvantages of current PAIO models*

The allostatic interoceptive framework offers multilevel explanations of dysregulated responses to environmental demands. This approach provides several advantages in understanding the complex interactions between the environment and the body in the context of brain health and disease. It involves a synergetic system that integrates multiple interoceptive, exteroceptive, and cognitive processes with environmental demands into a common framework for understanding brain function (Deco et al., 2021; Luppi et al., 2022b). It also allows for integrating levels between the muscular system, viscera, biomarkers, brain activity, and cognition in brain health and disease, providing a more comprehensive understanding of the complex interactions between these levels (Sterling, 2014; Kleckner et al., 2017b; Schulkin and Sterling, 2019b; Petzschner et al., 2021b; Quigley et al., 2021a; Migeot et al., 2022a; Nord and Garfinkel, 2022). The approach is also compatible with dynamic principles of brain activity and the degeneracy principle (Hartwigsen, 2018), which suggests that a system can perform a given (dis)function using different elements or mechanisms. This allows for the evaluation of the adaptability and plasticity of the brain in the face of changing environmental demands. Another advantage is its compatibility with dimensional and transnosological physiopathological mechanisms of brain diseases(Ibanez and Zimmer, 2023). These models are being applied to different psychiatric (Adams et al., 2016; Paulus et al., 2019; Jeganathan and Breakspear, 2021; Smith et al., 2021) and neurological disorders (Goldstein and Kopin, 2018; Birba et al., 2022b; De Felice et al., 2022a; Migeot et al., 2022a; Waliszewska-Prosół et al., 2022) which allows for the development of more comprehensive models to better understand brain health and disease across different conditions(Ibanez and Zimmer, 2023).

However, there are several caveats to the current approach (Ibanez, 2022; Ibanez et al., 2023). One major disadvantage is that the hierarchical times and anatomy described in the model seem to be incompatible with dynamical changes and synergetic brain activity (Deco et al., 2021; Luppi et al., 2022b). The models often describe a linear sequence of inferences and prediction errors, which may not fully capture the brain's parallel and simultaneous processing of these signals. Although certain specific accounts of predictive coding suggest that brain regions can send and receive both prediction and prediction error signals, and also propose non-linear interactions (i.e., (Barrett and Simmons, 2015), for discussion), the models themselves do not provide non-linear spatiotemporal explanations of predictions and errors. A truly synergistic approach requires more flexible spatiotemporal models.

The interoceptive, exteroceptive, and cognitive signals are intertwined in complex, poorly understood ways, like their intricate spatiotemporal interplay and how they influence each other (Ibanez, 2022). Current models often assess time in a linear arrow when describing inferences and errors. However, the evidence suggests that the interaction between these different signals is non-linear (or nonadditive) rather than linear; the resulting activity is either higher or lower than the simple addition or sum of their single activities (He, 2013; Huang et al., 2015; Wainio-Theberge et al., 2021; Wolff et al., 2021; Braun et al., 2022). This requires us to understand better their temporal dynamics that include multiple, simultaneous timescales to provide a more accurate representation of the complex interactions between these processes. We therefore converge such temporal dynamics and synergetics with the allostatic interoceptive predictive coding approach (Ibanez, 2022; Migeot et al., 2022b).

3. From allostatic interoceptive coding to the brain's intrinsic neural timescales

PAIO highlights the critical role of multiple levels of interaction between different inputs. These inputs concern interoceptive inputs from within the inner body, exteroceptive inputs from the outer environment, and cognitive inputs (like predictions) from the inner milieu of the brain itself. The predictive coding framework establishes the computational interaction between these different inputs: cognitive inputs provide predictions for the intero- and exteroceptive inputs, which, in case of actual exposure to intero- and/or exteroceptive inputs, feedback together with other cognitive triggers the prediction error (Friston, 2010). How must the different inputs be processed to make possible their computational interaction in terms of predictive coding?

3.1. *Converging different inputs – Intrinsic neural timescales*

Interoceptive, exteroceptive, and cognitive inputs have different origins, outer environment, inner body, and inner brain (Pezzulo et al., 2021), involving different types of information. Seemingly disparate neural systems relay that information within the brain, the interoceptive systems/pathways like the mainly subcortical autonomous network with an innate alarm system (Lanius et al., 2017; Rabellino et al., 2017), the primary sensory unimodal regions, and the higher-order associative regions (Margulies et al., 2016a). Given these differences in their origin, information, and neural pathways, the question of the possible interaction of intero- and exteroceptive and cognitive inputs become even more virulent.

For intero- and exteroceptive and cognitive inputs to interact, they must share certain features. Consider the example of language. A German and an Argentinean scientist can interact and exchange information when they share a common language like English. If, in contrast, they do not share such a common language but speak only Spanish and German respectively, they will remain unable to interact and exchange information. The same applies to the brain and its different inputs. Intero- and exteroceptive and cognitive inputs must share certain features that make their interaction possible. Despite their different origins, information, and pathways, they share a primary feature that makes their interaction possible and integration in predictive coding (Friston, 2010). This basic shared feature consists in their dynamics, the INT based on their "common currency" (Northoff et al., 2020a; b).

How can we more precisely determine the common interoceptive, exteroceptive, and cognitive input currency? In some (but not all) predictive accounts, a common currency underlies the synergy between cognition, emotion, perception, and action, suggesting that these aspects emerge from shared computational pathways (e.g., (Westlin et al., 2023)). Similarly, cognition also includes social cognition and socio-emotional aspects. Our approach to cognitive processes assumes a blending between cognitive processes and less compartmentalized distinctions (Ibanez, 2022). New models need to partially blurs the boundaries between these processes, often considered in isolation (Ibanez, 2022). The INT introduces a dynamic view of this common currency. Dynamics refers to the pattern of change over time, which is primarily stochastic (Pezzulo et al., 2021). One key feature is the degree to which the subsequent time points' activity (like the strength of following inputs over time) correlate with each other. This autocorrelation of the inputs with themselves over time can be measured by the autocorrelation window (ACW) that plots the degree of correlation against the time lags (Honey et al., 2012; Murray et al., 2014; Golesorkhi et al., 2021a; Golesorkhi et al., 2021c). One can then determine the degree of temporal autocorrelation at 50% of the correlation as standardly calculated, e.g., ACW 50 (Honey et al., 2012; Murray et al., 2014; Golesorkhi et al., 2021a; Golesorkhi et al., 2021c). This has been complemented by measuring the ACW when the autocorrelation function crosses the zero line, e.g., ACW 0; results show that ACW-0 and ACW-50 are not identical but index distinct neural (Golesorkhi et al., 2021a) and psychological (Smith et al., 2022; Wolman et al., 2023) information. ACW-5 indexes a shorter time window, that is, at an earlier point of correlation, while ACW-0 signifies a more extended time window. These shorter (ACW-5) and longer (ACW-0) time windows or timescales in the brain's neural activity are vital for making possible the interaction of intero- and exteroceptive and cognitive inputs that allow for their interactive processing as the basis of predictive coding on the computational level.

3.2. *Hierarchy of Intrinsic neural timescales within the Allostatic interoceptive network*

For interoceptive, exteroceptive, and cognitive inputs to interact in their processing, they must somehow converge in their neuroanatomical pathways. As we see it, this convergence is well realized in the allostatic interoceptive network (AIN), with its different regions exhibiting distinct timescales.

The higher-level regions of the AIN, such as the prefrontal cortex and the anterior/mid-cingulate cortex, facilitate transmodal processing, which, in turn, contributes to cognitive functions (Margulies et al., 2016b; Smallwood et al., 2021; Klar et al., 2023). These higher-order cortical regions also display the most extended intrinsic neural timescales, that is, long ACW in both rest and task (Golesorkhi et al., 2021a; Golesorkhi et al., 2021c; Wolff et al., 2022b) as well as the longest temporal receptive windows (TRW) in relation to continuous inputs like music, language, and movie (Honey et al., 2012; Hasson et al., 2015; Müsch et al., 2020; Yeshurun et al., 2021). The long temporal windows are ideal for integrating the different inputs across their distinct time points (Wolff et al., 2022b). Specifically, interoceptive, exteroceptive, and cognitive inputs may be featured by distinct temporal patterns in their stochastics: interoceptive inputs from the heart may be more regular than exteroceptive inputs from the environment (Golesorkhi et al., 2021b; Golesorkhi et al., 2021c). The long-time windows of the top-down regions of the AIN, like the prefrontal cortex and anterior cingulate, are ideal for pooling and processing the different timescales of these inputs together within one longer window (Himberger et al., 2018; Wolff et al., 2022b). The resulting top-down prediction of these regions to the lower regions of the AIN is thus transmodal and featured by longer timescales: a signal resulting from the convergence of different inputs within longer temporal windows operates as top-down prediction for modulating and predicting lower-level, more specific interoceptive or/and exteroceptive inputs that operate in shorter temporal windows, that is, on shorter timescales.

Even within the AIN's top-down regions, one can observe a hierarchy of timescales. Traditional predictive coding accounts assume slightly different notions of processing hierarchies in terms of specific brain gradients (Barrett and Simmons, 2015; Kleckner et al., 2017b; Westlin et al., 2023). The neurons that assemble or compute prediction signals in the cerebral cortex, for instance, are at the top of an anatomical hierarchy. In the context of our proposal, prediction signals are regarded as intrinsic neural activity within the AIN. The intrinsic neural timescales of the prefrontal cortex and the orbitofrontal cortex are longer than those of the anterior insula and the amygdala (Hasson et al., 2015; Golesorkhi et al., 2021a; Scalabrini et al., 2021). While the timescales of the relay regions like the thalamus and hypothalamus are shorter than those of the top-down regions (Hasson et al., 2015; Golesorkhi et al., 2021a). Convergently, the temporal dynamics of prediction and prediction error signals follow an expected pattern according to the INT: prediction signals exhibit slower oscillations in the beta range, for example, while prediction errors demonstrate faster oscillations in the gamma range (Pastalkova et al., 2008; Geisler et al., 2010; Lundqvist et al., 2018). Together, this suggests that the anatomical, temporal and computational processing hierarchy of the AIN in terms of prior/-prediction and prediction error converges with an elaborate temporal hierarchy of longer and shorter timescales: the longer the timescales of a particular region, the more likely that that region may exert a prediction or empirical prior for the next lower region and so forth (Wolff et al., 2022b).

3.3. *Timescales and predictive capacities in the allostatic interoceptive network – Temporal integration and segregation*

Following the temporal characterization of the AIN, we now propose a dynamic model of their processing and how that yields its predictive capacities (Fig. 2). The INT/ACW are critical for input processing (Golesorkhi et al., 2021b; Wolff et al., 2022b): sequences of both short and long inputs are more or less adequately represented in their temporal duration by the neural activity duration of sensory regions like the visual cortex that shows short ACW. Hence, there is almost one-to-one correspondence in the temporal durations of both input and neural activity. This suggests a high degree of temporal segregation of the INT/ACW in the lower-order mainly subcortical regions of the AIN, with their short timescales ideal for distinguishing different inputs.

In contrast, inputs are no longer temporally segregated from each other in the neural activity duration of higher-order regions like the prefrontal cortex and the anterior cingulate cortex as these show longer ACW (Golesorkhi et al., 2021b; Wolff et al., 2022b): rather than being segregated in the neural activity, exteroceptive, interoceptive and cognitive inputs are now temporally smoothed together within one longer neural activity duration – this presupposes temporal integration rather than temporal segregation.

Different stimuli can be characterized by their occurrence at different points in time. These may be processed independently of each other, with the stimuli at different times inducing separate and temporally segregated activation amplitude. The stimuli at each point in time are thus represented in different activities. This is different in the case of temporal integration. Here, the different time points of other stimuli are processed no longer independently but together, resulting in one activation amplitude for several stimuli. This amounts to temporal integration (see (Wolff et al., 2022a) for details).

Together, the anatomical and computational hierarchical gradient within the AIN may converge with a temporal-dynamic gradient that establishes a processing hierarchy along a gradient of temporal integration and segregation. The lower the hierarchy of the AIN, the shorter the timescales and the more temporal segregation of different inputs (extero-, interoceptive, and cognitive). The predictions of these lower-order short timescale regions are consequently temporally more short-term and more specific regarding a particular type of stimulus. This contrasts with the predictions of the higher-order regions within the AIN. Due to their longer timescales, the predictions of these higher-order AIN regions are longer-term while at the same time, given their high degree of temporal integration of different inputs, remaining transmodal and thus unspecific and global in their input prediction.

The relationship between the exteroceptive and interoceptive markers, interoceptive process, and pathophysiological pathways proposed by the current model could be modeled with whole-brain models (Deco and Kringelbach, 2014; Ibanez et al., 2023). Generative whole-brain models involve differential equations that can incorporate multiple interactions across brain dynamics and non-cerebral measures and levels. They are termed "generative" as they simulate and produce patterns mirroring empirical brain activity data. Whole-brain models can restrict the behavior of the formal system with empirical indexes of the exposome and whole-brain health via priors and parameters, highlighting the model's generative capacity to integrate information from

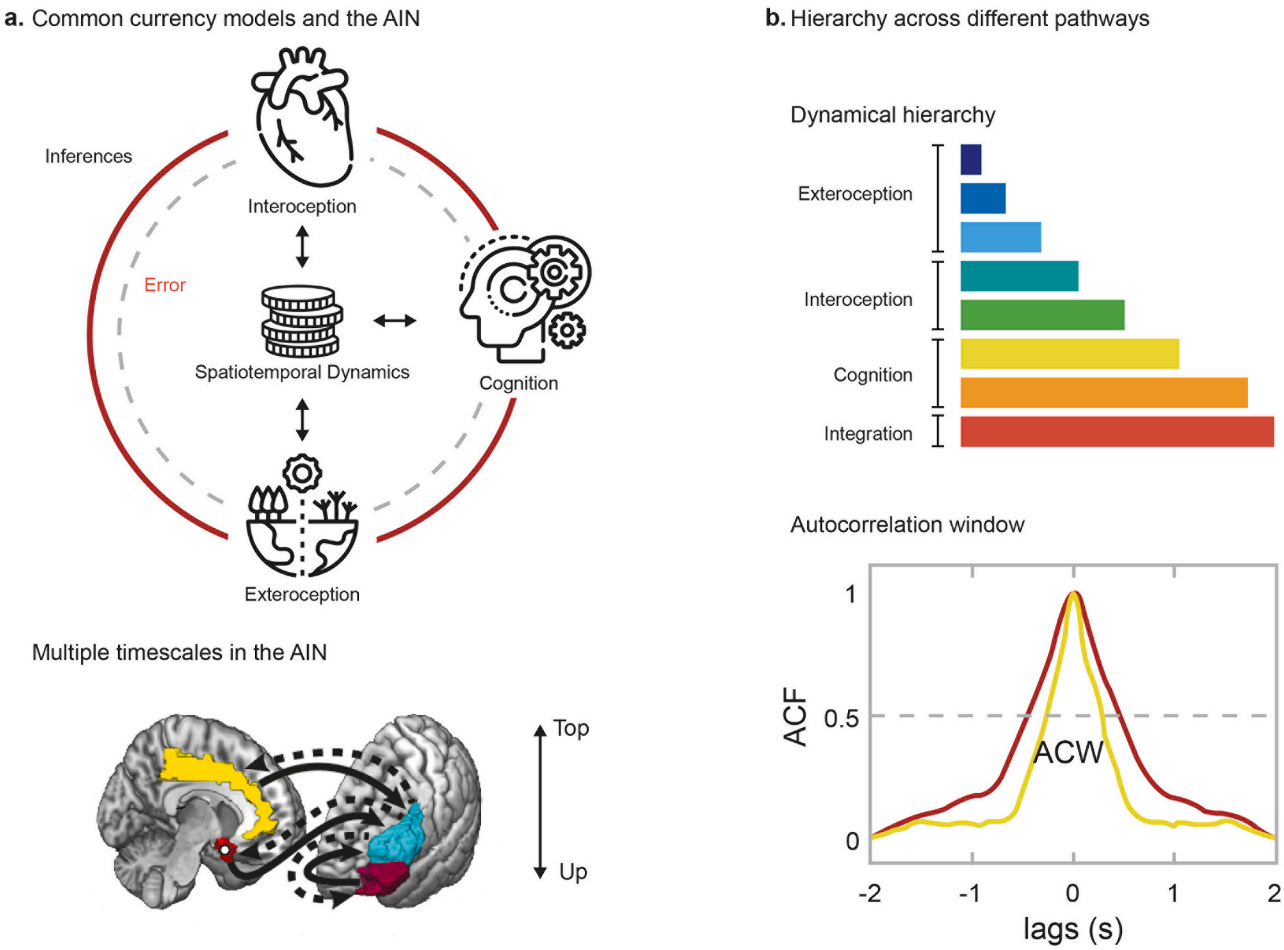


Fig. 2. The integrative PAIO-INT approach. A. This approach proposes a common currency among interoceptive, exteroceptive, and cognitive inputs, established by spatiotemporal brain dynamics self-regulated through multiple inference/error pathways. The Allostatic Interoceptive Network (AIN) offers complex yet low-dimensional hierarchies for this common currency. B. These dynamic hierarchies can be identified through the intrinsic time scales of each input (exteroceptive, interoceptive, and cognitive) and their subsequent integration. The autocorrelation window (ACW) presents a straightforward measure for examining such hierarchies via EEG/MEG or fMRI dynamics.

the body and environment (Ibanez et al., 2023).

4. Towards synergetic spatiotemporal hierarchies in brain diseases

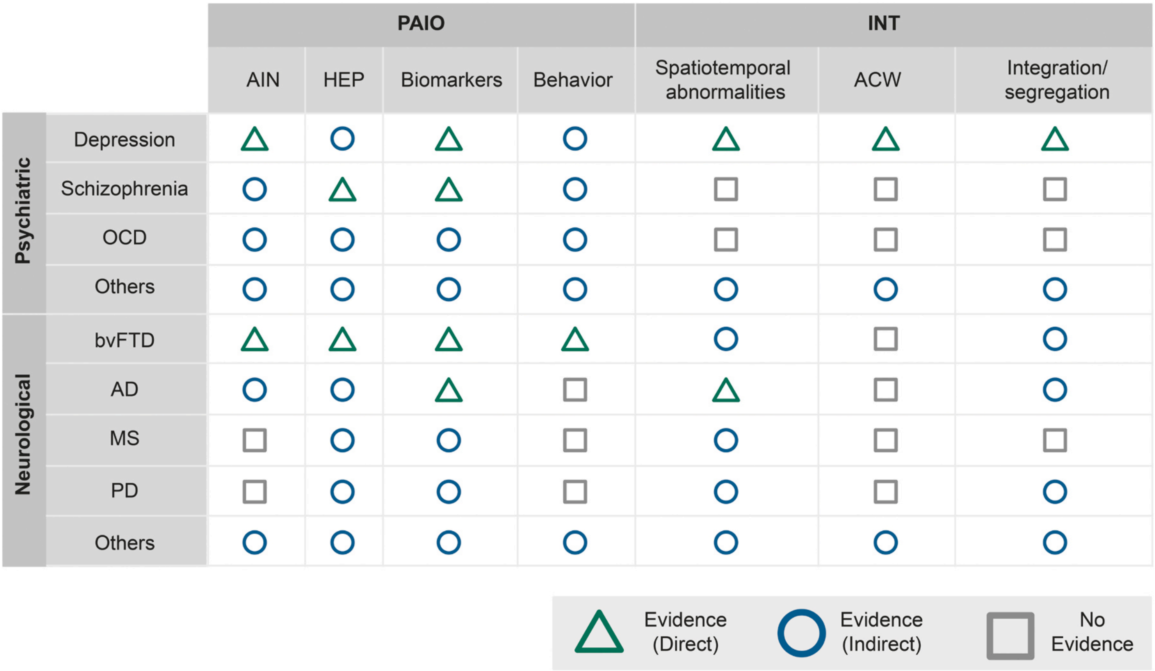
The combination of PAIO and INT offers novel inroads to understanding neurological and psychiatric disorders (Fig. 3). it considers the complex interactions between different regions of the brain and the influence of intrinsic timescales on brain activity. A dynamical spatiotemporal hierarchy (Toga and Thompson, 2003; Lord et al., 2017) is not entirely fixed at spatial and temporal dimensions across uni-transmodal networks. It involves transitions related to the temporal blending of exteroceptive, interoceptive, and cognitive inputs. Here we focus on two prototypical examples from psychiatry (depression) and neurology (frontotemporal dementia) and provide additional insights into other conditions (Boxes 1 and 2).

4.1. PAIO and INT in psychiatric (depression) and neurological (dementia) disorders

Depression is a psychiatric disorder characterized by the co-occurrence of interoceptive dysfunctions (somatic, affective), dysregulated responses to external demands (i.e., apathy, negative bias), and cognitive impairments (Barrett et al., 2016a). Correspondingly, depression is associated with abnormal allostatic interoceptive predictive coding, with deficits in predicting and integrating signals from internal and external inputs (Shaffer et al., 2022). For instance, individuals with depression exhibited abnormal heart rate variability (Gorman and Sloan, 2000), which reflects increased sympathetic nervous system activity and impaired autonomic brain regions (Sgoifo et al., 2015). Other studies have found abnormalities in the processing of bodily signals and allostasis (Barrett et al., 2016a). Several symptoms of depression, such as fatigue, distress, context insensitivity, reward insensitivity, and motor retardation, are linked with energy regulation, allostasis, and interoception (Shaffer et al., 2022). These findings suggest that depression is characterized by a disruption in the predictive coding of interoceptive signals and impaired allostasis to generate adaptive responses to the environment. Similarly, depression is associated with abnormal timescales/INT that are too long, leading to reduced speed in processing the prediction error (Gupta et al., 2021); which may contribute to symptoms such as slowed thinking, anhedonia, and impaired decision-making (Northoff et al., 2018; Lu et al., 2022).

Accordingly, depression supports the convergence of timescales/INT to allostatic intero-exteroceptive coding. The combination of PAIO and INT can help to explain the temporal and dynamic deficits in depression. Abnormal intero-exteroceptive allostatic predictive coding in depression may be related to changes in the intrinsic processing timescales of different brain regions, leading to changes in their functional properties and behavior.

Another representative case from neurology is the behavioral variant



		PAIO				INT		
		AIN	HEP	Biomarkers	Behavior	Spatiotemporal abnormalities	ACW	Integration/ segregation
Psychiatric	Depression	△	○	△	○	△	△	△
	Schizophrenia	○	△	△	○	□	□	□
	OCD	○	○	○	○	□	□	□
	Others	○	○	○	○	○	○	○
Neurological	bvFTD	△	△	△	△	○	□	○
	AD	○	○	△	□	△	□	○
	MS	□	○	○	□	○	□	□
	PD	□	○	○	□	○	□	○
	Others	○	○	○	○	○	○	○

△ Evidence (Direct) ○ Evidence (Indirect) □ No Evidence

Fig. 3. PAIO and INT accounts in psychiatric and neurological disorders. This illustration summarizes previous studies in terms of direct (triangle), indirect (circle), and no evidence (square). Psychiatric conditions include depression, schizophrenia, and obsessive-compulsive disorder (OCD). Neurological diseases comprise behavioral variant frontotemporal dementia (bvFTD), Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), and other conditions. Boxes 1 and 2 describe these deficits in psychiatric and neurological conditions. Measures associated with PAIO include the structure and function of the allostatic interoceptive network (AIN), the heart-evoked potential (HEP) and other cardiocerebral measures, multiple blood biomarkers of allostatic and autonomic/interoceptive dysregulation, and inadequate responses to environmental demands (e.g., disinhibition, social inappropriateness, apathy). Proxies of INT encompass spatiotemporal brain abnormalities, direct measures of the autocorrelation window (ACW), and metrics of dynamic brain integration/segregation.

frontotemporal dementia (bvFTD). Studies have provided evidence for abnormal allostatic interoceptive processing in bvFTD (Migeot et al., 2022b). These abnormalities include structural and functional changes in the AIN, dysregulation of the HEP, and atypical allostatic biomarkers (Gupta et al., 2021; Birba et al., 2022a). These changes have been linked to the breakdown of social and emotional processing, loss of empathy, and emotional blunting that characterize this disorder (García-Cordero et al., 2016; Kleckner et al., 2017b; Abrevaya et al., 2020a; Salamone et al., 2021a; Birba et al., 2022b). As in depression, there is a co-occurrence of interoceptive, allostatic, and cognitive symptoms (Baez et al., 2017; Van den Stock et al., 2020; Kamalian et al., 2022). Regarding INT, the primary disturbance underlying these symptoms is similar to that in depression but with a twofold transient state leading to slow (apathy) or fast (disinhibition) neural states and a disbalance regarding external vs. internal signals. This disbalance would be characterized by a temporal breakdown of external stressors and the internal interoceptive deregulation of these demands (Yoris et al., 2018). Similarly, the twofold transient state in bvFTD may be related to changes in

Box 1
INT and PAIO in psychiatric disorders.

Beyond depression, the combined approach of PAIO and INT would be relevant across psychiatric disorders. Research suggests that allostatic interoception overload and deficits in predictive coding may be involved in various psychiatric conditions (Adams et al., 2016; Paulus et al., 2019; Jeganathan and Breakspear, 2021; Smith et al., 2021). In anxiety disorders, there is evidence of increased interoceptive awareness and interoceptive hypersensitivity (Teed et al., 2022), potentially leading to heightened physiological arousal and predictive coding deficits, particularly concerning threat detection. In eating disorders, impairments in interoceptive accuracy may contribute to altered body perception and regulation of food intake (Jenkinson et al., 2018). In obsessive-compulsive disorder, there is evidence of excessive interoceptive checking and monitoring, which may be related to deficits in error prediction and monitoring (Yoris et al., 2017). In post-traumatic stress disorder, deficits in interoceptive and exteroceptive information integration may contribute to altered emotional processing and symptomatology. These findings suggest that a better understanding of the interplay between allostatic interoception and predictive coding may provide insights into the underlying mechanisms of various psychiatric disorders(Khalsa et al., 2018).

Similarly, multiple studies evidenced brain spatiotemporal deficits across psychiatric conditions resembling the predictions of INT(Golesorkhi et al., 2021c; Northoff et al., 2021). In schizophrenia, disrupted connectivity within and between neural networks and altered intrinsic neural timescales may contribute to the disorder's characteristic positive and negative symptoms (Wengler et al., 2020). In bipolar disorder, disruption of intrinsic interoceptive timescales could contribute to cognitive deficits and manic symptoms (Perry et al., 2019). In anxiety disorders, alterations in intrinsic timescales between the amygdala and the prefrontal cortex could contribute to dysregulated fear processing. In OCD, altered intrinsic dynamics in the anterior cingulate cortex may play a role in inhibition (Kang et al., 2013). These emerging findings suggest that the INT approach can provide new insights into the underlying neural mechanisms of these disorders and may lead to the development of novel treatments (Golesorkhi et al., 2021c; Northoff et al., 2021).

the intrinsic processing timescales of different brain regions, leading to changes in their functional properties and behavior. Accordingly, new insights may be gained about their specific mechanisms by understanding the temporal and dynamic nature of these disturbances.

Beyond these two prototypical cases, this framework facilitates the integration of flexible multimodal mechanisms, various types of inputs, and diverse psychopathological processes. Different psychiatric (Box 1) and neurological (Box 2) disorders can be related to different levels in the hierarchy of the allostatic interoceptive system and its timescales (Fig. 3). However, direct integration of both approaches is still lacking. Examining the relevance of the combined PAIO and INT approach to dimensional, transnosological cognitive synergies, symptomatology, and physiopathology in brain diseases (psychiatric and neurological) can offer new insights into theoretical models, potential treatments, and intervention strategies(Ibanez and Zimmer, 2023).

4.2. *Integrative dimensional and transnosological approaches*

The combination of PAIO and INT can be combined to assess the complex interplay between physiopathological pathways (i.e., inflammatory, immune, cardiometabolic), environmental stressors, and neurocognitive deficits in psychiatric and neurological disorders (Hitchcock et al., 2022). Examining the spatiotemporal dynamics of these diseases, including the relationship between exposome and physiopathological pathways (Vermeulen et al., 2020) can be integrated within a converged PAIO-INT framework. Synergetic interactions in terms of hierarchies and spatiotemporal dynamics are observed across multiple levels in diseases (Ibanez and Zimmer, 2023), including gene expression and epigenetics (Day, 2019), multiple allostatic biomarkers such as neuroimmune, inflammatory, and neurochemical imbalance (Hampel et al., 2021), circadian regulation (Morris et al., 2020), brain dynamics and cognition (Atasoy et al., 2018; Lurie et al., 2020; Deco et al., 2021; Luppi et al., 2022b), and high-level constructs such as adaptation, phylogeny, and ontogeny (Badcock et al., 2019). Dimensional approaches can identify common dynamics of dysregulated responses to environmental demands.

Our model carries important transnosological implications. It assumes that multiple dysfunctions can lead to similar symptoms, such as cognitive impairment, affective disturbances, and interactive/somatic complaints, which, in turn, can be traced to underlying physiological mechanisms, such as inflammation, immune dysregulation, and stress. Moreover, this approach can help identify specific synergies across different disorders (Fig. 4). For example, the co-occurrence of interoceptive, allostatic, and cognitive symptoms in multiple diseases can manifest a primary disturbance in allostatic interoceptive predictive coding linked to abnormal timescales/INT. This can provide potential explanations of the symptomatic overlap among different psychiatric and/or neurologic disorders.

In sum, combining these two theories can provide a better understanding of how the allostatic interoceptive network operates temporally and dynamically. For instance, the "overload" in the allostatic interoceptive system can be understood as a failure of INT, which is a failure of proper temporal integration and segregation among the various inputs. This can lead to a dimensional disbalance between extero/interoceptive inputs across brain dynamics and whole-body organismic levels, including cardiometabolic, cardiovascular, inflammatory, immune, and microbiome levels. Moreover, the temporal dynamics of INT may better explain the mechanisms driving the predictive capacities, including their changes in neurologic and psychiatric disorders. This integrative approach opens multiple avenues for further research (Box 3). In summary, the combination of PAIO and INT can offer a more dynamic and temporal system to understand the complex interplay between exteroceptive, interoceptive, and cognitive signals and how they interact with each other at different levels of organization.

5. Conclusions

Despite the significant progress in the cognitive neuroscience of brain diseases, there remain several challenges in current models. Some of these challenges are linked to the complex spatiotemporal dynamics, hierarchy, and common coding involved in allostasis, interoceptive and cognitive processes in brain diseases. Here we presented an integrative and synergetic approach combining PAIO and INT. Converging these theories' timescales (INT) and coding (PAIO) principles offers a more dynamic approach to understanding brain function and dysfunction. This can help to overcome some of the limitations and challenges of traditional approaches and provide a more effective framework for understanding and treating brain diseases. Such an integrative framework opens new avenues for more holistic research and may help advance our understanding of brain diseases by developing more effective treatments.

Box 2

INT and PAIO in neurological disorders.

As in the case of psychiatric disorders, the PAIO with the INT can help to understand multiple abnormalities across neurological conditions beyond the bvFTD. Allostatic interoception overload and deficits in predictive coding have been reported across neurological diseases (Goldstein and Kopin, 2018; Birba et al., 2022b; De Felice et al., 2022a; Migeot et al., 2022a; Waliszewska-Prosół et al., 2022). In particular, multiple dementia subtypes can be integrated into this framework. In multiple sclerosis (MS), patients exhibit increased allostatic overload (Waliszewska-Prosół et al., 2022), atypical interoceptive awareness, and greater salience attributed to interoceptive signals (Salamone et al., 2018), which may contribute to fatigue and other symptoms (Gonzalez Campo et al., 2020). In Parkinson's disease (PD), interoceptive deficits (Yoris et al., 2018) may relate to motor allostatic overload (Goldstein and Kopin, 2018). In Alzheimer's disease (AD), multimodal allostatic dysfunctions (De Felice et al., 2022a) and partial dysregulation of interoceptive neural networks(Abrevaya et al., 2020b) may contribute to cognitive deficits and neuropsychiatric symptoms. Disrupted allostatic interoception and predictive coding in each disease may result from a synergetic interplay of underlying physiopathology, genetic and epigenetic factors, and environmental stressors (Yoris et al., 2018; De Felice et al., 2022a; Migeot et al., 2022b).

INT theory can be linked to multiple spatiotemporal deficits in neurological conditions (Toga and Thompson, 2003; Lord et al., 2017; Courtney and Hinault, 2021). Changes in the intrinsic processing timescales of different brain regions can result in variations in their functional properties, leading to changes in behavior and cognition. For example, in Alzheimer's disease, a disruption of the brain's intrinsic temporal irreversibility may underlie cognitive impairments (Cruzat et al., 2023). In Parkinson's disease, changes in the intrinsic timescales of the basal ganglia and other regions (Reitsma et al., 2011; van den Brink et al., 2019) have been implicated in motor and cognitive deficits. In multiple sclerosis, changes in the intrinsic networks have been associated with fatigue and interoception (Salamone et al., 2018). These deficits in intrinsic neural timescales can lead to abnormalities in predictive coding, as the brain's ability to generate accurate predictions about the environment is compromised.

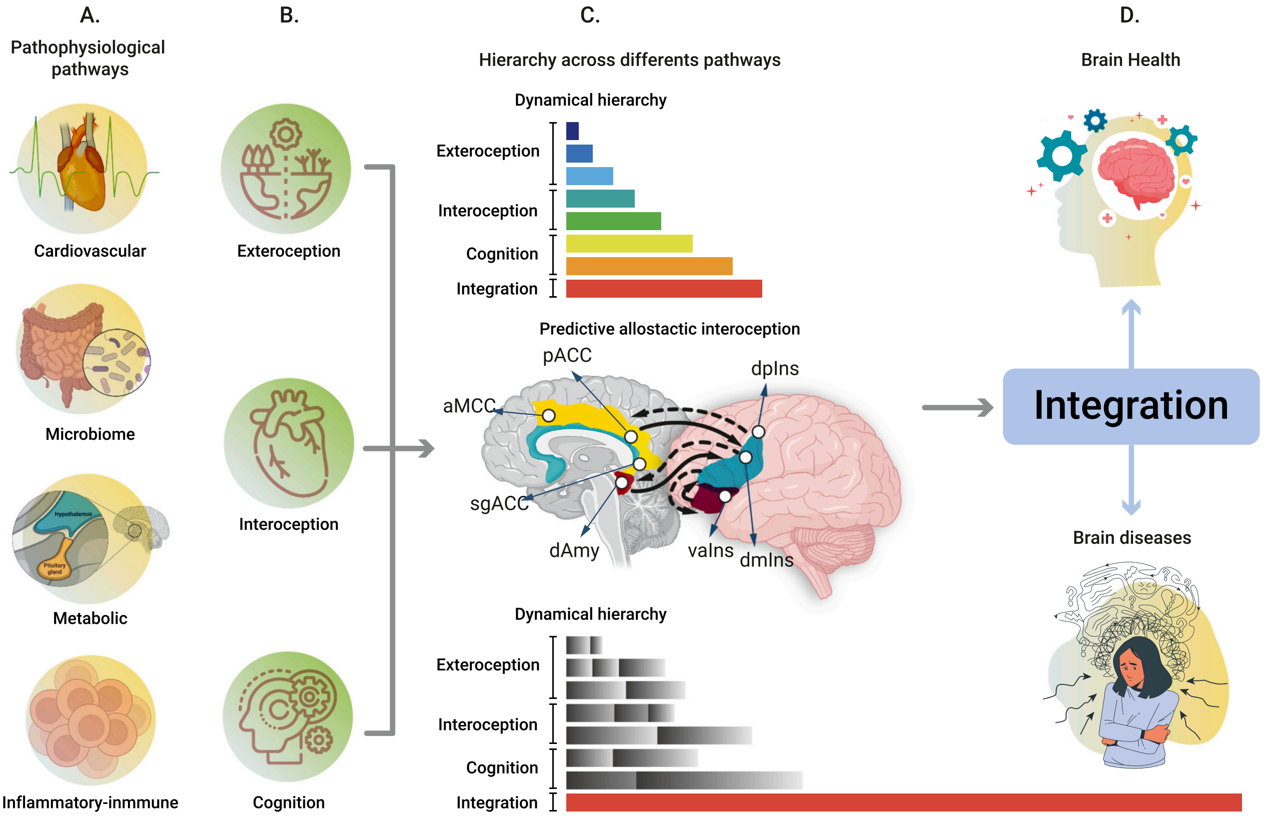


Fig. 4. An integrative framework for brain health and disease. The predictive coding theory of allostatic interoceptive overload (PAIO) and the intrinsic neural timescales (INT) theory can be integrated into a model to address the continuum between brain health and disease. The framework is aimed at addressing the connections between brain structure and function, the diversity of brain phenotypes, and the necessity for dimensional and transnosological explanations. A. Different levels of bodily systems (cardiometabolic, cardiovascular, inflammatory, and immune systems) relate to (B) integrated processing of exteroception, interoception, and cognition. C. These inputs converge in dynamic hierarchies across different pathways, which are then processed across different intrinsic timescales over the allostatic interoceptive network. Spatiotemporal dynamics are notably longer when information is more complex. D. The upward and downward arrows refer to the spectrum of brain health, contrasting healthy brain function with the alterations seen in brain diseases. The longer integration timescales are associated with brain diseases, implying a lack of proper temporal segregation and integration, leading to a failure in managing allostatic load and interoceptive information. This failure can result in symptoms across cognitive, affective, and somatic domains.

Box 3
Questions for future research.

1. How could the combined framework of the predictive coding of allostatic interoception and the intrinsic neural timescales be further developed and validated in the context of neurological and psychiatric disorders?

2. What methods can be used to effectively understand and integrate the complex relationships between brain dynamics, cognition, and diseases into low-dimensional, integrative models of brain activity?

3. How can allostatic interoceptive overload be refined and operationalized to capture better the complex interplay between extero/intero/cognitive inputs and inferences/errors linked to the temporal dynamics of the intrinsic neural timescale's theory?

4. What approaches can be used to better understand and integrate the topographical organization and uni-transmodal networks of the brain into the allostatic interoceptive dynamics framework and link these interactions to temporal structures of blending external, interoceptive, cognitive, and affective inputs?

5. In what ways can the allostatic interoceptive dynamics framework be extended to understand the subtle dynamic of body-brain-environment signals across many psychiatric and neurological conditions?

6. Can synergetic principles of hierarchy and spatiotemporal dynamics be extended to multiple psychopathological immune, genetic/epigenetic, inflammatory, stress-related, and neurodegenerative pathways and connected with neurocognitive dynamics in brain health and disease?

7. What are the potential avenues for integrating the allostatic interoceptive dynamics framework with other emerging frameworks and theories in cognitive neuroscience to provide a more comprehensive and integrative understanding of brain activity, cognition, and brain diseases?

8. How can the allostatic interoceptive dynamics framework inform the development of personalized and effective treatments for brain diseases by considering the specific mechanisms underlying each disease?

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Declaration of Competing Interest

The authors report no competing interests.

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