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Review

Brain–body states as a link between cardiovascular and mental health

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Numerous studies in humans have demonstrated a strong link between heart and brain function at different timescales. We conceptualize this functional coupling using different dimensions of brain–body states, formed through the integration of the central and peripheral nervous systems (PNS and CNS, respectively). Using concepts from dynamical systems theory, we discuss how patterns of brain–body dimensions traverse a state space. Attractors signify stable configurations, which we categorize as micro-, meso-, or macro-states according to their duration and reversibility. These reflect different underlying mechanisms, such as neural interactions, hormonal signaling, and structural plasticity. Longer-lasting states restrict the space of possible (shorter-term) brain–body states underlying the mutual dependence of cardiovascular and brain function over the lifespan and in the development of diseases such as hypertension and depression. These considerations, which can be further generalized to include immunological and metabolic dimensions of brain–body states, have broad conceptual and clinical implications.

Highlights

Changes in mental and cardiovascular functions occur concurrently even at short timescales down to subsecond dynamics.

Brain–body states arise from the tight integration of the CNS and autonomic PNS with the endocrine and cardiovascular systems.

We characterize brain–body states in terms of dimensions such as blood pressure, heart rate, and brain activity that underlie mental functions such as cognition and emotion.

Using a dynamical systems approach, we conceptualize brain–body states as continuously traversing a state space. We define stable parts of trajectories within this space as micro-, meso-, or macro-states, depending on their duration and reversibility.

Instances of emotions are prototypical examples of brain–body microstates, and stress is an example of a mesostate, whereas depression, anxiety, and hypertension represent macro-states.

The link between heart and brain in health and disease

There is compelling epidemiological evidence of a broad link between cardiovascular diseases and mental health disorders [1–4]. This co-occurrence is often explained by unidirectional or bidirectional causation or by common causes for both types of diseases. For example, the higher incidence of cardiovascular diseases in people with depressive disorders has been attributed to lifestyle factors associated with depression, such as smoking and physical inactivity [2]. Conversely, the higher risk of developing a mental health disorder in people with cardiovascular diseases [5] has been explained by psychological stress after the diagnosis or by the direct sequela of ischemic brain damage [6]. Some researchers assume bidirectional causal factors potentially leading to a joint 'downward spiral' [2].

One problem with the concept of directional causation between mental health disorders and cardiovascular diseases is that it focuses on the timeline beginning with a disease state in one of these domains and often overlooks earlier subclinical processes. A drawback of the shared risk factor/mechanism concept is the necessity to establish two different pathways to explain how these factors/mechanisms affect both the cardiovascular system and the mental domain.

Building on strong evidence of tight links between cardiovascular and neural function [7], we view them as two dimensions of integrated brain–body states [8]. We propose a conceptual framework that describes brain–body states across different temporal scales with different underlying mechanisms. This framework applies to healthy physiology but also to pathological states. The co-occurrence of cardiovascular diseases and disorders of mental health becomes a natural manifestation of this organization. Instead of considering how a particular (risk) factor affects two separate entities, we examine how the brain–body system functions as an integrated whole and how it reacts to internal or external factors and challenges. The proposed

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conceptualization leads to the testable hypothesis that certain variations in the integration of cardiovascular and neural function predispose to and reflect diseases that are classically characterized as either 'cardiovascular' or 'mental' diseases.

In the following sections, we first discuss evidence for the close relationship between cardiovascular and neural function (as well as the mental domain). This relationship manifests not only over extended time periods, as sometimes assumed, but even at subsecond temporal scales, which form the basis of integrated brain–body states (Figure 1). These states form trajectories in multidimensional latent spaces, where the axes represent different dimensions of physiological activity, such as the CNS and PNS and the cardiovascular system. We then propose using a dynamical systems approach to categorize stable patterns of brain–body dimensions, or attractors, as micro-, meso-, or macro-states, depending on their duration and reversibility, which reflect different underlying mechanisms. Finally, we present paradigmatic examples to demonstrate their relevance to the development and co-occurrence of cardiovascular and mental health conditions.

Co-occurrence of changes in cardiovascular, brain, and mental functions

The rapid onset of cardiovascular changes, alongside motor tasks and physical activity, can be seen in the context of active inference as reflecting anticipation of increased metabolic demand. However, characteristic patterns of changes in heart rate, both decreases and increases, also go along with many – perhaps all – mental events. A prime example is the orienting response, characterized by behavior aimed at extracting information from the immediate environment [9]. Associated with the orienting response, cardiac deceleration has been confirmed in many different contexts and studies [10]. Typically, an initial parasympathetically driven cardiac deceleration is followed by a sympathetically driven acceleration [11]. Cardiac deceleration is typically seen with unclear or attention-demanding information, which – in a Bayesian framework – can be interpreted as a way to decrease noise or improve perceptual precision before subsequent action and heart rate acceleration [11]. Consistent with this idea, stronger cardiac deceleration during a somatosensory detection task was associated with greater perceptual uncertainty [12]. Further examples of heart rate changes have been observed during social/affective touch [13] and

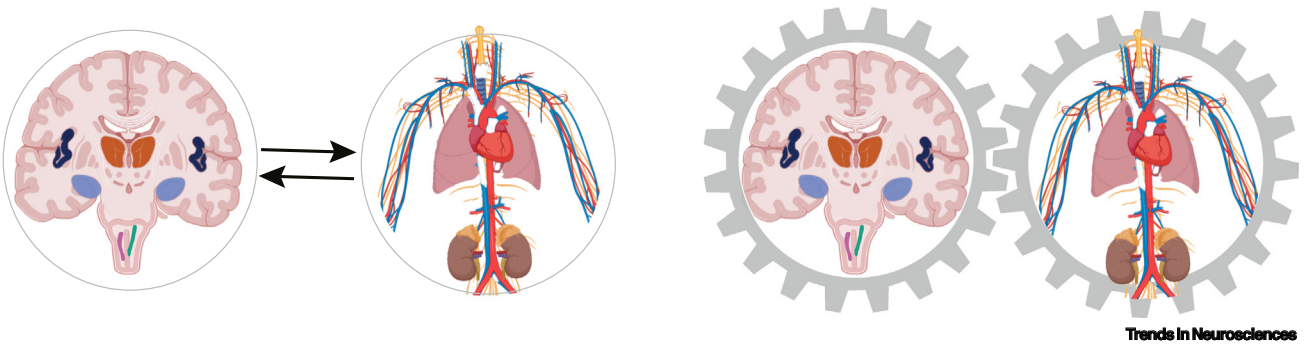

Figure 1. Conceptual framework for brain–body states. Left: Classical views often consider unidirectional or bidirectional information flow or causation as indicated by the arrows. Right: Our proposal of integrated brain–body states highlights the co-occurrence of changes in brain–body activity. Cardiovascular control involves rapid neuronal reflexes such as the baroreflex and slower hormonal cascades (e.g., hypothalamic-pituitary-adrenal axis), forming integrated states that evolve on different timescales. These micro-, meso-, and macro-states are associated with plasticity and manifested in both physical and mental domains (Figure 2). The cogwheels indicate that changes in one dimension (e.g., brain, body) are always linked to changes in the other, and this idea of control loops and integrated brain–body states naturally extends to other bodily systems (e.g., metabolic, immunological) and the social domain. Highlighted brain structures include bilateral insula, amygdala, thalamus, nucleus of the solitary tract and nucleus ambiguous. Highlighted bodily structures include the heart, lungs, kidneys, autonomic PNS, and vasculature. The schematics includes regions of both the CNS and the autonomic PNS, recognizing their specific roles in the integration of visceral function and the brain. However, given the close connection of the autonomic PNS with other central and peripheral neural structures, we include them all in our general framework. This figure was created by the authors and the graphics department of the Max Planck Institute for Human Cognitive Brain Sciences in Leipzig.

exclusion/inclusion during a virtual ball-tossing game [14]. During reinforcement learning, feedback was associated with cardiac deceleration, which scaled with the strength of the prediction error [15]. In the general context of decision-making, the 'somatic marker hypothesis' suggests that the ventromedial prefrontal cortex is involved in learning the association between certain complex situations and 'bioregulatory states' [16]. When faced with similar situations, these learned associations trigger bodily changes and feelings that guide decision-making [17]. Vagal activation, which changes the heart rate, is a core component of such bodily changes, and a recent study linked vagal reactivity and recovery to better decisions [18]. The aforementioned examples could be interpreted as a 'top-down leg' or 'brain-to-heart view' of the interaction. Importantly, the reverse 'bottom-up' or 'heart-to-brain' perspective also demonstrates robust coupling between heart and brain function, which can be observed even within each heartbeat. For example, studies comparing cardiac phases of higher (systole) and lower blood pressure (diastole) found a reduced perception of pain [19] and (nonpainful) somatosensory stimuli [20], as well as lower (late) somatosensory potentials [21] in systole compared with diastole. Interestingly, movement initiation [22] and motor excitability [23] were higher during systole than diastole. Thus, a characteristic modulation of sensorimotor function occurs with each cardiac cycle. Variations of sensory perception over the cardiac cycle were also found in other modalities (e.g., hearing [24], vision [25]) and for multisensory (audiotactile and visuotactile) stimuli [26]. Furthermore, visual attention [27] and short-term memory [28] as well as social pain [29], fear processing [30], and even the expression of racial stereotypes [31] are modulated over the cardiac cycle. The rhythmic coupling of heartbeat, brain activity, and the mental domain extends to the respiratory cycle, during which there is a modulation not only of heart rate but also of sensory perception [12,32] and other types of cognitive functions [33].

A classification of integrated brain–body states

As discussed in the previous section, cardiovascular changes regularly co-occur with changes in neural and mental function and vice versa. The neurovisceral integration theory [7,34,35] suggests that adaptive behavior and emotional regulation depend on the integration of the brain and the PNS. Subsequently, we build on these notions and introduce a classification of brain–body states based on their duration and reversibility, further developing the theory to provide a scaffold for research on both subclinical and clinical links between mental and cardiovascular health. Here we distinguish between the physical and mental domains. The former encompasses (among others, see following sections) cardiovascular and neural dimensions of brain–body states. The mental domain, which manifests as cognition and emotion, is conceptualized as a product of neural activity.

The functioning of neural networks can be effectively described using concepts from dynamical systems [36]. These concepts are also applicable to brain–body interactions [7,34,37]. Within this framework, various patterns of physiological activity ('brain–body states') traverse a state space where an attractor signifies a stable configuration of parameters linked to, for example, a specific emotional state, such as anger. The axes in this state space represent activity relating to the CNS and PNS and the cardiovascular system (Figure 2). A basin of an attractor defines a set of parameter values that will lead the system to a particular attractor. The system's adaptability and healthy dynamics relate to its ability to move freely in a state space. Dysfunctions of brain–body interactions may be conceptualized as the system being locked in maladaptive attractors, exemplified by the development of depression (see below) associated with a particular configuration of body–brain parameter values [35,38]. Although brain–body studies have proposed the use of state space models to capture hierarchical, multilevel neural dynamics [7] and to address various temporal aspects of brain activity and behavior [8], an important aspect that remained to be explored is categorizing these dynamics into distinct temporal classes or levels that capture

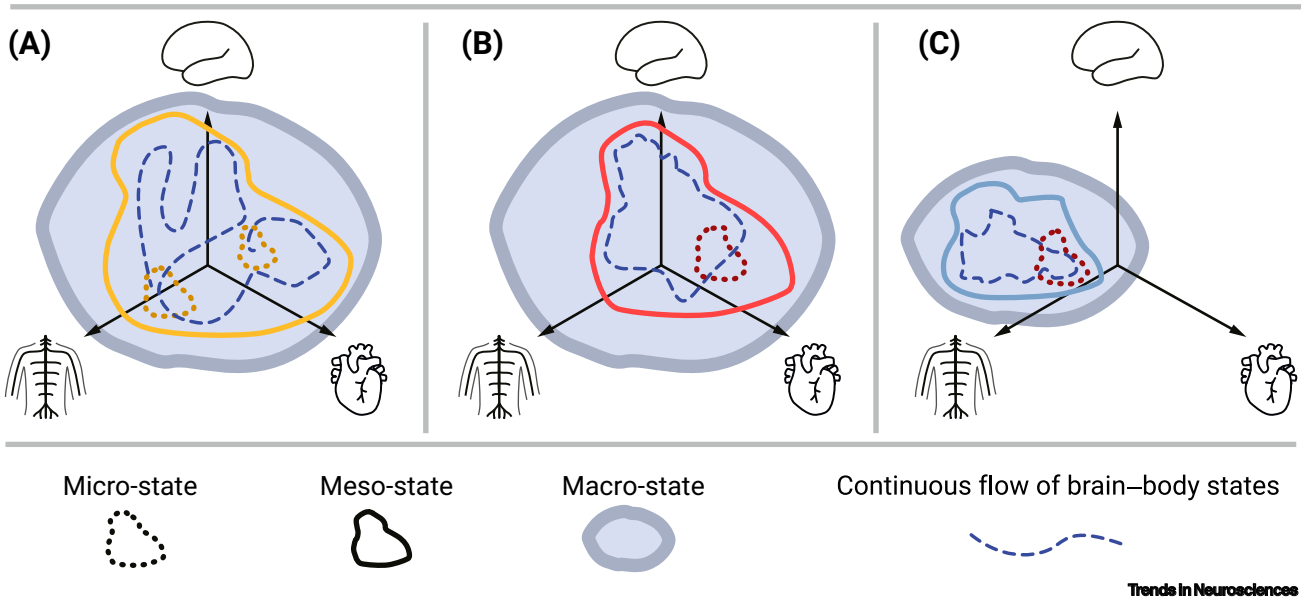

Figure 2. Brain–body micro-, meso-, and macro-states can be distinguished on the basis of their duration and reversibility. A brain–body state can be defined as a specific point in a multidimensional space where axes correspond to physiological activity in the CNS, autonomic PNS, or cardiovascular system. (A), (B), and (C) depict different scenarios for the interplay between micro-, meso-, and macro-states. (A) A typical everyday situation where a given microstate (e.g., emotion) may occur in a relatively large state space (macro-state) and is also affected by a current (physiological) meso-state (e.g., at a specific circadian interval or a phase in a menstrual cycle). Over time, other micro- and meso-states (e.g., other circadian phases, transient moods, etc.) occur during healthy macro-states (e.g., young versus middle-aged brackets). Importantly, all micro- and meso-states are transient and reversible. (B) An example where, during a certain meso-state (e.g., stress or phase of the menstrual cycle), micro-states are relatively restricted within the state space; yet, a healthy macro-state is still sufficiently large to allow a potential recovery of normal trajectories for micro-states once the 'narrower' meso-state has resolved. (C) An example where the macro-state is restricted, which affects the flexibility and reversibility of both micro- and meso-states. Such macro-states would be linked, for instance, to clinical conditions relating to depression, anxiety, hypertension, or arteriosclerosis. This figure was created by the authors and the graphics department of the Max Planck Institute for Human Cognitive Brain Sciences in Leipzig.

specific body–brain processes. Here we introduce such a classification, attributing body–brain states to micro-, meso-, or macro-levels, depending on their duration and reversibility. A limited reversibility here may relate to pathological attractors, as mentioned above, restricting brain–body dynamics to a specific part of a state space. However, irreversibility (driven primarily by structural changes) also includes processes generally occurring during the lifespan, such as early stages of development, aging, or menopause, and thus encompasses both healthy and pathological phenomena. This classification aims to enhance the understanding and discussion of concurrent body–brain processes in both health and disease. In the following section, we elaborate on this classification and provide examples for each level (Table 1, Figure 2).

Brain–body microstates are brief patterns in bodily and neural physiology that last during relatively short intervals, from a few seconds to minutes, and that are reversible. They are typically identified by the associated mental state; prime examples include specific emotions or periods of acute pain. Obviously, all brain–body states can only 'move' in the state space within certain limits, which are defined by physiological constraints such as the possible ranges and reactivity of blood pressure and heart rate or neural activity.

The term 'macro-state' refers to long-term attractors defining the range of possible brain–body states, typically lasting months to years. Beyond the limits provided by general human physiology and anatomy, there are further individual structural constraints that depend, for example, on age, sex, and genetic disposition. Hence, macro-states have boundaries within which brain–body

Table 1. Neurocardiovascular brain–body states

State	Micro-state	Meso-state	Macro-state
Duration and reversibility	• Reversible • Seconds to minutes • Many times per day	• Reversible but may induce adaptive or maladaptive plasticity • Hours to days	• Structural changes, irreversible • Long-lasting, typically weeks to months or even years
Prototype example	• Emotions • Acute pain	• Acute stress • Chronic stress (often associated with disrupted plasticity and transition to pathological macro-state)	• Depression • Hypertension These conditions contribute to one overall macro-state
Other examples	• Feelings associated with decision-making and perceptions	• Moods	• Neurodegenerative diseases • Schizophrenia • Anxiety disorder • Stroke • Atrial fibrillation • Heart failure • Predispositions to diseases
Ontogeny-related examples	At any age but changing over the lifespan	• Phases of menstrual cycle	• Infancy • Puberty • Phases of adulthood • Pregnancy • Menopause
Cardiovascular dimensions examples	• Heart rate deceleration/-acceleration • (Brief) blood pressure change	• Heart rate variability • Blood pressure	• Heart rate variability • Blood pressure (variability)
Neurocognitive dimensions (examples)	• Emotions with arousal-valence • Confidence • Prediction error • 'Gut feeling'	• Mood with arousal-valence • Emotion regulation • Attentional focus	• Depression, mania • Psychosis • Emotion regulation capability or tendency • All cognitive abilities • Personality traits
Potential biomarkers (examples)	• Event-related potential • Cardiovascular reactivity to stimuli	• Longitudinal hormonal profiles • Heartrate variability • Cardiac peptides	• Volumes of brain structures • Amyloid/Tau imaging (positron emission tomography) • Intima-media thickness • Resting blood pressure • Cerebrospinal fluid biomarkers of neurodegeneration • Cardiac injury markers (e.g., troponin, probrain natriuretic peptide)

states can move with changes in the internal and external world. Importantly, certain diseases, such as hypertension, cardiac failure, or depression, add additional constraints to the macro-state that may, for example, restrict the range of emotional experience (in the case of major depression), shift the arterial blood pressure range (hypertension), or decrease the cardiac ejection fraction (cardiac failure). Macro-states are assumed to be irreversible because their structural determinants, such as increased arterial stiffness or neurodegeneration, lead to permanently different dynamics of the system. The range of possible brain–body states might be assessed by brain–body responses to specific physiological and mental challenges (after excluding transient hormonal influences as in meso-states) or by long-term real-life monitoring (e.g., using wearable

devices). However, it might be more practical to look for other possible biomarkers. In the neural dimension, these may include brain age [39] or the volume of certain brain structures; in the vascular domain, they may include measures of vascular aging, such as intima media thickness [40] or resting blood pressure; and for heart–brain interaction, they may include long-term resting-state heart rate variability (HRV) or heart evoked potential.

We emphasize that at any given time, there is just one macro-state. Thus, the examples given (see also Table 1) (e.g., depression, hypertension) are contributors to the respective macro-state.

Meso-states are brain–body states that stand between micro- and macro-levels. We conceptualize them as lasting from hours to days, and they are typically governed by hormones. With hormones' short-lived presence in the bloodstream, they influence cognition, emotion, and the cardiovascular system and thus transiently limit the range of possible brain–body microstates (within the boundaries of the macro-state). Although meso-states are in principle reversible, some may have longer functional and structural impacts, which can alter the macro-state (i.e., altering permanently the dynamics of the system). A prototype example of a meso-state is acute stress, which goes along with transient elevations of cortisol and catecholamines. It is reversible, but in some cases, stress can lead to profound changes in the macro-state (see following sections). Other physiological examples include cyclical events such as the menstrual cycle governed by sex hormones [41] or circadian modulations influenced by external factors such as daylight and fluctuations of hormones, particularly cortisol [42]. Meso-states are best defined by the temporal course of the corresponding hormones (e.g., cortisol, sex hormones, or thyroid hormones).

Finally, we emphasize that brain–body states encompass more than cardiovascular and neural dimensions. Rather, in comprehensive models, other dimensions of bodily events and their mutual relationships are to be included, an endeavor that goes beyond the scope of this review. For discussions on the interactions of other body organs and systems with the brain, we refer readers to recent reviews on gut–brain [43,44], respiration–brain [43,45], kidney–brain [46], immune system–brain [47], liver–brain [48], and thyroid–brain [49] interactions.

Mechanisms underlying brain–body states

Mechanisms underlying the continuous flow of brain–body states and microstates

As outlined next, the different timescales underlying heart–brain coupling reflect different mechanisms. Baroreceptors that contain mechanosensitive Piezo 1 and 2 ion channels [50,51] are important sensors of the state of the cardiovascular system. The activity of high-pressure baroreceptors in the aortic arch and the carotid arteries reflects arterial blood pressure, whereas the activity of low-pressure baroreceptors in the cardiac atria, vena cava, and pulmonary vasculature reflects blood volume. The 'baroreflex' is a core reflexive loop continuously linking the heart and the arterial part of the cardiovascular system with the brainstem: High-pressure baroreceptor signals reach the nucleus tractus solitarius (NTS) in the brainstem, increasing and decreasing parasympathetic and sympathetic activity, respectively, and lowering levels of the hormone arginine vasopressin [50], thus decreasing heart rate and blood pressure. Importantly, the reflexive core of the baroreflex is closely interconnected with other brain areas. The NTS connects, for example, to the midbrain (parabrachial nucleus, periaqueductal gray), the pons (locus coeruleus), the hypothalamus, or the amygdala and via the parabrachial nucleus, locus coeruleus, or thalamus, to the cortex (e.g., insula, sensorimotor cortices, prefrontal cortex, anterior cingulate cortex, and hippocampal formation) [52]. That is, brainstem regions also link input from baroreceptors to 'higher' brain areas that integrate homeostatic or interoceptive information with emotion, perception, well-being, sleep patterns, and ultimately conscious experience [7,35,53–57]. Stimulation of baroreceptors has been shown to promote sleep [53], to reduce pain [58], to inhibit the Achilles

tendon reflex [59], and to dampen the auditory startle reflex [60], suggesting that at least some of the observed modulation of brain function along the cardiac cycle is mediated by these receptors. Besides baroreceptors, other mechanisms underlie heartbeat-related effects on brain activity. In mice, arterial pressure pulsations were shown to directly entrain the local spiking activity of mitral cells in the olfactory bulb, likely mediated by Piezo 2 channels [61], with similar effects found in the hippocampus and neocortex [61]. A study involving intracranial *in vivo* recordings in humans successfully used the electrophysiological properties of recorded neurons during the cardiac cycle to differentiate cell types [62]. Furthermore, there are direct afferent neuronal connections from the heart to the brainstem (e.g., area postrema, NTS) via sensory neurons innervating the myocardium and epicardium, which transmit proprioceptive information [63].

Together, these continuous mutual interactions of cardiovascular and brain function underlie the continuous flow of integrated brain–body states and short-term stable configurations (i.e., micro-states). The mutual impact of cardiac and neural activity in the generation of emotions (i.e., micro-states) has been confirmed by animal studies on anxiety-like behavior and fear. In freely moving mice in which a rise in heart rate was selectively induced by optogenetic stimulation, tachycardia induced anxiety-like behavior only in a potentially risky but not a safe environment [64]. The link between the increased heart rate and the environmental context seemed to be established by the insula [64]. A similar role of the insula in regulating fear by integrating external sensory and internal bodily signals (particularly heart rate) was also revealed using vagal nerve stimulation and optogenetic inhibition of insular activity in mice [65]. This also confirmed the integration of central and peripheral mechanisms in the genesis and maintenance of fear and anxiety-like behavior.

Longer-lasting states determine range of possible brain–body states

Although the short-lasting micro-states consist of characteristic constellations of neural and cardiovascular changes, they are further shaped by longer-lasting brain–body states. For example, in a recent mouse study on defensive states, it was shown that although neurons in the periaqueductal gray send the signals to orchestrate a defensive microstate, the cardiovascular effects depended on the context (i.e., longer-lasting brain–body state) [66].

Macro-states set the outer fixed boundaries for all brain–body states. They are determined by structural characteristics that (i) are species-specific (e.g., heart rate in humans is typically between 60 and 100 beats/min, whereas in mice it is ~500–700/min), (ii) show interindividual differences (e.g., variations due to sex, genetics, epigenetics), and (iii) are further modified throughout life (e.g., by developmental stage, aging, and long-term environmental exposures). Well-established structural changes that codetermine and set boundaries to cardiovascular and brain function during healthy aging include increasing arterial stiffness [67], characteristic patterns of brain atrophy [68], and long-term imbalance of the autonomic PNS [69], which likely underlie changes in interoceptive awareness [70], emotion regulation [71], and overall cognitive abilities [72]. Interestingly, although there is a multitude of data characterizing these effects as well as other ontogenetic phases such as puberty or menopause in isolation, there is little systematic assessment of their impact on the integrated brain–body network defining the macro-state in health and disease.

Mechanisms underlying meso-states and their impact on macro-states

The space (in the mathematical sense; see Figure 2) of macro-states accommodates the continuous flow of brain–body states, short-lasting micro-states, and also longer-lasting meso-states. The latter refers to transient states of intermediate duration (hours to days), which are governed mainly by hormones. Stress is a paradigmatic example of a meso-state: The hypothalamus

coordinates stress responses through two pathways, the hypothalamic-pituitary-adrenal-axis and the sympathetic-adrenomedullary axis. The former acts through the release of cortisol, whereas the latter involves the sympathetic nervous system and the release of adrenaline and noradrenaline [73]. The cortical origin of top-down influences on the adrenal medulla involves motor, cognitive, and affective networks, providing an anatomical and functional basis for integrating movement, emotion, and cognition with bodily changes during demanding and stressful tasks [74]. Cardiovascular changes during the stress response include increased heart rate and blood pressure as well as decreased heart rate variability. In the mental domain, changes in attentional focus on the stressor are typically coupled with altered sensations, thoughts, and feelings, among other effects. For example, different types of stress can lead to stress-induced analgesia or hyperalgesia [75]. Stress also differentially impacts emotion regulation. Early sympathetic-adrenomedullary axis activation tends to impair emotion regulation, whereas (the later) hypothalamic-pituitary-adrenal axis activation may enhance it [76]. Taken together, via the release of hormones, acute stress represents a brain–body meso-state that transiently restricts the flow of brain–body states (including micro-states) in order to adapt optimally to the stressor. As is typical of meso-states, the acute stress response as well as the hormonal changes associated with it are generally reversible; the stress response, however, can lead to learning and associated plasticity (manifested in structural changes), thus shaping the (long-term) brain–body macro-state.

If an acute stressor is overcome successfully, these structural changes can be positive or adaptive and hence can improve resilience [77]. However, there are situations where the stressor is not overcome and stress becomes chronic, leading to maladaptive plasticity (see following section), or the acute stressor is so overwhelming that the stress response (or components of it, such as the sympathetic response) is so strong that it acutely leads to a pathological state. In takotsubo cardiomyopathy [78], which occurs mostly in postmenopausal women, an extreme sympathetic stress response induces a characteristic cardiomyopathy, thus exemplifying a transition to a state characterized by structural damage, a macro-state. Another example of such a link is ‘stroke heart syndrome’ [79], characterized by damage to the heart following a stroke. It occurs preferentially when the stroke has affected the right anterior insula [80] and is also characterized by an overshooting sympathetic stress response triggered by the brain lesion. Post-traumatic stress disorder occurs after major traumatic events and is characterized by flashbacks, nightmares, severe emotional distress, and other psychological symptoms, as well as by an imbalance of the autonomic PNS (increased sympathetic and decreased parasympathetic tone) and a reduced baroreflex [81]. Congruent with the idea of integrated brain–body states, long-term functional and structural changes affect the hippocampus, amygdala, insula, and medial prefrontal cortex, where dysfunction is associated with impaired control of the cardiovascular system [81].

In addition, if a stressor is not adequately addressed, stress can become chronic. The two main signatures of chronic stress are prolonged elevation of cortisol concentrations and sympathetic activity inducing maladaptive plasticity with a cardiovascular and a neurobehavioral dimension. The cardiovascular consequences include endothelial dysfunction, driven by proinflammatory cytokines and oxidative stress [82], which can progress to atherosclerosis, coronary heart disease, and stroke [82]. Neurobehavioral consequences include memory impairment, depressive symptoms, and many other psychological changes, through functional and structural plasticity, particularly in the hippocampus, amygdala, and prefrontal cortex [83]. In sum, chronic stress is associated with gradual changes affecting all dimensions of the long-term brain–body macro-state and hence an increased risk of both mental health disorders (e.g., depression or schizophrenia) and cardiovascular diseases.

Hypertension and depression as exemplary determinants of brain–body macro-states

Blood pressure fluctuations (even below the threshold of hypertension) have been linked to behavior and health. Several studies have reported a positive association between higher blood pressure levels, better quality of life, and fewer negative emotions in children, adolescents [84], and adults [85,86]. However, this seems to contradict other studies that associate hypertension diagnosis with mental health disorders, particularly depression [87,88].

In a recent study using UK Biobank data, both of these seemingly contradictory findings were reconciled [89]. It was found that the hypertension-related effect (more depressive symptoms, worse well-being) was already present 5–10 years before the hypertension diagnosis. That is, at a given baseline blood pressure, individuals who went on to develop hypertension 5–10 years later had worse well-being and more depressive symptoms at baseline than people with the same baseline blood pressure who did not develop hypertension [89]. Thus, individuals at risk for hypertension may have a macro-state where higher blood pressure is required for equivalent well-being, and this macro-state could drive behavior favoring higher sympathetic activity at the expense of increasing long-term hypertension risk. Interestingly, such a macro-state may impact the shorter-term brain–body micro-states because higher blood pressure has been associated with reduced emotional responses [90,91], lower pain perception [92], and diminished social pain [93]. Furthermore, although psychosocial stressors are established risk factors for hypertension [94], studies on subjective stress perception showed inverse associations with blood pressure [95,96]. This suggests a potential dissociation between stressors, stress, and their subjective perception with higher blood pressure, indicating an impact of the macro-state (chronic blood pressure elevation) on the meso-state (stress), which subjectively feels less 'stressful,' potentially driving further blood pressure increases.

Although conventional explanations using directional causation suggest that low well-being may lead to hypertension, the framework of integrated brain–body states offers an alternative and unified perspective: The same brain–body macro-state that requires higher blood pressure for equivalent well-being as compared with people without hypertension is present before and after the hypertension diagnosis. This integrated approach also simplifies understanding of shared mechanisms – such as chronic stress and hormone elevation or inflammation – affecting cardiovascular and mental health. It is no longer necessary to construct two different pathways of how these mechanisms lead to both types of disorders. Rather, any influence on one dimension is paralleled by changes in the other (Figure 1). Potential mechanisms for the altered brain–body relationship in people with hypertension could be differences in baroreceptor sensitivity or in the central processing of baroreceptor information. Such alterations might be either determined genetically (e.g., mutations in PIEZO channels) or developed under certain lifestyle conditions. Longitudinal studies are needed to disentangle the baseline macro-state characteristics in childhood or early adulthood [97] from subsequent changes developing over the lifespan.

Depression is sometimes seen as a 'purely mental' disorder, whereas the body, at least superficially, 'appears to be fine.' Even when somatic conditions such as hypertension, early coronary artery disease, or other subclinical metabolic abnormalities are present, the clinical focus typically remains on the mental component.

The view that depression is part of a brain–body macro-state is supported by many observations. Not only is clinical depression often associated with cardiovascular diseases, but, even in the absence of clinically diagnosed cardiovascular diseases, subclinical cardiovascular changes are

common [98]. Individuals with depression often have reduced resting heart rate variability (even in children and adolescents) [99,100] and may display subclinical blood pressure elevations and subclinical atherosclerosis [101]. The clinical efficacy of vagal nerve stimulation, a recognized therapy for drug-resistant depression, further underscores this connection. Several studies also suggest that HRV biofeedback reduces symptoms of depression [102], although some authors suggest that low HRV may predispose individuals to depression rather than directly reflecting its presence [103]. Interestingly, transcranial magnetic stimulation over the dorsolateral prefrontal cortex, an effective treatment of depression, may engage a frontal-vagal network, as indicated by heart rate deceleration, supporting the 'frontal-vagal network theory' of major depressive disorder [104], which fits well with the concept of a brain–body macro-state. In addition, the finding of a disturbance of interoception or interoceptive awareness [105] in depression and other mental health disorders [105–107] may also provide a pathophysiological explanation for the link between mental and cardiovascular symptoms (see following section).

Two additional examples of 'cardiological diseases' that may be better understood as conditions with altered brain–body states are atrial fibrillation and takotsubo cardiomyopathy, as discussed in more detail in Box 1.

Brain–body states and Bayesian frameworks of interoception

An overarching question concerns the underlying 'rules' for the formation of brain–body states. Bayesian frameworks of 'interoceptive inference' formalize how the brain integrates internal bodily signals (interoception) with external sensory inputs (exteroception) to maintain homeostasis and guide behavior in health [7,108–111] and pathology [106,107]. It posits that the brain uses generative models of the internal and external environment to predict sensory inputs. Predictions act as priors, whereas incoming sensory signals generate prediction errors (likelihoods) used to update these models. This process allows continuous bidirectional communication between

Box 1. From altered brain body macro-state to 'cardiological disease'

Two clinical entities – atrial fibrillation and takotsubo cardiomyopathy – traditionally viewed as cardiological diseases may be better understood as conditions with altered brain–body states that emerge even before the occurrence of the disease. This perspective, discussed in more detail below, bears relevance for prevention.

Atrial fibrillation is a cardiac arrhythmia affecting approximately 60 million patients worldwide. It is classically thought of as a cardiac disease, with risk factors such as hypertension and being overweight [114]. There has been some indication that atrial fibrillation may be related to an altered heart–brain interaction as indexed by a reduced heart evoked potential [115]. A recent study using a Mendelian randomization approach was able to show that decreased functional connectivity in brain areas such as the angular gyrus, precuneus, cingulate gyrus, and parietal lobe was associated with increased risk of developing atrial fibrillation [116]. Because these are key areas for autonomic regulation and stress response, these findings can be interpreted as an altered neurocardiovascular brain–body macro-state that might lead to repetitive dysregulation of short-term heart–brain interactions (short term brain–body states) and as a consequence to the development of atrial fibrillation. Predictive biomarkers (heart evoked potential, brain connectivity) might be derived from these findings, with potential relevance for preventive measures.

Takotsubo cardiomyopathy is classically thought to be caused by an acute stressful situation that leads to an acute cardiomyopathy (see also the main text). It is well-documented that takotsubo cardiomyopathy preferentially affects postmenopausal women. As reported in a recent review [117] people who develop takotsubo cardiomyopathy seem to be characterized by an altered reaction to stress. In the authors' meta-analysis of studies in which a stressor (e.g., cold pressor test) was applied during clinical testing, they found that, compared with control subjects, patients with takotsubo cardiomyopathy had significantly elevated plasma norepinephrine levels after the stressor, whereas baseline levels were essentially unchanged. At the same time, this was accompanied by a significantly smaller increase of left ventricular ejection fraction in the patient group, which, in some studies, even fell below the baseline level. In other words, these patients seem to have a different inner working of the neural–cardiovascular relationship (i.e., the brain–body macro-state) going along with an alteration of the stress response (meso-state), which – in the case of severe acute stress – induced damage to the heart. The clinical consequence could be that perturbing and measuring the neurocardiovascular coupling (e.g., with a cold pressor test) could serve as a future biomarker for prediction and possible prevention.

hierarchical control loops, enabling both bottom-up (i.e., sensory-driven) updates and top-down (i.e., model-driven) modulation. In this framework, sensory inputs can come from the internal body (e.g., via baroreceptors), emphasizing its role in autonomic regulation, emotion, and selfhood [108–111]. Conversely, brain–body states underlying mental phenomena, such as emotions, can modulate predictions at lower levels, creating a looplike continuous interplay between mental functions and physiology. Importantly, these relatively short-term interplays can be further modulated and constrained by macro-states. These mechanisms connect peripheral physiology (e.g., baroreceptors), autonomic PNS components, and regions in the brainstem and the cerebrum (e.g., insula [112]), as illustrated by the cogwheel type of interaction in Figure 1. Thus, interoceptive signals co-occur with the formation of feelings and influence other mental phenomena such as decision-making at 'higher' hierarchical levels ('bottom-up'), whereas mental phenomena can modulate predictions that influence loops at 'lower' hierarchical levels in the body ('top-down'). Using Bayesian modeling, it was found that precision estimates assigned to cardiac signals were not adjusted to perturbations in several mental health disorders, such as depression and anxiety disorders [106,107], indicating disturbed central 'interpretation' of visceral (bodily) signals. Given the close relationship between interoception, emotions, and well-being, not only might this disturbance contribute to the pathophysiology of mental disorders, but also disturbed processing of visceral signals likely leads to inappropriate feedback to the periphery and hence contributes to the codevelopment of cardiovascular disease.

Similarly, the well-established finding that inflammation can affect both cardiovascular and mental health [113] might be explained by impaired cardiovascular interoception caused by inflammation-induced endothelial dysfunction and reduced vascular reactivity.

Concluding remarks

We propose that integrated brain–body states evolving over multiple timescales (micro-, meso-, and macro-levels) underlie the tight links between cardiovascular function and mental processes from subsecond to yearslong timescales. This concept applies to healthy physiology across the lifespan but also provides an explanation of the co-occurrence between cardiovascular diseases and mental health disorders. Of note, in the proposed framework, no additional assumptions are necessary regarding the directional causations or common causes for the two types of diseases. Future work (see Outstanding questions) should address the computational and molecular mechanisms of brain–body interactions at micro-, meso- and macro-levels; identify clinically relevant transition thresholds; include other physical dimensions (e.g., respiration, gastrointestinal and immunological processes); and leverage emerging digital technologies as potential biomarkers.

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Declaration of interests

The authors declare no competing interests in relation to this work.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process

During the preparation of this work the authors occasionally used DeepL and Perplexity to proofread sentences in English. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Outstanding questions

Micro-, meso-, and macro-level brain–body states are superimposed and interact with each other. What are the computational, molecular, and cellular bases of these interactions?

Meso-states, such as the menstrual cycle or stress, which are typically reversible, can sometimes lead to entrenched structural plasticity (e.g., in takotsubo cardiomyopathy or post-traumatic stress disorder). Can we identify tipping points for these structural changes to develop preventive biomarkers and treatments for them?

Macro-states can be characterized by diseases such as depression and hypertension, which currently are mainly defined in the mental (depression) and cardiovascular (hypertension) domains. To gain a more comprehensive clinical insight, can we design diagnostic criteria that address all aspects of the underlying brain–body states?

This article covers the neurocardiovascular dimensions of brain–body states. What is the impact of other physical dimensions (e.g., respiratory, gastrointestinal, immunological activity) and other domains? Future work should integrate additional bodily dimensions (and eventually all of them) as well as the domains of social interactions and the environment.

Digital technologies are transforming peoples' lives. Wearables, prosthetics, brain–computer interfaces, neurofeedback devices, and immersive virtual reality are increasingly used in medicine as well as in daily life. Can these technologies be used to assess the full range of brain–body states to derive biomarkers of macro-states that predispose to diseases?

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