The self in context: brain systems linking mental and physical health

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Abstract | Increasing evidence suggests that mental health and physical health are linked by neural systems that jointly regulate somatic physiology and high-level cognition. Key systems include the ventromedial prefrontal cortex and the related default-mode network. These systems help to construct models of the 'self-in-context', compressing information across time and sensory modalities into conceptions of the underlying causes of experience. Self-in-context models endow events with personal meaning and allow predictive control over behaviour and peripheral physiology, including autonomic, neuroendocrine and immune function. They guide learning from experience and the formation of narratives about the self and one's world. Disorders of mental and physical health, especially those with high co-occurrence and convergent alterations in the functionality of the ventromedial prefrontal cortex and the default-mode network, could benefit from interventions focused on understanding and shaping mindsets and beliefs about the self, illness and treatment.

Historically, health was considered a matter of balance among interacting forces. Diagnosing and treating disease required an understanding of the whole person — including dietary habits, activities and personality. Today, however, mental health and physical health are viewed by many as separate, unconnected domains. Although integrative medicine and biopsychosocial models of health[1] emphasize interconnections between mind, body, behaviour, social context and health, they still represent a minority view in the face of Western clinical practice and health care policy. Physical diseases are typically viewed as resulting from many discrete forms of pathology with mechanisms that must be individually uncovered, studied and remedied[2]. Modern approaches to mental disorders have followed a similar blueprint, fractionating clinical science, practice and policy. Although this approach has been extremely successful in some areas (for example, promoting the development of vaccines and antibiotics), other areas have enjoyed little progress in treatment development — for example, psychiatric disorders, sleep disorders, obesity and chronic pain[3].

In this Perspective, we suggest that these latter disorders may share something in common: changes in the function of brain systems that govern how we conceptualize ourselves and our relationship to the world. Building on other recent theoretical developments[4–11], we propose that individuals construct mental representations of the 'self-in-context': models of the situations in which we find ourselves and their implications for our current and future well-being (FIG. 1). Such models extend recent concepts of 'task states'[7,12] or 'cognitive maps'[6,13,14] to incorporate personal well-being and brain–body feedback loops, consistent with other emerging views that emphasize the predictive and regulatory role of conceptual representations[4,5]. Self-in-context models allow individuals to assign personal meaning to events and integrate them into long-term narratives about who they are. When these models bear on the self — on one's current and future well-being — they become affective, driving motivated behaviour and physiological responses in the body in ways that are jointly relevant for mental and physical health.

We suggest that the default-mode network (DMN; a large-scale network of interacting brain regions that is central to internal and conceptual thought[15,16]), and particularly the ventromedial prefrontal cortex (vmPFC) and other key multimodal processing hubs within it[17], play a crucial part in generating conceptual mental models of the self-in-context. At the same time, the vmPFC (alongside other frontal regions[4,5,18,19] and in interaction with other systems, such as the mesolimbic dopamine system[20]) also mediates psychological influences on behaviour and on the body's organs[18,21], shaping autonomic and neuroendocrine responses[19], inflammation and other aspects of immunity[19,22–24]. By linking conceptual models of the self-in-context and the regulation of behaviour and peripheral physiology, the vmPFC is positioned as a key mediator of both mental health and physical health (FIG. 1).

According to this view, maladaptive models of self-in-context and erroneous attributions of causality are common factors underlying multiple forms of psychopathology. This may help explain the ubiquity of alterations in the vmPFC and DMN in psychopathology[25], substance use disorders[26], neurological disorders such as dementia[27] and chronic pain[28]. Alterations in self-in-context representations and meaning-making are likely to take different forms in different disorders and individuals, posing challenges for measurement and diagnostic models. However, on the bright side, self-in-context representations can be influenced by psychological treatment, social interactions and culture. Indeed, if conceptual processes — the links we forge among different events and concepts — can adapt to provide flexible control in changing contexts, they should be able to change rapidly with new information, if one is open to receiving it. This malleability provides new impetus for building on and improving psychosocial treatments for both mental health and physical health.

Common influences on health

Converging lines of evidence suggest that shared mechanisms may influence psychiatric and physical diseases. There is a growing awareness of high co-occurrence across mental and physical health disorders[2,29,30] and potential common transdiagnostic genetic risk factors[31,32] and

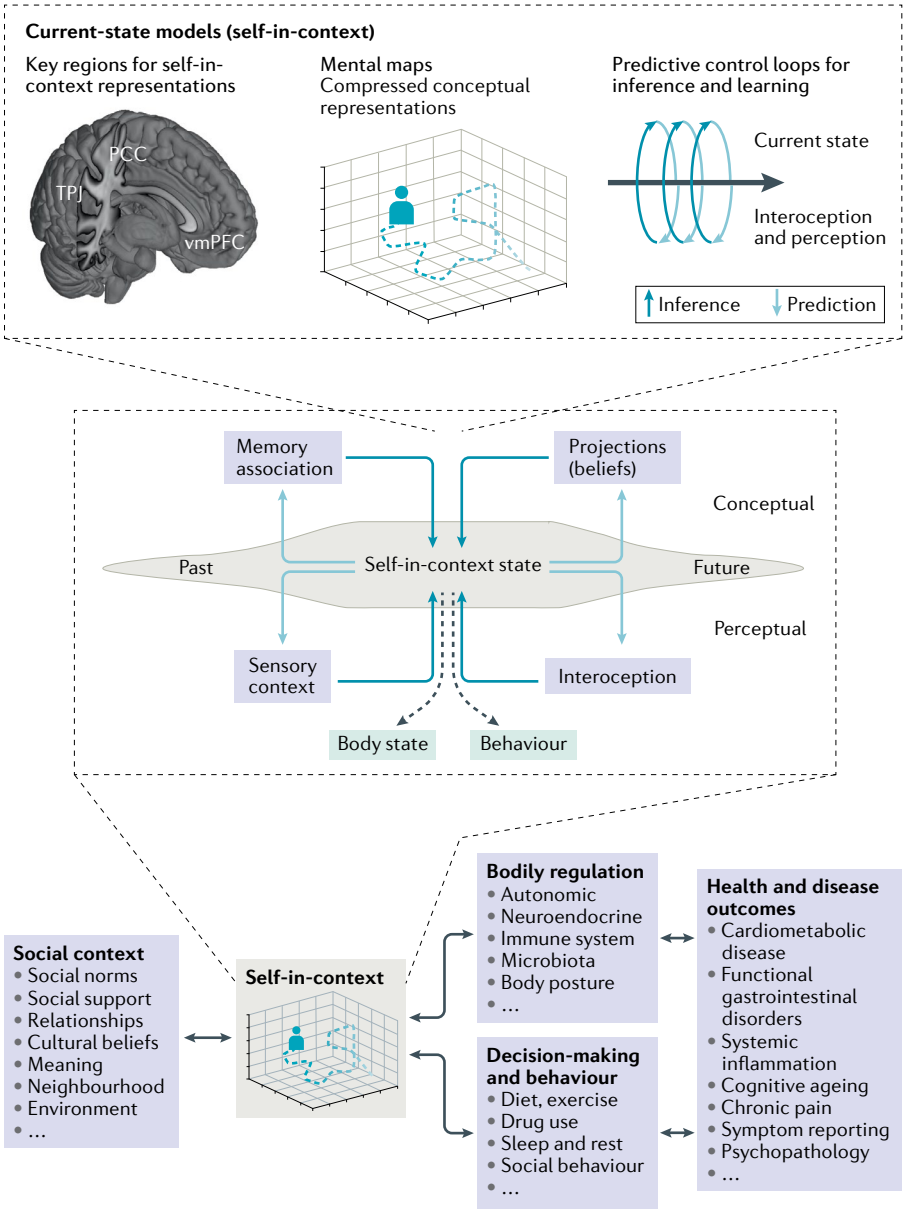


Fig. 1 | **A schematic of self-in-context models and their role in health and disease.** The ventromedial prefrontal cortex (vmPFC), together with other key regions of the default-mode network, such as the temporoparietal junction (TPJ) and posterior cingulate cortex (PCC), locates the current position of the self in a compressed low-dimensional space that captures the essential features of a situation. Locating the current state of the self on a mental or conceptual map is central to the process of 'meaning-making'. 'Self-in-context' models are inference-based models of the current state that predict sensory and interoceptive input and guide behaviour and physiological regulation on the basis of predictive codes. They also shape and are shaped by beliefs, associative memory and learning. Self-in-context models are influenced by the social and environmental context of the agent, including but not limited to social norms, relationships, cultural beliefs and neighbourhood characteristics. In turn they can regulate visceral outflow via vmPFC projections to the hypothalamus and the brainstem. Self-in-context models also influence decision-making and health-relevant behaviour (for example, dietary choices and how one works and connects with others) via vmPFC connections with the basal ganglia and the mesolimbic reward circuit or frontostriatal loops[20]. Together, the dual pathways — influences on bodily physiology and decision-making — can exert long-term effects on mental and bodily health in multiple ways, such as via their effects on inflammation and allostasis, or their interactions with other health-relevant systems, such as microbiota (for example, via dietary patterns). For instance, maladaptive thought patterns and self-in-context models may lead to a dysregulation of the autonomic nervous system, which leads to allostatic load and diminished recovery, with long-term effects on bodily organs. At the same time, self-in-context models may lead to changes in health-related behaviour such as unhealthy food choices, drug use or insufficient exercise, which also impact health in the short term and the long term.

disease mechanisms[33,34]. For example, some estimate that more than 50% of individuals who qualify for one mental health diagnosis qualify for at least one other, and 50% of those who qualify for two diagnoses qualify for three[35]. Accordingly, several large-scale analyses have pointed to the possibility that a common factor might underlie multiple types of psychopathology[29,30]. Many psychiatric disorders, especially depression, are also highly co-morbid with various somatic health problems, including chronic pain[36] and cardiovascular disease[37], with evidence for bidirectional causality (TABLE 1). In addition, shared risk is driven partly by shared genetic risk factors, which have also been associated with measures of negative affective style (such as neuroticism)[31,32]. A common thread is vulnerability to negative interpretations of life events, negative conceptions of the future and persistent ensuing negative emotion.

Many disorders also share common physiological risk factors. Increased sympathetic drive and reduced parasympathetic autonomic drive[38,39] are features of acute and chronic psychosocial stress[40,41]. This pattern of altered autonomic function is a feature of multiple psychiatric conditions, including depression, post-traumatic stress disorder, anxiety and addiction[42,43]. Autonomic and neuroendocrine outflow influence systemic inflammation, which is a risk factor for multiple diseases and symptoms[34,44]. Systemic increases in the levels of several proinflammatory cytokines — such as interleukin-1β (IL-1β), IL-6 and TNF — have been associated with depression[45], type 2 diabetes[46], coronary heart disease[47] and chronic pain[48]. In some cases, blocking the actions of peripheral proinflammatory cytokines can reduce depression[49]. Recent work has identified common patterns of inflammatory gene expression across 11 rodent models of diseases (including models of diabetes, asthma, obesity and neuropathic pain)[34], and identified consistent gene expression alterations that occur in humans in response to adverse environments[50].

A key integrative concept is Cole's conserved transcriptional response to adversity, a patterned, proinflammatory shift in gene expression in blood leukocytes that may confer resistance to infection and promote rapid energy mobilization in adverse environments[51]. However, in the long term, this shift can confer vulnerability by diminishing the capacity of negative-feedback systems that regulate inflammation (for example, glucocorticoid resistance[52]). These changes seem to be

Table 1 | **Associations among psychosocial factors, physiology and health outcomes**

Psychological and social factors	Physiological correlates	Health outcomes	Refs[a]
Anger, hostility	↑ Adrenaline and noradrenaline ↑ Cardiovascular stress reactivity ↑ Systemic inflammation ↑ ACTH and CORT ↓ Parasympathetic cardiac control	↑ Risk of CHD events in non-patients ↓ Prognosis in patients with CHD ↑ Risk of future stroke in non-patients	211–215
Depression	↑ Adrenaline and noradrenaline ↑ Systemic inflammation ↑ ACTH and CORT ↓ Parasympathetic cardiac control	↑ CHD mortality in patients with unipolar and bipolar depression ↓ Prognosis among patients with CHD ↑ Risk of CHD events in non-patients ↑ Cancer progression ↓ Survival in patients with cancer ↑ Risk of death in diabetes ↑ Risk of diabetes in non-patients	208,216–219
Anxiety	↑ Systemic inflammation ↓ Parasympathetic cardiac control	↑ CHD mortality in patients with anxiety disorders ↑ Risk of CHD events in non-patients	213,220–223
Chronic stress	↑ ACTH and CORT in early phase ↓ ACTH and CORT in later phase ↓ Immune function ↑ Systemic inflammation ↑ Glucocorticoid resistance	↑ Risk of CHD events and CHD-related death in non-patients ↓ Survival in patients with cancer	224–226
Positive emotionality	↓ CORT ↓ Inflammatory responses to psychological stressors	↓ Risk of death ↓ Risk of CHD-related death in non-patients ↓ Risk of death in patients with renal failure and HIV ↓ Risk of stroke ↓ Susceptibility to rhinovirus and influenza	227–230
Social support	↓ Cardiovascular stress reactivity ↓ HPA axis stress reactivity ↓ Systemic inflammation	↑ Survival after CHD event ↓ Risk of death ↓ Risk of CHD events ↑ Survival in patients with cancer ↓ Risk of cognitive decline	231–233
Social integration	↓ Systemic inflammation	↓ Risk of death ↓ Risk of future CHD events and CHD-related death in non-patients ↓ Risk of dementia and cognitive decline ↓ Risk of stroke ↓ Risk of developing respiratory infections ↑ Survival in patients with cancer	234–239
Acute stress reactivity	↑ Adrenaline and noradrenaline ↑ HPA axis stress reactivity ↑ Cardiac contractility ↓ Parasympathetic cardiac control ↑ Blood pressure ↑ Heart rate ↑ Ventricular dysfunction ↑ Systemic inflammation	↑ Risk of CHD events and CHD-related death in patients and non-patients ↑ Risk of hypertension	59,240–243

ACTH, adrenocorticotropic hormone; CHD, coronary heart disease; CORT, cortisol; HIV, human immunodeficiency virus; HPA, hypothalamic–pituitary–adrenal.
[a]A general note on the advantages of prospective studies (such as those referenced here) is provided in Supplementary information S2.

governed by descending sympathetic nervous system efferents[53], and recent rodent studies support this notion. Stimulation of the ventral tegmental area, a major source of brain dopamine, reduces inflammation, boosts innate and adaptive immunity in response to a bacterial infection[54] and slows tumour growth in a metastatic melanoma model[24] via sympathetic nervous system

innervation of bone marrow, a central site for leukocyte production[24,54].

Autonomic and inflammatory pathways are sensitive to conceptualization and mental models of events — that is, inferred personal meanings, credited hidden causes and imagined potential futures. Psychosocial stressors, such as a fight with a family member or giving a speech before a panel of critical judges[55], acutely increase levels of systemic inflammatory markers[56] and cardiovascular risk markers[57]. Indeed, psychosocial stressors increase the risk of developing cardiac disease[58]. In patients with coronary artery disease, psychosocial stress can cause cardiac ischaemia, which prospectively predicts mortality 5 years later[59]. The conserved transcriptional response to adversity is also enhanced with social isolation in animals and perceived isolation (loneliness) in humans, and responds to psychological interventions (reviewed in[51,52]).

Persistent psychosocial stress is one example of a transdiagnostic risk factor with effects that depend on how one conceives of oneself and one's relationship with the world. Psychosocial stressors begin as conceptual threats, not physical ones. They depend entirely on our ability to represent, for example, another person's displeasure with us and to imagine that this is a dire signal of future failure in love and work. Such conceptualizations are defining features of other transdiagnostic risk and resilience factors, including depressed mood, anxiety, persistent anger and hostility, loneliness, and positive emotion (TABLE 1). Conceptualizations can be spread through words and culture, and may constitute socially communicable risk factors that enhance resilience or disease susceptibility. For example, loneliness is a feeling supported by a set of beliefs (for example, "I am unlovable" or "I will always be alone"). As with other beliefs, loneliness can spread through social networks to negatively influence health outcomes[60].

Finally, a common set of psychosocial treatment principles are effective for multiple mental and physical conditions. Across disorders, symptoms and dysfunction can be ameliorated by activities and events that enhance purpose, self-efficacy (the perceived capacity to deal with novel or challenging situations appropriately), feelings of connection to others, social engagement and positive treatment expectancies[57]. These 'common factors' are thought to mediate most of the benefit of psychotherapy, irrespective of the particular type of treatment and psychopathology[61]. In both mental health conditions and physical health conditions, studies of placebo effects show that the act of receiving treatment in itself — along with the cognitive changes that accompany it — can confer benefits in both short-term experimental studies and long-term clinical studies across multiple disorders[62–65]. Placebo treatments can have clinically meaningful effects on pain and other disorders, including Parkinson disease, depression, anxiety and sleep disorders[62,63,66]. The benefits of non-specific treatment factors are not limited to formal clinical treatments: changing beliefs and mindsets in everyday life can also have beneficial consequences for health outcomes[67].

Mental models of self-in-context

Most organisms can predict and learn about environmental threats and opportunities. Learning has often been assumed to be based on simple associations between cues or actions and rewards or punishments. However, humans (and probably other mammals[68]) can form abstract, multimodal representations of the underlying contexts, or 'situations,' that cause events to occur (FIG. 1). Such 'situation representations' are conceptual, and are closely related, although not identical, to the heuristic notions of schemas or mindsets[69]. They are mental models of both sensory information and action–outcome contingencies, organized around recurring causal structures (for example, 'betrayed by a friend' or 'alone in a dangerous place'). Situation representations have several core properties. They integrate across sensory modalities and timescales, enabling context-dependent behaviour and generalization to new, similar scenarios[7,70,71]. The specific sensory cues in a given environment are less important to the construction of situation representations than are the conceptions of the latent causes — intentions, motives and hidden processes — behind actions and events. Thus, situation representations are essentially compressive, reducing complex sets of sensory cues to low-dimensional characterizations. Their formation and use is often automatic and effortless, forming the backdrop of our everyday cognition — but they can also be responsive to deliberation, conferring flexibility based on diverse cognitive and sensory inputs. Such internal models have an adaptive function: they extract causal structure from a complex jungle of sensory and interoceptive signals[7,72], distilling what is crucial to predict future events and guide anticipatory action.

Here we are concerned with schemas that involve the self. Self-in-context representations connect states — features and action–outcome contingencies relevant for decisions — to signals of current pleasure and pain. However, they are also multitemporal, extending representations of bodily and social well-being into the past and future (FIG. 1). For example, the situation 'stock market crash, lost my life savings' can increase one's blood pressure because it is tied to one's conception of long-term future well-being. The more relevant for the well-being of the self, the more affectively charged the event, and the more strongly the body responds by mobilizing cognitive and metabolic resources for action. Self-in-context models thus represent information along dimensions that are relevant for the self, imbuing sensory features and potential actions with personal meaning.

Self-in-context representations confer a crucial evolutionary advantage over simple associations. They allow prediction of future outcomes from latent causes (for example, another person's hidden intentions) inferred from the integration of sensory and interoceptive signals with prior conceptual knowledge[11,73]. Such predictions can arise from minimal input (such as a single word), can rapidly shift predictions when important relationships change and can generalize to similar situations with very different physical cues. Models can include representations of one's perceived status and coping resources[74]. For example, one's response to being pushed will probably be different if the push was accidental, or if the pusher is a small child. Mental models can also integrate across timescales, combining events that happened seconds ago with those that happened years earlier, permitting reinterpretation of past events in light of new evidence.

The idea of self-in-context models builds on recent work on decision-making, in which simple situation representations were modelled using partially observable Markov decision processes[12]. These models encapsulate the idea that an organism infers its underlying state (a set of causal contingencies) from sensory cues but cannot directly observe the underlying causal structure. Cognitive maps — sets of conceptual relationships between objects and events based on their positions in an underlying dimensional space — describe the inferred transitions among underlying states[6,12]. Markov models capture transitions among discrete task states over time; but at a cognitive level, situation representations are not constrained to the present, and exist as sets of causal contingencies untethered from any particular moment in time.

The predictive control afforded by self-in-context representations may influence perception as well as action, including perception of exteroceptive signals from the environment and interoceptive signals from within the body[11,73,75–77]. According to theories of predictive coding, sensory input is compared with 'top-down' predictions generated by an internal model (exemplified by self-in-context representations). Sensory systems pass forward only differences from expectation, not all sensory input, which serve to update the model (that is, learning). Perception is thus an inference based on both sensory input and prediction-generating situation conceptions (FIG. 1). This view emphasizes perception as a constructive process: we perceive what we should perceive in order to optimize perception and behaviour in noisy or uncertain conditions[9]. Predictive coding has been proposed as a general principle of information processing in the brain[9,11,73,75], whereby higher levels of a processing hierarchy are sources of top-down information, often represented in Bayesian models as formal priors (probability distributions of the likelihood of an event). It has recently been applied to understanding pain[78], interoception[4,5,8], physiological regulation and reactivity to stress[79], depression[77], social cognition and interpersonal behaviour[80,81], among other phenomena. Although prediction–inference feedback loops may be a general feature of computational systems, including artificial neural networks, self-in-context representations incorporating the future well-being of the self require specific types of information integration; we suggest below that they are implemented in particular brain systems.

In sum, self-in-context representations are internal models of situations and underlying causal structures that bear on our future survival and well-being. They integrate perceptual information across exteroceptive and interoceptive senses with conceptual information from memory and prospective faculties into a low-dimensional representation that jointly influences sensory perception and behaviour (FIG. 1). Self-in-context representations are: generative, in that they allow one to simulate the consequences of potential actions; interpretive, as they allow one to understand incoming sensory signals as clues to one's current state; attributive, as sensory events are assigned to latent causes; instructive, as causal attributions shape what is learned from experience; and predictive, in that they predict what one will experience in a given situation. Finally, because they are tied to well-being, such representations can become affectively 'hot' and have a special ability to mobilize physiological (for example, autonomic, endocrine or metabolic) systems.

Self-in-context in the brain

Constructing and acting on mental models necessitates a brain substrate that integrates and flexibly updates many different cognitive, affective and physiological processes. We suggest that the construction of mental models that integrate self and environment is an emergent process enabled by brain systems centred on the vmPFC (FIG. 2), in connection with other DMN regions and other brain networks[5,11].

The vmPFC is a cortical zone that spans multiple cytoarchitectonic regions (FIG. 2a,b) and that is anatomically and functionally positioned to integrate conceptual thought with peripheral physiology. Presumed vmPFC homologues in rodents include the infralimbic and paralimbic cortex (Supplementary information S1), but the mapping with functional zones in primates is complex[82], and some functional roles may differ between species[83]. The vmPFC receives few direct sensory inputs. However, it has strong bidirectional links with sensory-integration regions in the lateral orbitofrontal cortex (OFC) and mediodorsal thalamus; interoceptive regions in the insula; motivational and reward-processing circuits, including the amygdala, hypothalamus and ventral striatum (including the nucleus accumbens; FIG. 2f)[20]: and circuits involved in memory and context, including the perirhinal cortex and hippocampus[84]. Strong descending projections from the vmPFC to autonomic and neuroendocrine control regions in the hypothalamus and brainstem, including the periaqueductal grey (PAG) and dorsal raphe[85] (FIG. 2d), enable the vmPFC to regulate visceromotor output[18,22].

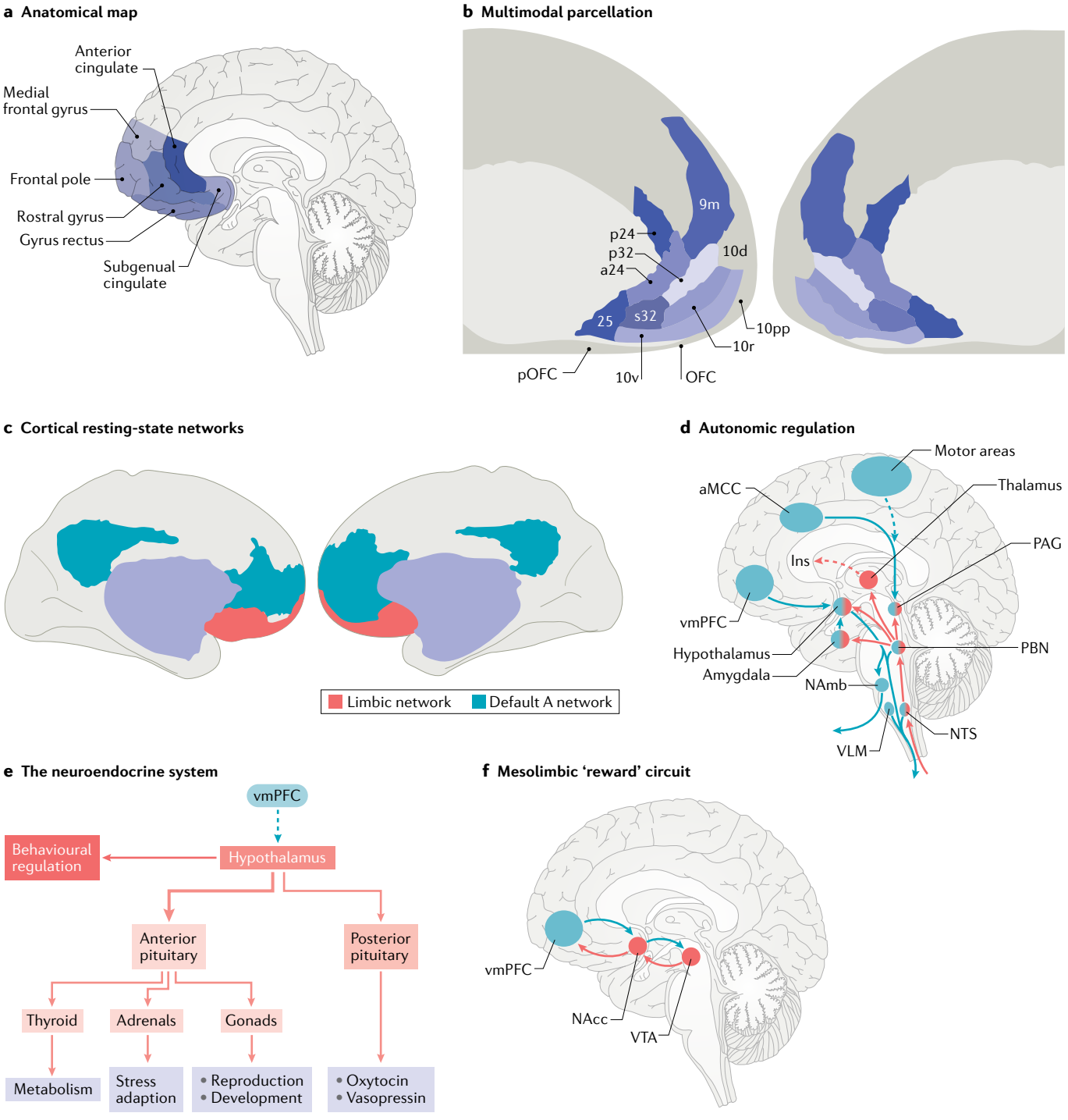
The vmPFC participates in multiple cortical networks that have been identified in resting-state functional MRI studies (FIG. 2c). The ventral vmPFC (or medial OFC) is part of the so-called limbic network[86] and is functionally coupled with the medial and anterior temporal lobes. In humans and other species, this network mediates stress-related autonomic and immune output[87]. The dorsal vmPFC is a core part of the DMN[86,88,89], and is coupled with the posterior cingulate cortex, precuneus and temporoparietal junction[90]. Both the dorsal vmPFC and the ventral vmPFC are connected to the lateral OFC, and some neuroanatomists have referred to the combined vmPFC–OFC network as the OMPFC[22]. Although the vmPFC and the OFC are functionally dissociable[91], lesions in rodents and primates often ablate these regions together, and many functions attributed to the OFC may be shared with the vmPFC as well.

The DMN and the vmPFC exhibit many of the hallmarks of rapid, flexible and integrative processes described above. Connectomics studies identify the DMN as an integrative hub network that sits at the top of a hierarchy combining multiple sensorimotor, unimodal processing and internal, multimodal processing[92,93]. The vmPFC in particular is crucial for regulating physiology and behaviour, putting it in a special position at the interface between conceptual thought, decision-making and bodily regulation (FIG. 3).

Conceptual thought

The DMN was named for its high metabolic activity during rest[94] and is central to self-generated spontaneous thought[95] and (in connection with the lateral prefrontal cortex) goal-directed thought[90,96].
In humans, the vmPFC in particular is activated during the retrieval of episodic (especially autobiographical) memories[97,98] and semantic memory[99]. It is crucial for prospection (imagining future events)[100,101]; vmPFC damage impairs people's ability to imagine the future in rich detail[102]. Activation patterns in the vmPFC and other core DMN regions are stable across film or story segments with coherent narrative themes[103], integrating past information[104] into representations of narrative meaning[105]. Activation patterns in the vmPFC, like conceptual understanding, can also shift suddenly when new information allows insight[106].

A key basic ability underlying conceptual thought is relational representation. For example, semantic memory is grounded in an interconnected web of concepts embedded in semantic space[107]. The vmPFC is robustly activated during semantic memory retrieval[99]. Along with the hippocampus, it also encodes position in other relational structures, including physical space, with functional MRI signal tracking activity in a hexagonal 'grid cell'-like pattern[108]. Grid cells are thought to help represent relationships among discrete locations (or object features) in a low-dimensional space — effectively, a compressed model that enables the representation of positional similarity and generalization[6]. Recent studies have found grid cell-like patterns of activity in the vmPFC that code information in conceptual



space as well, for example when retrieving relationships among newly learned object categories[14,109]. Thus, the vmPFC may facilitate the formation of cognitive maps[6] that represent the position of objects, persons and situations in a relational space[110] (BOX 1).

At a computational level, the vmPFC and the OFC enable the representation of latent states: hidden environmental states that determine outcomes (such as safety or harm) and guide value-based decision-making and learning. The simplest stimulus–response associations can be learned and expressed without the prefrontal cortex, but most natural environments require inferences about what the relevant states of the environment are and which sensory signals indicate them[7,72]. The OFC is crucial for learning in these situations, when states are "perceptually similar but conceptually dissimilar"[7,72], or when the cues that indicate a state are only partially observable[111]. Indeed, the very ability to form an expectation of a specific future outcome (for example, "if I press, I will get juice") seems to require the vmPFC and/or the OFC[68,112].

Another example of conceptually driven relations is counterfactual learning or fictive learning tasks, in which the reward value of an action depends on what might have been had one chosen differently. In such tasks, vmPFC activity is a strong correlate of regret[113], and counterfactual emotions such as regret are reduced in individuals with vmPFC lesions[114].

◀ Fig. 2 | **Anatomy and functional connectivity of the ventromedial prefrontal cortex. a** | The anatomy of the ventromedial prefrontal cortex (vmPFC) includes the ventral anterior cingulate cortex and the subgenual cingulate cortex, the gyrus rectus, the medial parts of the rostral gyrus and frontal pole, and inferior parts of the superior or medial frontal gyrus. **b** | Multimodal parcellation of the vmPFC and adjacent areas, based on an established whole-brain parcellation[244], illustrating the heterogeneity of the vmPFC in terms of anatomical features and functional co-activation patterns. **c** | Cortical resting-state networks. Most of the vmPFC is part of the default-mode network (DMN), especially the default A network or core DMN (here based on the parcellation by Yeo et al.[86]), which serves as a hub between the medial temporal and dorsal subnetworks of the DMN[89]. The most ventral part of the vmPFC (that is, the rostral gyrus and parts of the subgenual anterior cingulate cortex) is part of the limbic network. **d** | Brain areas associated with autonomic regulation include the vmPFC and its connections with limbic and brainstem areas (simplified overview based on REFS[18,245,246]). Red denotes ascending tracts and blue denotes descending tracts. Autonomic regulation involves connections from areas of different large-scale networks, including limbic, default-mode, salience and somatomotor areas. More details are provided in Supplementary information S1. **e** | Via its close connections to the hypothalamus, the vmPFC can also influence the neuroendocrine system. **f** | Together with the ventral striatum–nucleus accumbens (NAcc) and the ventral tegmental area (VTA), the vmPFC is part of the mesolimbic reward circuit[20] (simplified here), which guides value-based decision-making and adaptive behaviour. 10d, dorsal part of area 10; 10pp, posterior polar part of area 10; 10r, rostral part of area 10; 10v, ventral part of area 10; 25, area 25; 9m, medial part of area 9; a24, anterior part of area 24; aMCC, anterior midcingulate cortex; Ins, insula; NAmb, nucleus ambiguus; NTS, nucleus tractus solitarius; OFC, orbitofrontal cortex; p24, posterior part of area 24; p32, pregenual area 32; PAG, periaqueductal grey; PBN, parabrachial nucleus; pOFC, posterior orbitofrontal cortex; s32, subgenual area 32; VLM, ventrolateral medulla. Part **b** adapted from REF.[244], Springer Nature Limited. Part **c** adapted with permission from REF.[86], American Physiological Society.

Self-referential thought and social cognition. The vmPFC is activated by self-referential processing across diverse task paradigms[115,116], including during processing of self-relevant words and personality traits[116], during interoceptive awareness[8,117] or when one is reflecting on one's feelings[118], self-ownership[119] and social position[120]. Structural connectivity between the vmPFC and the ventral striatum correlates with individual differences in self-esteem[121].

Thinking about others and their mental states (known as mentalizing) also activates the dorsomedial prefrontal cortex (dmPFC) and the vmPFC, along with other DMN regions[122,123]. Whereas the vmPFC is engaged by thinking about others who are close or similar to oneself[124,125], the dmPFC is more strongly engaged in impression formation and mentalizing about others[116]. When one is making a choice between immediate and delayed rewards, vmPFC activation tracks personal subjective value[126], whereas dmPFC activation tracks value on behalf of another person with dissimilar preferences[127]. But when decisions need to be made on another's behalf, the vmPFC encodes value for the other[127]. The vmPFC and interconnected regions also encode others' positions in a social network[128,129], and predict warm and empathetic responses to others in distress[130]. Conversely, vmPFC damage impairs affective perspective taking and empathy[131,132] and the ability to care about potential future harm to others and oneself[133]. Thus, the vmPFC seems to be important for both representing value for the self and representing others' feelings and preferences. A flexible frame of reference enables people to self-project — to "walk a mile in someone else's shoes" — a crucial ability for maintaining social relationships.

Value and affect. In connection with subcortical networks, the vmPFC is central to the representation of affective value[134–137] and the generation of both positive and negative emotions[138,139] across induction methods and emotion categories[11,140]. Across studies, it tracks the value and pleasantness of stimuli across different modalities, including money, food and social rewards[134,141]. On the aversive side, the vmPFC is thought to provide context signals that inhibit threat-related responses in the amygdala after threat extinction in humans, primates and rodents[142]. Its role is broad but selective: the vmPFC–OFC system does not seem to be necessary for basic behavioural and physiological responses to threats or rewards, for reward preferences or for behavioural inhibition per se[10]. However, it does seem to be necessary for the flexible use of context information to guide behaviour and physiology[143]. Several recent lines of work highlight the constructive and conceptual nature of valence. For example, when participants imagine meeting a person they like in a neutral place, the place becomes more liked[144]. This associative generalization is encoded by the vmPFC. Patterns of vmPFC activity also encode attitudes related to racial stereotypes[145], and vmPFC activity during the experience of pain tracks perceived racial discrimination and statistically mediates enhanced pain sensitivity in African Americans[146]. African Americans show stronger vmPFC responses to painful stimulation, and stronger responses are predictive of greater pain in African American individuals.

We suggest that value and valence are psychological descriptors of how self-in-context models operate. Self-in-context models compress data about the internal and external world into reduced-dimensional space. But which dimensions of the myriad possible ways of organizing experience should be represented? A useful simplified model must focus on those that are most central for the survival and well-being of the organism (see also[73]) and are therefore intrinsically linked to value or valence. We suggest that stronger relevance for bodily integrity and well-being is what makes a situation more affective and imbues it with positive or negative valence and other motivational properties (such as approach–avoidance motivation). According to this view, self-in-context models and the likelihood of well-being are updated on the basis of new events or information. The nature and magnitude of the update (that is, its derivative) determines the affective value ascribed to the event, and the possible paths to long-term well-being given the current model state determine mood, optimism and self-related affect[147,148].

The vmPFC and the DMN help construct this representation of the self in this low-dimensional space. This might explain the abundance of vmPFC–OFC neurons that encode both positively and negatively valenced signals[149] and the dysregulation of emotions and real-life behaviour after vmPFC damage[132]. Finally, a hallmark of affective valence and processing priority alike is the mobilization of physiological resources. As we outline next, the DMN — and the vmPFC in particular — is positioned to guide physiological responses and behavioural decisions based on self-in-context models.

Regulation of body and behaviour

The vmPFC and the DMN, directly and via connections with other networks[11] (BOX 1; FIG. 3) are positioned to influence mental and physical health through influences both on health-relevant decision-making and on autonomic and endocrine systems, which together confer vulnerability or resilience over time.

Health-related decision-making. In the biopsychosocial model of health, value-based decision-making — what to eat, what to avoid and when to exert effort — is

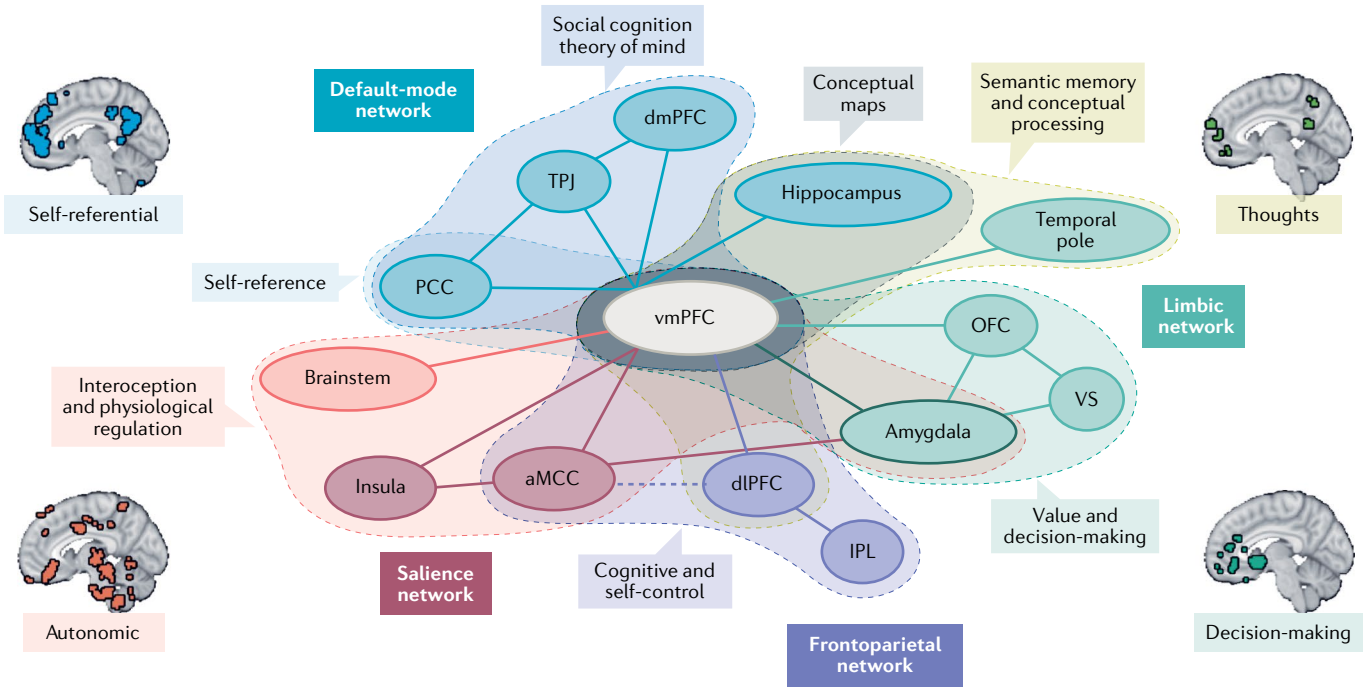


Fig. 3 | **Functional associations of ventromedial prefrontal cortex with connected brain networks.** The ventromedial prefrontal cortex (vmPFC) is closely connected to areas of the default-mode network. Together with other regions of the default-mode network, including the temporoparietal junction (TPJ), the dorsomedial prefrontal cortex (dmPFC), the hippocampus and the posterior cingulate cortex (PCC), it is involved in social cognition and self-referential thought. Both the hippocampus and the vmPFC show evidence for grid-like coding of spatial and conceptual maps, and together with other temporal and frontal areas are involved in semantic memory and conceptual processing more broadly. The most ventral part of the vmPFC is connected to the limbic network, including the orbitofrontal cortex (OFC), the ventral striatum (VS) and other subcortical areas. Together with the VS, the vmPFC is important for reward processing and decision-making. Therefore, it is amenable to interactions with the frontoparietal network, especially the dorsolateral prefrontal cortex (dlPFC) and the inferior parietal lobule (IPL), involved in executive function and self-control. Together with areas of the salience network (especially the anterior midcingulate cortex (aMCC) and the anterior insula) and subcortical regions, the vmPFC is involved in interoception and physiological regulation. Representative Neurosynth[247] term-based meta-analytic association maps (with a threshold at false discovery rate $q < 0.01$, reproducible and available for download from https://neurosynth.org) illustrate the role of the vmPFC with self-referential processing, conceptual thoughts, decision-making and autonomic regulation. See Supplementary information S3 for instructions and code to recreate the visualizations of the maps seen here.

paramount. The vmPFC and the OFC are particularly important when decisions are guided by context-dependent affective value, consistent with the idea of self-in-context representations. Lesions of vmPFC homologues in rodents and non-human primates do not affect basic reward preferences, reward learning, unconditioned threat responses or basic conditioned threat acquisition or extinction (for a review, see[10]). However, vmPFC and OFC lesions do affect behaviours that depend on the integration of situational (for example, place), social, temporal or interoceptive (for example, satiety-related) information into reward-guided or threat-guided behavioural decisions. For example, in rats, vmPFC lesions or inactivation do not affect threat learning or extinction but impair the ability to consolidate and use memories when a context changes from being threatening to being safe[150]. When shocks are escapable, a representation of perceived control (that is, an action–escape contingency) in the vmPFC suppresses threat-related responses in the dorsal raphe nucleus and associated threat behaviours[151]. Inactivation of the vmPFC suppresses the benefits of perceived control, and vmPFC stimulation confers similar benefits for behaviour even when shocks are inescapable[151]. Lesions of the vmPFC also disrupt other context-dependent appetitive behaviours, including selective satiety — a shift in food preferences when one has consumed enough of a particular food — and rapid shifts in choice behaviour when reward contingencies change[152,153]. In humans, lesions of the vmPFC do not generally disrupt basic value preferences but do disrupt the ability to generate behaviours and emotions appropriate to the situational and social context[154,155].

Accordingly, in human imaging studies, the vmPFC responds to manipulations of the social and informational context that shape reward-driven and threat-driven behaviour. In threat-learning studies, it responds during extinction recall[156], reversals of cue–shock contingencies from threat to safety[157] and manipulations that increase perceived control[142]. Suggestions that a placebo treatment is an effective analgesic activate the vmPFC and the OFC, increase vmPFC connectivity with the PAG[158] and promote opioid release in the vmPFC and the PAG[65]. In reward studies, the vmPFC responds to selective satiation signals that guide food choices[159] and influences of suggestion on value[135,160]. The vmPFC also responds to vicarious reward, experienced when rewards are given to similar others[161], and encodes information about social categories related to racial and sociocultural stereotypes[145,162].

The vmPFC is also prominently involved in cognitive self-regulation, a set of techniques for altering appraisals (conceptualizations of the meanings of situations and events in terms of their hidden causes and likely future trajectories), attributions and construals of affective meaning. Dietary self-control (the ability to regulate behaviour and impulses to achieve long-term goals) is positively correlated with functional activation[136,137] and grey matter density[163] in the vmPFC and the dorsolateral

prefrontal cortex (dlPFC). Focusing on the tastiness of food increases functional connectivity between the ventral striatum and the vmPFC, whereas focusing on health aspects of food increases connectivity between the dlPFC and the vmPFC[136,137]. Acute stress changes value signals in the vmPFC to favour high-calorie foods and increases vmPFC–ventral striatum connectivity[164]. Conversely, reframing appetitive smoking cues by thinking about the long-term consequences of smoking can reduce cigarette craving and vmPFC activity[165]. Another form of self-regulation is engaging in prospective thought and evoking positive memories, both of which can shift value-based choices towards long-term rather than immediate gains (that is, reduce delay discounting). Positive prospection also increases vmPFC activity[166,167]. By contrast, successful cognitive downregulation of negative emotion and pain is also mediated by activation of a pathway from the vmPFC to the nucleus accumbens[168,169]. An emerging view of self-regulation is that it involves selective reinforcement of certain ingredients of self-in-context models — for example, a focus on the future self, or the undesirable properties of cigarettes — that alter the way affective value is constructed.

The consequences of these context-guided and value-guided decisions can manifest themselves over time in the form of the long-term effects of health-related behaviours: how we sleep, eat, play, work and connect. For example, vmPFC responses to health-related messages (for example, to quit smoking) predict long-term attempts at behaviour change (such as calls to helplines[170]; reviewed in[171]).

Peripheral regulation. In addition to shaping behaviour, the vmPFC has a key role in controlling the autonomic and neuroendocrine systems, which shape the body's physiological health over time[19,172]. Chronic uncontrollable stressors result in 'wear and tear' on bodily systems that adversely affects health[173]. Whether we conceive of events as threatening and out of our control is particularly important[51,69,174–176]. Low socio-economic status, low perceived social standing, adverse childhood experiences and perceived racial discrimination constitute risk factors for poor mental health and reductions in longevity[177,178].

The vmPFC is part of a system that controls the autonomic nervous system via its efferent projections (FIGS 2d,3; Supplementary information S1) to structures in the hypothalamus, forebrain (such as the amygdala and nucleus accumbens) and brainstem (such as the PAG)[18,19,41,179]. The sympathetic and parasympathetic branches of the autonomic nervous system influence all of the body's organs, from the heart to the bone marrow (where many immune cells are produced). The vmPFC also governs hormone release via the hypothalamic–pituitary–adrenal axis and the sympathoadrenal medullary axis[18], which regulate stress responses and homeostatic adaptation; the hypothalamic–pituitary–thyroid axis, which regulates the body's metabolism; and the hypothalamic–pituitary–gonadal axis, which regulates developmental and reproductive functions (FIG. 2e). In turn, autonomic and hormonal responses influence the expression of systemic proinflammatory and anti-inflammatory cytokines and chemokines[172,180].

Activity of the vmPFC correlates with stress-evoked and task-evoked autonomic responses, including heart rate, heart rate variability, blood pressure and skin conductance[179,181]. In non-human animals, vmPFC–hypothalamus and vmPFC–PAG pathways seem to be topographically organized by behavioural functions that are related to the optimal response to strong threats (for example, 'avoid', 'escape', 'fight', 'flight', 'surrender' or 'defecate')[182,183].

The vmPFC also has a role in modulating levels of systemic inflammation[44,184]. A meta-analysis of human brain–immune correlations identified a network involving the medial prefrontal cortex, amygdala, ventral striatum, hippocampus, hypothalamus and pons[23], including areas of both the DMN and the limbic network. Brain correlates of immune markers were identified in both the dmPFC and the posterior (subgenual) vmPFC. The vmPFC was the region most strongly co-activated with the brainstem, and its activity correlated with inflammatory measures during emotion-induction tasks (rather than cognitive tasks) in particular. Thus, vmPFC–subcortical pathways may mediate inflammation driven by conceptualization of the self-in-context.

Box 1 | Beyond the ventromedial prefrontal cortex and default-mode network

Although our discussion focuses on the ventromedial prefrontal cortex (vmPFC), other interconnected regions of the default-mode network (DMN) and other brain networks are important for conceptual processing and probably contribute to self-in-context representations and bodily and behavioural regulation. The posterior cingulate cortex is often co-activated with the vmPFC, including in tasks such as social cognition, self-referential thought and mind-wandering[90]. Together with the vmPFC and the temporoparietal junction (TPJ), it may form a central brain system for appraisal and meaning-making[64]. The TPJ is implicated in conceptions of agency, others' intentions[248] and the bodily representation of the self[117], and may also be important for self-projection and mental representation of future events[249]. Thus, the TPJ may have an important role in shifting perspectives across time and social agents: processes that are important for flexible and adaptive self-in-context models.

The hippocampus is crucial for the formation of long-term memories and cognitive maps, and for spatial orientation[6,13,108]. Similarly to the vmPFC, the hippocampus and parahippocampal cortex have grid cell-like properties for representing conceptual relationships[14]. Although they may jointly contribute to constructing conceptual maps of the self-in-context, conceptual maps may also differ between areas. For example, the vmPFC may be especially important for self-referential conceptual maps that prioritize information relevant for bodily integrity and well-being — a particular type of egocentric map — whereas the hippocampus might preferentially encode information relevant for allostatic spatial and conceptual maps less directly involved in physiological regulation.

Networks beyond the DMN are also important for interoception and physiological regulation. The EPIC (embodied predictive interoception coding) model has been proposed to explain how intrinsic brain networks underlie allostasis, unifying interoception and visceromotor control[4]. This model proposes that agranular cortical regions (including the cingulate cortex and anterior insula) control visceromotor function via their connections to subcortical areas and, in parallel, send sensory prediction signals to granular cortical regions, especially primary interoceptive cortex[4]. Testing this model, a recent study found evidence for two large-scale networks around several key visceromotor regions, closely aligning with the DMN[15] and the salience[250] (or 'ventral attention'[86]) network, which together may form a unified brain system for allostasis[5].

One intriguing hypothesis is that the DMN and the salience network may underlie allostasis in two distinct but complementary ways, in line with the distinct dynamics of these two networks: DMN regions such as the vmPFC may predictively regulate body function and behaviour on the basis of conceptual information and self-in-context models, whereas the salience network may do so reactively, on the basis of the detection of salient events or new information that requires adjustments or switching of states. These and other hypotheses could be tested in future work.

Future outlook

A common factor

Alterations in the vmPFC and interconnected areas of the DMN have been implicated in multiple psychiatric

conditions, including major depressive disorder, anxiety, schizophrenia, attention deficit–hyperactivity disorder, post-traumatic stress disorder and substance-use disorders[25]. Pathology in this system may represent a common underlying factor across disorders[29,30], and may explain the high rate of co-occurrence of different disorders. Grey matter reductions in the DMN and the vmPFC in particular were among the features most consistently associated with psychopathology in a recent meta-analysis of transdiagnostic features in attention deficit–hyperactivity disorder, major depressive disorder, post-traumatic stress disorder, anxiety disorders, autism, bipolar disorder, obsessive–compulsive disorder and schizophrenia[185] (although the dlPFC is also important[186]). Resting-state hypoconnectivity in the ventral DMN and hyperconnectivity in the dorsal DMN was also a transdiagnostic feature, along with reductions in negative coupling between DMN and frontoparietal networks[185]. These brain features may extend to somatic disorders as well: Reductions in vmPFC grey matter are also consistently associated with chronic pain across studies[187], paralleling functional and structural changes in medial prefrontal cortex–nucleus accumbens circuits in rodent models of chronic pain[188].

Such alterations need not reflect only 'organic' changes in brain organization independent of cognition. Rather, they might reflect the cumulative effects of altered self-in-context models. For instance, depression and anxiety are associated with negatively biased beliefs regarding the self and/or its ability to cope with events. Chronic pain may be increased and maintained by perceiving pain as threatening and body movement as potentially dangerous. Over time, these models may manifest themselves as maladaptive alterations in behavioural and physiological responses to life events — for example, avoidance of novel situations or exercise, or dysregulation of the autonomic or neuroendocrine system.

Leverage points

Self-in-context models can be thought of heuristically as mindsets that shape what information we are open to accepting, to which hidden causes we attribute past and current events, and what we learn from experience. Healthy mindsets reduce negative beliefs about the future (such as hopelessness) and unwarranted blame and hostility (towards the self and others), and induce openness to potential benefits and opportunities[69]. Unhealthy mindsets, particularly negative self-evaluation and negative beliefs about the potential for positive change, are associated with poor health. For example, random assignment to the suggestion that one is genetically intolerant of exercise reduced running endurance and measures of lung gas exchange[189]. Negative beliefs about ageing are associated with lower engagement in healthy behaviours[175] and reduced longevity[176]. Having a negative stress mindset — the belief in stressors as debilitating (versus as helpful opportunities for growth)[190] — can amplify negative effects of stress. In a study of more than 28,000 individuals, high perceived stress coupled with the belief that stress negatively affects health was associated with a 43% increase in death rate compared with the absence of either risk factor[191].

Recent studies suggest that the vmPFC and OFC mediate effects of several types of brief mindset interventions[192,193], supporting the centrality and malleability of self-in-context representations. Suggestions that other people experienced a painful stimulus as particularly intense can increase both pain experience and autonomic responses[194,195]. Conversely, social manipulations, such as receiving supportive touch from a romantic partner[196] or voluntarily accepting pain on behalf of another person[197], reduce pain experience and measures of pain-related brain activity. All these effects are mediated by changes in vmPFC and OFC activity. Brief training in mindful acceptance[198] or meditation[199] also reduces pain and negative emotion, along with associated brain responses[198], including reduced activity in the vmPFC and other DMN regions during pain[199]. These interventions can meaningfully affect physiology; they influence the most sensitive and specific brain measure related to pain currently available, with effect sizes larger than those found in placebo interventions[200].

Mindsets also shape what we learn from experience, creating benefits or harms that compound over time. For example, individuals with social anxiety disorder have a negative mindset about themselves and their social standing. In laboratory experiments, individuals with social anxiety disorder learn more quickly from negative social feedback than from positive social feedback, in contrast to positively biased non-anxious controls[148], potentially creating a self-reinforcing cycle of anxiety and self-doubt. Expectations about pain can also become self-reinforcing, such that one 'gets the pain one expects'[201]. Computational models of self-reinforcing feedback cycles indicate that two key factors are required: first, that experience is assimilated to initial beliefs (that is, negative expectations enhance pain); and second, that experiences incongruent with initial beliefs are discounted or ignored[201].

Psychotherapy may work by reshaping one's self-in-context representations over time. Many forms of psychotherapy focus on helping individuals foster health-promoting appraisals, causal attributions and meaning-making. In addition, much of the benefit of therapy is not due to specific protocols but is due to common factors such as positive expectation, self-efficacy and engagement[61], which shift patients' mindsets. The vmPFC–OFC, hippocampus and amygdala are among the regions most consistently altered after psychotherapy in various mental health disorders[202,203]. The benefits of common factors are not exclusive to any particular treatment and can have substantial effects on diverse medical conditions, including migraine, depression, anxiety, Parkinson disease, asthma, irritable bowel syndrome and arthritis[204].

Beyond formal psychotherapy and medical treatment, shifts in conceptual thinking towards healthier self-in-context representations can be influenced in various ways: through interactions with friends, family and communities; through mindfulness and self-regulation training; and through public health policy. For example, across more than 300 trials of psychological interventions in individuals with cancer[205], people with strong social support networks survive longer[206]. Psychosocial interventions can increase survival time, particularly for those who are more socially isolated[207], and improve cancer-relevant immune measures[205,208]. Two randomized trials of psychosocial interventions showed improvements in mood, in cancer survival 7–11 years later and in measures of cellular immunity, including natural killer cell cytotoxicity and lymphocyte proliferation[209,210].

The effects of psychosocial interventions and changes in mindsets are undoubtedly complex, and we have much to learn. Self-in-context representations inherently differ across individuals and may be maladaptive in myriad ways across different disorders. In addition, they surely depend on complex neural interactions involving multiple brain regions and systems. However, the central idea here is that there is a focal point, a neural hub for integrating the various elements of experience into a coherent view of the world and our trajectory through it. Understanding this

as a common, driving force underlying well-being may help us reconceptualize the role of the brain in mental and physical disorders alike. And, because self-in-context models are fundamentally ideas, there is hope that people can learn to change them for the better in themselves and in those they care for.

Code availability

Instructions and the code to generate the visualizations of the term-based meta-analytic association maps in FIG. 3 are included in Supplementary information S3.

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