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Migraine as an allostatic reset triggered by unresolved interoceptive prediction errors

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ABSTRACT

Until now, a satisfying account of the *cause* and *purpose* of migraine has remained elusive. We explain migraine within the frameworks of *allostasis* (the situationally-flexible, forward-looking equivalent of homeostasis) and *active inference* (interacting with the environment via internally-generated predictions). Due to its multimodality, and long timescales between cause and effect, allostasis is inherently prone to catastrophic error, which might be impossible to correct once fully manifest, an early indicator which is elevated *prediction error* (discrepancy between prediction and sensory input) associated with internal sensations (*interoception*). Errors can usually be resolved in a targeted manner by *action* (correcting the physiological state) or *perception* (updating predictions in light of sensory input); persistent errors are amplified broadly and multimodally, to prioritise their resolution (the migraine *premonitory phase*); finally, if still unresolved, progressive amplification renders further changes to internal or external sensory inputs intolerably intense, enforcing physiological stability, and facilitating accurate allostatic prediction updating. As such, migraine is an effective 'failsafe' for allostasis, however it has potential to become excessively triggered, therefore maladaptive.

1. Introduction

Migraine is a characterised by headache, autonomic changes and noxious hypersensitivity to internal and external stimulation, (Goadsby et al., 2017) often accompanied by neurological symptoms. The migraine *attack* itself is often preceded by a *premonitory phase*, lasting hours to days, (Karsan et al., 2018) characterised by changes in mood, energy levels, autonomic function, and cravings. We use the term 'migraine episode' to refer to the attack itself and surrounding phases. Around 20% of the population has a clinical diagnosis of migraine based on International Headache Society (IHS) criteria of at least 5 attacks meeting particular criteria (https://ichd-3.org), often responding to one or more physiological triggers; there is considerable underdiagnosis, (Burch et al., 2019) many more have episodes with aspects of migraine phenomenology but not meeting IHS criteria, and perhaps a majority of people experience occasional migraine-like episodes during exceptional situations such as viral illness or major disruption to routine. Despite centuries of study, a satisfying account of the purpose and mechanistic principles of migraine has not been proposed. This may be in large part due to its complex underlying biology, with nearly every biological system (e.g. endocrine, (Silberstein and Merriam, 1991) metabolism, (Rainero, 2015) neural transmission, (Mulleners et al., 2001) immune, (Kemper et al., 2001) circulatory) (Moskowitz and Macfarlane, 1993) showing altered function in people prone to migraine, or in temporal proximity to migraine episodes. These alterations are often described as *causing* migraine, but they have not been placed within a mechanistic theoretical framework that can explain *how* or *why* they contribute to, or result from, migraine episodes. Migraine medicines have advanced significantly in recent years, but are still unable to satisfactorily treat a significant proportion of patients. Furthermore, the lack of a mechanistic understanding of migraine means clinicians still operate with uncertainty as to whether they are truly modifying aetiological

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Box 1
Glossary of terms.

Accuracy:

The inverse of inaccuracy or prediction error. Technically, the (log) likelihood of a particular set of sensory observations according to a model of how those sensations were generated.

Active inference:

A first principles account of sentient behaviour, under a generative model of the environment, in which the discrepancy between sensations and predictions (prediction error) is resolved through a combination of perception (updating predictions) and action (acting on the world or body to realise those predictions).

Action:

In active inference, action is the attempt to reduce prediction error through motor or autonomic reflexes, which realise proprioceptive and interoceptive predictions, respectively.

Allostasis:

The flexible regulation of physiology, underwriting maintenance of variables within specified ranges by pre-emptive responses based on current and predicted future physiological states, external environments and behavioural goals. In essence, a more flexible form of homeostasis.

Allostatic load:

The 'wear and tear' on the body associated with chronically high levels of stress and arousal, e.g. due to persistently elevated irreducible interoceptive prediction errors.

Allostatic reset:

A term we introduce here (unrelated to its use in opioid addiction) to refer to a process where there is a temporary shift from relatively allostatic (i.e. flexible) to homeostatic (i.e. rigid) physiological control, for the purpose of resolving (interoceptive) prediction errors.

Chronic migraine:

A migraine pattern defined clinically as more than 15 headache days monthly, of which at least 8 feature overt migraine.

Complexity:

The cost, in free energy terms, of the updating of predictions over time. Technically, the divergence between posterior and prior beliefs, during the process of inference or belief updating.

Efficiency:

The inverse of the free energy cost (i.e. complexity) incurred during active inference. Can be considered a correlate of the inverse of allostatic load over extended periods of time.

Exteroception:

Perceptual inference based on sensory signals originating from outside the body (e.g. vision, hearing, touch, taste, smell).

Free energy:

The key informational quantity in active inference, inspired by the concept of thermodynamic free energy in physics. It scores the surprise (self-information) of sensory data (i.e. sensory prediction error). Free energy comprises complexity and inaccuracy. Minimising free energy optimises the balance between the accuracy and simplicity of explanations for sensory data.

High-frequency episodic migraine:

A migraine pattern defined clinically as between 4 and 15 headache days per month.

Homeostasis:

The regulation of physiology, in which variables are maintained close to set points, which can be considered target values. In earlier notions of homeostasis, set points were fixed. Homeostasis has since been subsumed by allostasis, to reflect that no complex organisms operate via fixed set points. In this article, homeostasis and homeostatic are only used in relative terms, to refer to the flexibility of set points (more rigid in homeostasis, and flexible in allostasis).

Inaccuracy:

Equivalent to prediction error, the discrepancy between a predicted and sensed representation. The complement of accuracy.

Interoception:

The processing of sensing and perceiving sensory signals relating to internal bodily states.

Interoceptive accuracy:

The degree of correspondence between actual and inferred bodily states.

Interoceptive awareness:

The correspondence between subjective and objective accuracy with respect to interoception.

Interoceptive prediction error (IPE):

In general usage, prediction error relating to interoceptive signals. In this article, we use the term to also encompass other prediction errors in

exteroceptive modalities relevant to interoception or allostasis.

Interoceptive sensibility:

The subjective strength or intensity with which interoceptive sensations are perceived.

Likelihood:

Refers to the sensory input, or the sensory signal passing from one hierarchical level to the one above. Technically, it is the likelihood of any input (i.e. consequence) under a particular state of the environment (i.e. cause).

Perception:

Updating beliefs about the causes of sensations to resolve prediction error. Also referred to as belief updating, perceptual inference, evidence accumulation, and so on.

Precision:

The reliability of a particular representation, such as a prediction error or prediction. Mathematically, precision is the inverse of variance. The brain must estimate the precision of sensory signals based on their statistical dispersion. Attention is mediated by increasing the precision on attended sensory signals. Precision control also determines the balance between perception (when precision of sensory inputs is relatively higher) and action (when precision of predictions is relatively higher).

Prediction:

A top-down input from one hierarchical level of a generative model to the level below, indicating the expected state of representation at the lower level based on the state of the higher level.

Prediction error:

The discrepancy between the predicted (from the hierarchical level above) and estimated states (in the level below). At the lowest level sensory prediction errors or the difference between predicted and sensed signals.

Premonitory phase:

A phase experienced by some people for hours or days before a migraine, characterised by altered sensory processing and/or autonomic function.

Prior:

A belief, expectation or representation prior to sampling some data (i.e. before belief updating). Often used synonymously with top-down predictions based on higher expectations.

Sensory attenuation:

The process by which action is accompanied by a decrease in precision of sensory inputs reporting the consequences of that action.

Trigger:

A change within the body or outside world causing or contributing to the development of a migraine attack.

processes, or are blocking some of their downstream consequences or masking symptoms. An intervention that addresses the underlying causes is arguably the ideal one for clinicians and patients, or, at a minimum, presents an additional treatment route to those presently available.

Here we offer a systems-level model of migraine that is novel in starting from a principled and high-level scale of description (i.e. *allostasis* – the situationally-flexible and forward-looking regulation of physiology), and in showing how the entirety of the migraine spectrum (in terms of its phases, frequency and chronicity) naturally ensues as an emergent property of these systems, both in terms of clinical phenomenology and neurobiological evidence. We use of the term 'emergent property' in the way previously applied to migraine mechanisms, to indicate the following features: "System behaviour evolves from the interaction of elements at a local level, without external direction or the presence of internal control.", and "No one element is in control or has an 'overview' of the system." (Kernick, 2005) Furthermore, we are able to show how migraine is, for the most part, adaptive, though in certain individuals/states can become maladaptive and therefore constitute a *disorder*. This contrasts with existing lower-level descriptions that fixate on findings of dysfunction of neural excitability, (Goadsby et al., 2017) circulation, (Ashina, 2012) and/or metabolism, (Gross et al., 2019) and characterise migraine as solely a *pathology* or *pathophysiology*. Our physiological regulation model posits that a migraine episode arises as a pre-emptive response to potential future inaccuracy of physiological control, and attempts to bring an individual's physiological state back within predictable bounds through heightened *perception*, and promotion of withdrawal behaviours – a process we term as an *allostatic reset*.

To state our thesis in the simplest possible terms, we contend that migraine can be understood as the brain's making itself more sensitive to stress temporarily, so as to reduce stress overall.

The paper is composed of five sections: 1) A primer on an *active inference* account of physiological regulation (Box 1 contains a glossary of key terms); 2) A description of our account: that physiological regulation mechanisms use interoceptive prediction error as an early marker of physiological unpredictability, and how the phases of migraine are second and third-line responses to resolving this, and restoring physiological stability; 3) A neuroanatomical and neuromodulatory account of migraine as it relates to processes of allostasis; 4) A reappraisal of several interesting and unresolved aspects of migraine, which are explained by our model; 5) Future research directions and testable hypotheses based on our model. In Box 2, we work through an example 'real world' migraine scenario to illustrate our claims.

2. Part 1: active inference account of allostasis

2.1. Allostasis and active inference

Homeostasis is the process of maintaining physiological parameters at fixed *set points* (Fig. 1a-b), with any deviation from the set point triggering a corrective action that pushes the parameter back towards the target value. It can also be termed 'stability through constancy'.

Box 2
A (hypothetical) 'real-world' example of the phases of migraine.

Imagine somebody engaged in the seemingly simple act of eating breakfast, and deciding what to eat, and how much of it. Whilst this may seem so straightforwardly familiar that it invites a simple answer along the lines of "What they feel like eating, and to eat until they feel full", the computations, estimates, assumptions, interdependencies and uncertainties involved in these processes, and the intuitive subjective sensations that seem to guide it, are immense in scale, and far from trivial.

Firstly, the individual has to intake food with the appropriate quantity and composition of nutrients to meet their requirements at a time, generally hours later, when its digestion is expected to complete. The energy requirements at that future time will depend on predicted physiological states, taking into account usual circadian and other rhythms (e.g. menstrual) and any other relevant considerations, and also the anticipated demands placed by the expected external environment at that time and anticipated voluntary actions (e.g. whether they will be resting quietly at home in the evening, engaging in physical exercise, or at a social or work event requiring known or unspecified interactions with other individuals). Similar considerations about states encountered in the intervening time need to be factored in, as these might affect the state of the autonomic nervous system, and therefore the speed of intestinal transit. They also need to base their estimates of future metabolic requirement on estimates of their current metabolic state, which needs to be indirectly inferred from a variety of interoceptive signals (e.g. temperature, heart and respiratory rate, visceral distension, chemical receptors, blood sugar, catecholamine levels) and estimates based on past experience. Then, they must estimate the nutritional content, quantity, and expected time course of alimentary transit and digestion/absorption of the food they are eating based on taste, smell and visceral stretch receptors, interpreted in light of past experience. Even with no unforeseen events intervening (like a surprise, period of stress, or unexpected urgent task), this is a highly complex task, with every involved measurement associated with a significant margin of error, and interactions between different states creating the potential for errors growing by orders of magnitude.

After eating this meal, there are many reasons why things might not proceed as anticipated: perhaps the food was spoiled and contained toxins, or perhaps it contained too much or too little sugar; maybe the individual was developing a viral illness; perhaps they faced some unexpected stresses which interfered with metabolism or digestion; maybe they carried out more physical activity than planned, leading to under-fuelling. Any of these eventualities would be associated with unexpected interoceptive signals, or IPE. However, a particular set of interoceptive sensations could indicate any one of these possibilities or others, and correctly inferring the true cause of the aberrant interoceptive signals is difficult, and requires many assumptions based on contextual information and past experience. Correcting the aberration involves even greater uncertainty, especially if there is significant doubt as to its cause.

In our example, the individual is rushing, and eats a meal containing a higher proportion of refined carbohydrates than they usually would, and does not have time to give much thought to the implications of this. They proceed to digest and absorb nutrients faster than predicted, leading to a rise in blood sugar, followed by a surge of insulin and rapid fall in blood sugar. They then face an unexpected delay due to road works, and are frustrated about this, leading to catecholamine release, causing elevated heart rate and increased glucose utilisation. They are busy all morning making up for lost time, give little attention to their internal bodily states due to competing demands for their attention, and end up being late for lunch as well. During this period, they have accumulated interoceptive prediction errors relating to metabolic state, heart rate, gastrointestinal signals and levels of stress hormones.

Had the individual attended to their interoceptive signals, they might have been able to make some early changes to correct this IPE, for instance: having a small snack, having a short period of relaxation or slowed breathing, or accepting that they are running behind - and that it is fine - and need not feel stressful for things to just take a bit longer. If they knew they would be late with lunch and could not have a snack, they might account for this by predicting feeling hungrier for longer than usual, by reducing the intensity of their activities, or if they were accustomed to intermittent fasting they could simply predict the instantiation of a short fasting period. If they were taken, these steps, alone or in combination, might or might not have sufficiently corrected the elevated IPE.

However, by the time their delayed lunch break is possible, the IPE have persisted and caused their own subcortical gain increases. The unexpected interoceptive signals are now not only still present, but much more prominent. Furthermore, there has been a rise in stress hormones such as catecholamines, and neuromodulatory changes are also influencing the behaviour and timescales of decision-making processes. The individual now feels aware that they feel different to usual, but may struggle to understand the cause or significance of this; allostasis requires understanding the causes of interoceptive signals rather than simply each modality in isolation, and causes are evident as differing combinations of signals across multiple modalities, without any one-to-one mapping of modality of signal to cause. Our illustrative person will 'interpret' and respond to this state in one or more of a variety of ways, perhaps feeling energised or irritable, and no longer hungry.

If the individual correctly identifies a migraine premonitory state (or a high-risk situation for developing migraine), they may use this knowledge to take actions they associate with preventing migraine, whether that be resting, eating, hydrating, or other calming activities. Or, they might focus on an early medical treatment approach, taking painkillers or having caffeine to try and stave off the impending migraine symptoms.

Alternatively, they might be inclined to persevere with their goal-related activities. They might recognise that they are in a state where they feel energised and capable of getting things done quickly and decisively. This could even embolden them to miss lunch altogether, especially if they no longer infer a state of hunger. And try and maximise their productivity. However, this course of action will almost inevitably fail to correct the underlying causes of IPE, and a migraine will ensue: perhaps subsequently and gradually in the working day as catecholamine levels gradually reduce, or perhaps quickly at home as soon as they begin to 'relax' from the 'stress' of work. The migraine is deeply unpleasant, temporarily disabling, and does not even involve what would (at the initial 'trigger' stage) have been the biggest underlying cause (relative hypoglycaemia). Conversely, it still is effective in stabilising the broad range of contributing factors to the migraine, and even regarding blood sugar achieves stabilisation through a period of fasting and gastrointestinal stasis (or purging) to 'reset' both blood sugar level and the processing of intestinal contents on course to further alter blood sugar. Migraine was not the only way (or even the 'best' way) of restoring the accuracy of allostasis, as earlier steps could have worked, but it was the most reliable way of ensuring that this was actually achieved, and in this scenario was the only method that actually did work. Perhaps even more importantly, of the corrective responses available, migraine was the one that would have worked most reliably if the inferred causes of the excessive IPE turned out to have been mis-inferred from interoceptive signals: e.g. if the altered heart rate, visceral distension, stress hormone levels and chemical receptor signals experienced actually had a totally different cause such as a viral illness or food poisoning). To recap, migraine, as a corrective mechanism, has advantages in situations where there is either uncertainty as to the causes of elevated IPE, and/or where there is uncertainty over the potential success of corrective actions for those causes.

Whilst, in the modern day, it might seem difficult to see why having this migraine is in any way advantageous, as it would seem rather fanciful to conjure up a scenario where the physical compromise associated with a single instance of metabolic mismanagement would lead to injury, for instance due to encountering an attacker who they were therefore unable to evade. However, firstly, during most of human evolution, such instances of risk of injury or death due to compromised emergency survival mechanisms would have been encountered relatively frequently. Also, had our person experienced early life adversity, their allostatic systems would have been 'primed' to infer a higher baseline risk of acute extreme threat in the environment, making it more important to limit situations where this might be faced whilst underprepared. This would manifest as a greater propensity to migraines. Furthermore, we are not merely considering the implications of a single instance, but also the cumulative effects of repeated instances of suboptimal allostatic regulation. Our example person, if not genetically prone to migraine, might be inclined to manage their activities in a similar way in future if they considered this day a 'success'. They might end up generating cumulative IPE, if each day's were not fully corrected before the next day's began, running excessively high stress levels, develop metabolic problems, poor sleep patterns, etc., and set themselves on course for other physical and mental health manifestations of poor allostatic regulation. Fig. 4 illustrates a two versions of the scenario described here: one where an episode of migraine prompts an allostatic reset, and one where migraine does not occur, and the consequences of ongoing allostatic inaccuracy are highlighted.

Being prone to migraine, our individual 'benefits' from being more 'protected' from both acute harm and from chronic health consequences of poor allostasis, by occasionally having 'enforced resetting' of their allostatic systems. However, they experience unpleasant symptoms in the process (much like pain serves a purpose but is nonetheless undesirable), and are sometimes left unable to function in the way they want when they want. They are also at some risk of developing high-frequency or chronic migraine if individual migraine episodes do not prompt the 'intended' restoration of allostatic efficiency. For instance, if our person is off work the next day with a migraine, they may feel compelled to rush back in the following day and 'make up for lost time'. They may therefore face even higher levels of IPE, for the original reasons but now subject to higher pressures, and increase their subsequent migraine risk further. They might further exacerbate the problem by using short-term pharmacological approaches such as increased caffeine and painkillers to suppress migraine, which would only serve to suppress the awareness of IPE for longer, allowing even higher levels to accumulate, and a vicious cycle ensuing. Conversely, with the appropriate understanding of the underlying 'mechanisms' of their migraine, and a sympathetic employer to work with them on the issues, they might be able to make a few small work and home lifestyle modifications to prioritise improving their allostasis, hence addressing the 'root cause' of their migraine.

We hasten to emphasise that this is just one hypothetical example scenario, and that every instance of migraine is likely different in many particulars, and many cases need not even involve any of the specific factors or processes mentioned here. We more just aim to illustrate the allostatic principles and complexities in which we argue migraine is rooted.

Complex organisms take homeostasis to a higher level by adapting these set points to particular situations, states and goals, based on both current and anticipated future situations. Corrective actions are largely pre-emptive, like a heating system firing up before the cold arrives. This is termed *allostasis* (Fig. 1c): stability through situational change (Sterling, 2012). It is increasingly argued that all physiological regulation in biological organisms is actually allostatic, which subsumes homeostasis as simply an incomplete description of allostasis (Lee, 2019). Nonetheless, in this article, to maintain the use of familiar terms, we use the terms 'allostasis' or 'allostatic' to refer to states of physiological regulation relatively favouring change and complexity, and 'homeostasis' or 'homeostatic' for states favouring constancy and simplicity, whilst acknowledging that these are simply different regions on a continuous spectrum. Allostasis requires the brain to predict the future states of the internal and external environment, to assess the accuracy of its own *predictions*, estimate the consequences of inaccuracies in those predictions, formulate possible courses of action (both internal and external), predict the outcomes of those courses of action, and select the most appropriate actions.

These processes are in turn encapsulated by the framework of *active inference* (Pezzulo et al., 2015; Barrett et al., 2016) (Fig. 2); the internal state is assessed (a process known as *interoception*), (Barrett and Simmons, 2015) and compared to existing predictions to generate *interoceptive prediction error* (IPE), prompting resolution of IPE through a combination of updating predictions in line with interoceptive input (i.e. *perception*) and taking *action* (e.g. autonomic reflexes or volitional actions) to make the internal environment resemble the predictions (Barrett et al., 2016; Bettinger and Friston, 2023; Tschantz et al., 2022). These systems are organised hierarchically, (Friston et al., 2006) with the lowest levels occupied by sensory epithelia, proprioceptors, skeletal and smooth muscle, and glandular tissue, the highest levels by areas involved in complex perception, volitional action and attention and physiological control (e.g. anterior insula and anterior cingulate cortex), and intermediate levels in subcortical brain structures (such as hypothalamus, thalamus and brainstem) and primary sensory cortices. The representation at each level is weighted by its *precision*, which is controlled by key neuromodulators (Friston et al., 2006; Moran et al., 2014; Feldman and Friston, 2010). Precision is a marker of the reliability or importance of a particular signal or representation, and is of vital importance in determining how, and the extent to which, each representation is used by the brain. Prediction errors are passed up the hierarchy to promote perception, and updated predictions passed down the hierarchy to generate action, in each case in proportion to the relative precisions of the interacting hierarchical levels (with the flow of influence being from higher to lower precision). Increasing precision at an intermediate hierarchical level can, potentially, trigger both perception and action, if that level's precision is higher than both the hierarchical levels above and below.

2.2. Neuromodulatory control of precision

Precision is principally controlled by the neuromodulatory system, small clusters of neurons that project widely to modulate the action of neurotransmitters, sometimes with high spatial and temporal specificity, and sometimes more diffusely. At the level of sensory cortex, acetylcholine is the key player, mediated by the basal forebrain cholinergic system (Moran et al., 2014). Precision is controlled rapidly and dynamically, with a high level of topographic and temporal resolution. Volitional and stimulus-driven attention can be considered as cortical-level precision modulation (Feldman and Friston, 2010). Conversely, neuromodulatory control of precision at a subcortical level occurs somewhat differently. The brainstem also contains a cholinergic neuromodulatory system, but its role is mainly in arousal and sleep-wake regulation, with roles in attention and sensory processing less clear (Slater et al., 2022). Other key neuromodulators include serotonin and noradrenaline, (Jacob and Nienborg, 2018) which have complex and incompletely understood roles. Noradrenaline promotes alertness, sensory adaptation and selective attention, (Jacob and Nienborg, 2018; Dahl et al., 2020) has a broad antinociceptive effect via the diffuse noxious inhibitory controls (DNIC), (Kucharczyk et al., 2021) and prioritises established behaviour over new exploration (Doya, 2002). Serotonin acts in a regional, rather than modality-specific, way, with its role in sensory processing complex and context-dependent (Jacob and Nienborg, 2018). Serotonin has also been considered as a

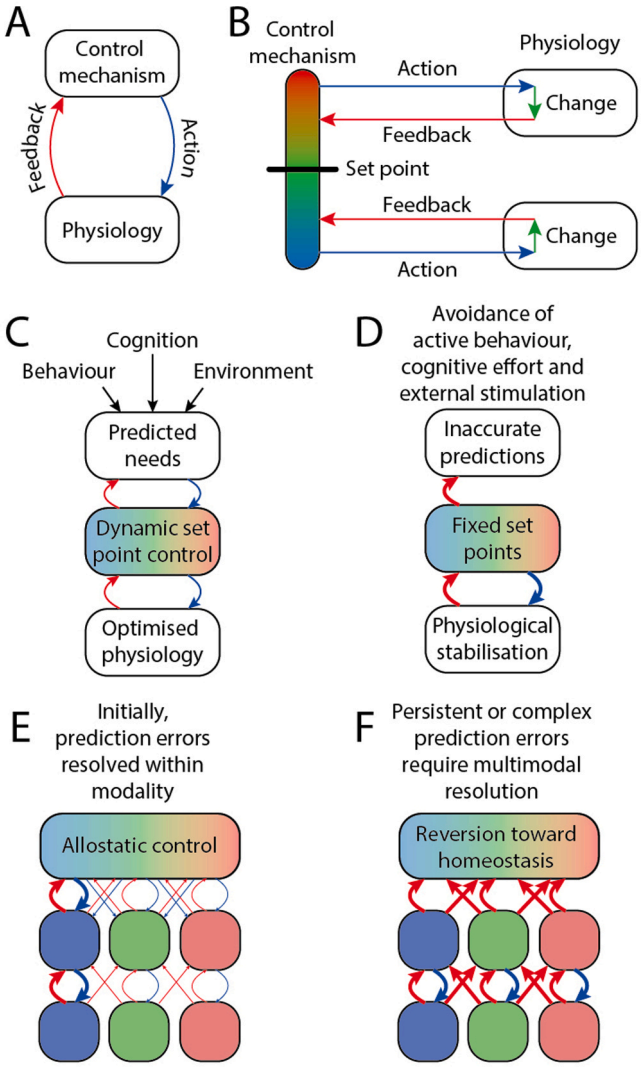

Fig. 1. Types of physiological control, and its failsafes. (A) Simple negative feedback loop for maintaining a single physiological parameter. (B) Homeostatic control over a single physiological parameter according to a fixed set point. Sensed values above the set point recruit physiological responses to reduce the parameter's value, and vice versa. (C) Allostatic control of multiple interdependent modalities, with dynamic set point control based on changing and anticipated internal and external environments, optimising physiology in accordance with these changes. Accurate prediction of physiological needs is fundamental to operating in this manner. (D) Requirement for an allostatic failsafe in the face of irreducible prediction errors. Removal of dynamic set point control (i.e. reversion to rigid homeostasis) promotes physiological stabilisation. Panels (E) and (F) illustrate these stepwise corrective measures within and across modalities. (E) The initial response to prediction error is increased gain on that error within its modality (each modality indicated by a specific colour), to resolve it through a combination of increased feedback (red arrows) and action (autonomic reflexes; blue arrows). (F) It is not always possible to resolve prediction error within its modality due to complex cross-modal interdependencies (diagonal red arrows); persistent prediction errors lead to a state of multimodal stabilisation, characterised by increased feedback from all modalities, loss of flexible allostatic control, and fixed set points.

key factor in favouring computing costs and rewards across longer timescales, compared to more immediate ones, in decision-making processes (Doya, 2002). Serotonin also impacts pain processing via the DNIC, with this pathway interacting with menstrual hormones in women (Kucharczyk et al., 2021; Paredes et al., 2019). A fundamental difference compared to cortical-level precision control is that brainstem-level neuromodulatory systems have broad and relatively indiscriminate projections, and therefore act widely across sensory modalities and topography, and over time. For instance, the locus coeruleus (the key noradrenergic centre) has only 30,000–50,0000 neurons to project to most of the brain (Mouton et al., 1994).

Dopamine has numerous central and peripheral actions, although many of its principal central actions have been explained under the umbrella process of mediating *reward prediction errors* (i.e. discrepancy between predicted and received reward) (Doya, 2002) and increasing the precision of beliefs about future plans (thus favouring taking action, by increasing confidence that an action will have its intended consequences). This factor is instrumental in how IPEs are responded to, affecting the balance between resolution through perception and resolution through action, the latter being promoted by dopaminergic activity.

Gain control also occurs in the peripheral nervous system, but has received less attention, and it is somewhat unclear how central and peripheral neuromodulatory control systems interact; serotonin acts broadly across peripheral sensory organs, (Masson, 2019; Vicente-Torres et al., 2003) and also influences the release of calcitonin gene-related peptide (CGRP), which facilitates nociceptive signalling in the trigeminovascular system (Aggarwal et al., 2012). CGRP and its receptors are also widely distributed across visceral (Mai et al., 2014; Deen et al., 2017) and exteroceptive (Deen et al., 2017; Blixt et al., 2017; Wang et al., 2016; Le Prell et al., 2021a) peripheral receptor systems.

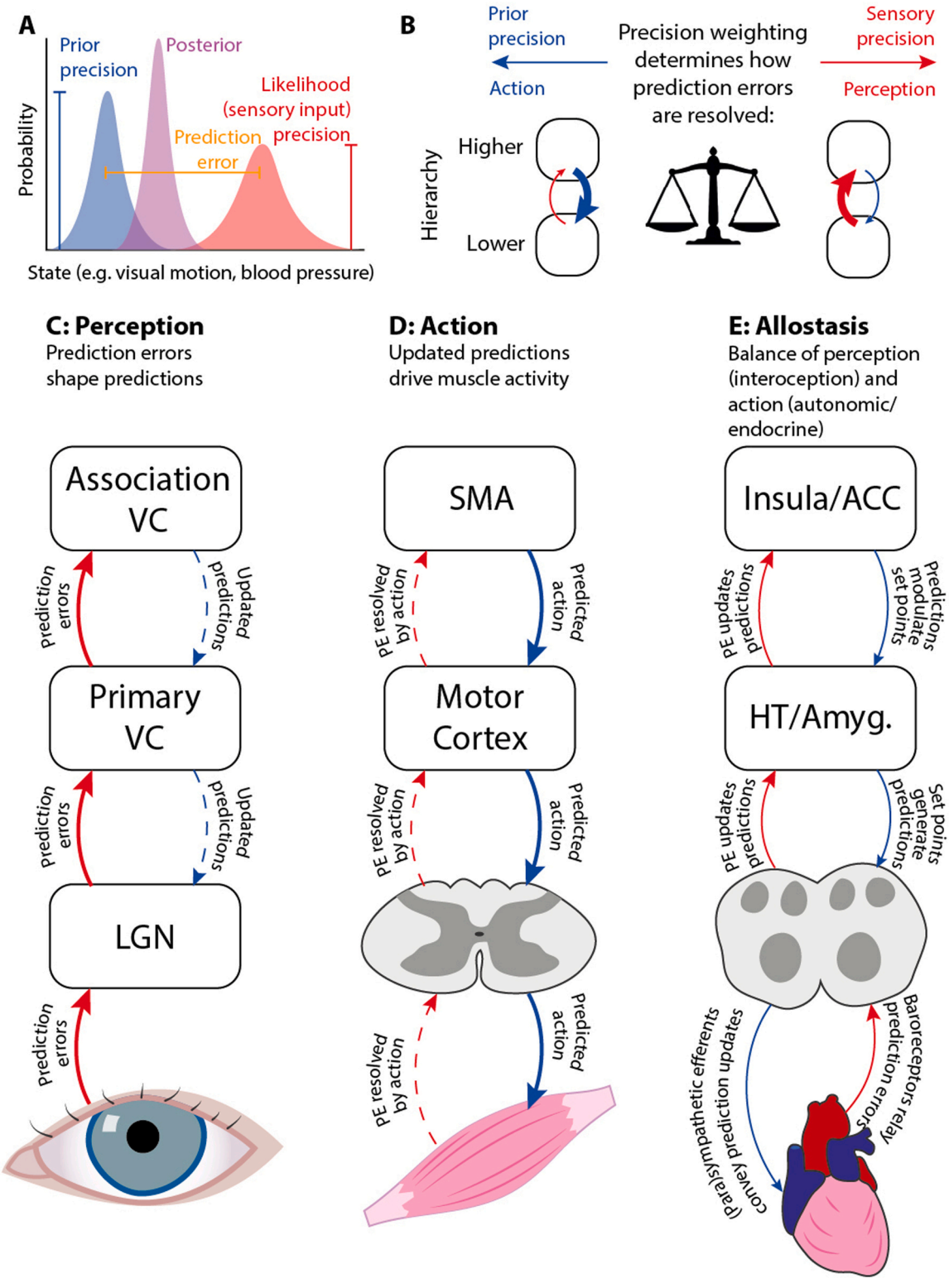

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Fig. 2. Active inference as a unifying mechanism for perception, action and allostasis. (A) Active inference occurs at every hierarchical level, with every prior and likelihood comprising a probability distribution over a perceptual space representing a particular state in the external or internal environment. (B) Each prior and likelihood is weighted by its precision (inverse of variance), resulting in an inferred posterior representation (i.e. updating prior beliefs to posterior beliefs based on new evidence). This precision-weighting depends on context and reliability of signals, is under neuromodulatory control, and determines the extent to which prediction errors result in updating of priors and/or action (B-E). All active inference networks are arranged from low (bottom) to high (top) hierarchical levels, with each level maintaining a prediction about the state of the respective part of the internal or external environment. (C) Perception occurs through the bottom-up passing of prediction errors (discrepancy between prediction at that level, termed the prior, and the input from the level below, termed the likelihood), beginning in the sensory organs, which update predictions in line with sensory input. (D) Action occurs through the top-down generation of prediction errors (discrepancy between the current state of the environment and its predicted state following the intended action), which cascade down the hierarchy where they trigger the resolution of proprioceptive prediction errors through muscle activity. (E) Allostasis involves a combination of perception (interoception: perception of internal bodily states) and action (e.g. autonomic reflexes via smooth muscle, endocrine and exocrine activity). Allostasis also involves volitional action on the external environment via skeletal muscle, as interacting with the external environment is interconnected with internal state regulation (e.g. relating to potential sources of food or threat). VC = visual cortex. LGN = lateral geniculate nucleus. SMA = supplementary motor area. PE = prediction error. ACC = anterior cingulate cortex. HT = hypothalamus. Amyg. = amygdala.

Although many details of neuromodulatory systems remain to be understood, the key principle here is the hierarchy of precision control systems, which are topographically and temporally specific at a cortical level, and broad-acting over slower timescales at subcortical and peripheral levels. Future advances in the understanding of the roles of these neuromodulators at a systems level may allow us to refine the details of this aspect of our model, but this level of detail is not required to describe, test, computationally model or clinically exploit the model as a whole.

2.3. Amplifying prediction errors prompts their resolution

Both cortically and subcortically, a core feature of prediction errors is that they drive precision control mechanisms, via reciprocal interactions with neuromodulatory centres, with strong prediction errors progressively increasing precision at that processing unit as a means of promoting resolution of those errors. This may seem counter-intuitive in the short-term (that the initial response to excessive prediction error is to amplify it further), as the immediate effect is an increase in the precision-weighted prediction error (PWPE), rather than the intended decrease. However, the increase in precision constitutes a shift of attention or focus, from tolerating and ignoring the persistence of a certain degree of prediction error, to identifying it as an aberration needing correcting, and thereby subsequently reducing it (assuming corrective action or perception is possible). A certain minimum level of prediction error may not be resolvable by any response available to the organism, and is termed *irreducible*. Distinguishing irreducible from resolvable prediction errors is fundamental to the organism's optimal functioning. The volitional direction of attention can be influential, as attending towards IPE can facilitate its resolution at an early stage, whilst attending towards other priorities can allow greater levels of IPE to accumulate unnoticed. Conversely, directing attention or gain towards irreducible prediction error only increases PWPE, with no ensuing benefit.

2.4. Complex systems create complex errors

An Achilles heel of a complex control system trying to optimise multiple parameters against uncertain and changing current and future states, where action is required hours or longer in advance of its goals, is the potential for inaccuracy, leading to 'corrective' actions making problems worse rather than better; this can apply due to inaccuracy in estimating the future state of a single parameter, or where interdependencies between parameters lead to correcting one parameter's error worsening another's (Tschantz et al., 2022). For example attempts to deliver improved cognitive performance on a work task may increase visual system gain, manifest as photophobia. Each factor relevant to allostasis comes with its own degree of error, for instance inference of internal bodily states based on visceral sensory inputs, or estimating the nutritional composition of ingested food based on taste and stretch receptors. Given the multiplicative effect of errors, and nonlinear interactions between factors, the potential for error is extremely large, and consequences potentially catastrophic.

In the context of physiological control systems relevant to migraine, *nonlinearity* has been described as a key feature, as exemplified by the following statements: "Systems cannot be understood by a reduction into their component parts" and "Rarely is there a simple relationship between cause and effect." (Kernick, 2005) Applying these principles to the numerous interacting states and domains relevant to something as multifaceted as allostasis underscores the near-impossibility of achieving a system that can consistently mount a corrective response to any combination of perturbations. Furthermore, the long timescales required to correct aberrant physiological states means that responding to critical errors only after they are overtly manifest may not be sufficient to avert disaster, whether that be a directly dangerous internal states, or inability to respond to external threat. Ashby's *Principle of Requisite Variety* (Ashby, 1956) states that, to be a control system, a system must have a repertoire of responses available to it that exceeds the number of unique states in its (in our case, both external and internal) environments that it might encounter (i.e. it must match the complexity of the environment in which it operates). Where this condition is not met, devices termed 'variety attenuators' can be employed to simplify the environment to allow the criterion to be met in the short term, but at the risk of precluding information important for longer-term success or efficiency.

To protect from the dangers of allostatic errors, either singularly catastrophic or recurrent and cumulative, the organism requires an early marker of system inaccuracy. In the following section, we describe this early marker, which we term *interoceptive prediction error* (IPE), how migraine is its eventual consequence, and how migraine can preemptively correct inaccuracies in allostasis to prevent potential serious acute or chronic harm, in effect acting as a variety attenuator.

3. Part 2: migraine as an allostatic reset

3.1. Migraine is triggered by interoceptive prediction error (IPE)

The triggers of migraine are diverse, can act alone or in combination, and broadly include almost any unexpected change in physiology (such as hunger, sleep disturbance, hormonal changes, unaccustomed exercise, temperature changes or viral infections), psychological stress (or demanding cognitive tasks), and/or strong external stimulation (such as light, sound or painful stimulus) (Casanova et al., 2022). In addition to menstrual links in some female sufferers, some patients also experience migraines on an apparently spontaneous cycle (Gallardo et al., 2022). We can generalise these under the singular category of IPE, (Tschantz et al., 2022; Allen et al., 2022) which we use to refer to errors in both directly interoceptive signals (e.g. cardiometabolic state), and in other modalities relevant to allostasis through their interdependencies with internal states (such as potential threat to, or action required by, the organism, in response to external senses, pain and cognitive factors). The organism needs to integrate these multifaceted, and nonlinearly

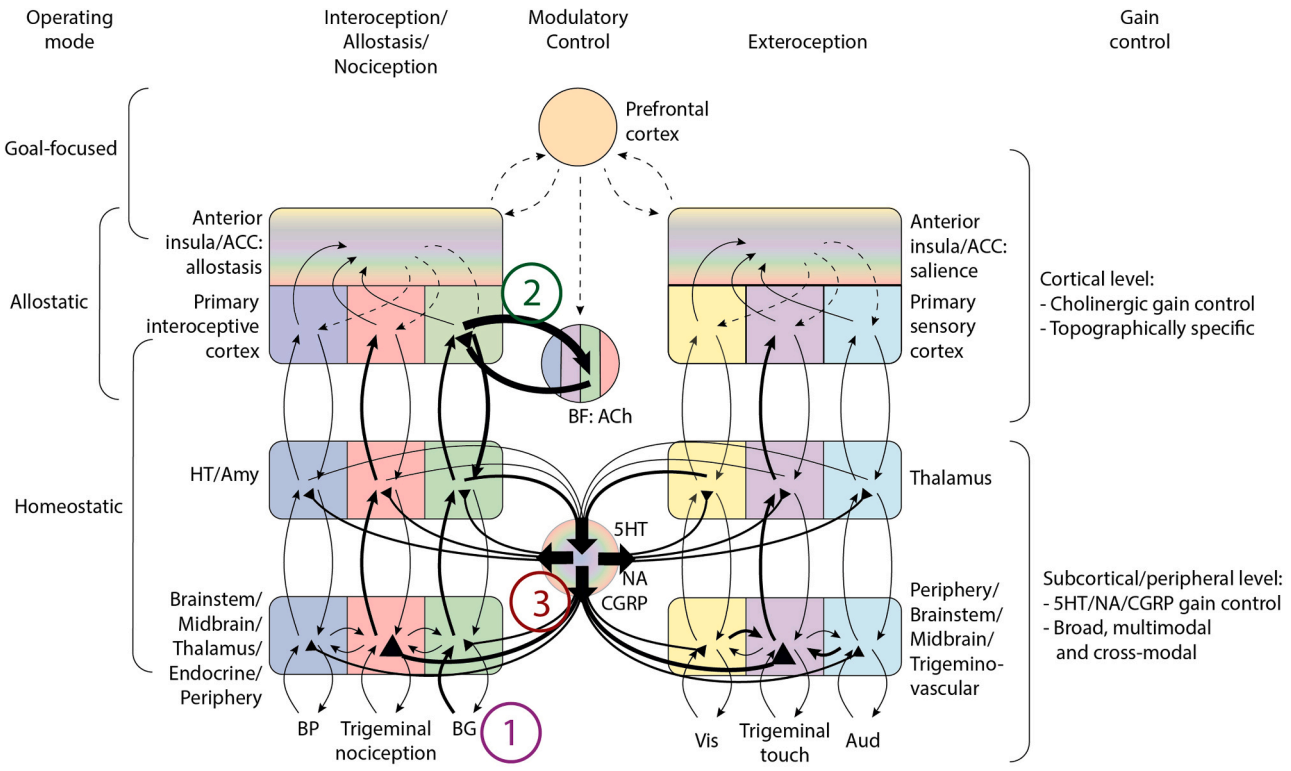

Fig. 3. Emergence of migraine within the hierarchy of interoceptive, exteroceptive and allostatic control mechanisms. Each modality is indicated by its colour. 1) Aberration in the input of one or more particular modalities triggers a prediction error, which ascends hierarchically. 2) Selective cholinergic gain enhancement increases the prediction error, promoting resolution through an updating of allostatic predictions (rainbow area in anterior insula/ACC), and/or autonomic reflexes via the hypothalamus and/or amygdala. 3) Persistent or multimodal prediction errors (if not resolved in step 2) at the level of hypothalamus/amygdala trigger monoaminergic gain enhancement in brainstem nuclei and the peripheral nervous system, amplifying ascending activity (including prediction error in other modalities) in a non-specific cross-modal manner, and hypersensitising the trigeminovascular system via CGRP release. The precision of allostatic predictions (dashed lines) is so low compared to precision of ascending sensory signals that higher control of allostasis is down-regulated, and the system moves towards rigid homeostatic functioning. ACC = anterior cingulate cortex. BF = basal forebrain. ACh = acetylcholine. S1 = primary somatosensory cortex. PIC = posterior insular cortex. HT = hypothalamus. Amy = amygdala. 5HT = serotonin. NA = noradrenaline. CGRP = calcitonin gene-related peptide. BP = blood pressure. BG = blood glucose.

interacting, components of IPE across modalities and over time, and to respond appropriately when it reaches a level indicative of a need to take corrective measures.

3.2. *Migraine is an emergent phenomenon of allostatic precision control mechanisms*

We consider that complex organisms can function across a spectrum of operating states, ranging from relatively flexible to relatively rigid. Progression through these states occurs as the singular and inevitable result of the magnitude and duration of IPE, linking these inextricably. The current state is determined by the dominant hierarchical level of precision control, which in turn is dependent on the magnitude of IPE; the smaller the IPE, the higher the hierarchical level of dominant precision, the greater the flexibility and volitional control of attention, and the larger the spatiotemporal scales of goal-focused behaviour and planning. Conversely, elevated IPE focuses attention on allostatic needs, increasing precision at lower hierarchical levels, and prioritising short-term physiological stabilisation over longer-term goals. We divide this continuum into five descriptive states, which mirror the three modes of allostatic control described by Tschantz et al., (Tschantz et al., 2022) (but, again, acknowledging that these are descriptive regions on a continuous spectrum rather than qualitatively distinct) and highlight how later stages constitute migraine. Importantly, migraine is not something additional that needs to have evolved separately, or been added on, to allostatic regulatory processes, but is simply the inherent consequence of the allostatic level of control nearing one end of the spectrum.

3.2.1. *Allostatic predictability (goal-focused)*

Levels of IPE are low, because internal and external environmental states correspond closely to predicted ones. The organism has full control over its state of attention and behavioural goals.

3.2.2. *Targeted correction (Fig. 1e; goal-focused or allostatic)*

The precision of one or more IPEs is increased in a localised manner at a cortical level. The specific unmet allostatic need may thus be highlighted, to prompt corrective perception change and/or action. However, competing cortical level attentional demands may lead to this state going unnoticed, or volitionally ignored.

3.2.3. *Broad correction (Fig. 1f; allostatic)*

Precision is increased in a broad and multimodal manner at low and intermediate hierarchical levels. This is the simple mechanistic result of the persistently increased precision of IPE at a higher level acting to increase the precision of IPE at the next level(s) down. Because this has now recruited broad-acting brainstem level gain control centres, a wide range of allostatic modalities/needs are highlighted, reflecting the complex interdependencies between modalities, often requiring multiple factors to be addressed simultaneously. Sharpness of perceptual representations is increased, and autonomic arousal occurs, in order to mobilise resources towards addressing allostatic needs. This corresponds to the migraine premonitory phase (Karsan et al., 2018) (in episodes where this occurs), which typically lasts hours or days, and is characterised by autonomic and mood changes (e.g. yawning, fatigue, irritability hunger, elation), and increased awareness of internal and external

sensations (e.g. enhanced sense of smell). However, in driving one modality to optimal awareness, another may be driven beyond its optimal functional range, leading to symptoms such as dysosmia (distortion of sense of smell).

3.2.4. Allostatic reset (Fig. 1d,f; homeostatic)

Broad-acting low-level precision increases have persisted, due to failure to resolve IPEs, which are now behaving as irreducible. Therefore, they continue to drive their own precision increases, and a positive feedback cycle ensues, generating the migraine attack.

The heightened state of gain/precision now results in activation of nociceptive systems, coinciding with loss of sympathetic drive and reduction in perceptual sharpness. A drop-off in sympathetic drive may even cause the transition into this phase, but direct evidence is lacking. The behavioural result is withdrawal from action, internal or external stimulation, because all such processes are now perceived as noxiously intense. There is a temporary shift from complex allostasis towards a more rigid form of homeostasis, with fixed set points and enforced stabilisation of physiological parameters, until the accuracy of interoceptive predictions can be restored. As well as prompting this state of withdrawal behaviour, the strong hierarchical gradient in precision (greatest at low levels) drives the updating of allostatic predictions in line with the organism's current state. Whilst in some ways maladaptive, as the organism is now less able to meet internal and external demands than before (and, from the individual's perspective, the symptoms are unpleasant and disabling), this state is highly effective at stabilising allostasis, and constitutes a last resort when high levels of IPE have occurred that have otherwise proven irresolvable.

3.2.5. Actual physiological harm

This state may be, in most respects, similar to the allostatic reset state (unless the harm has triggered a strong sympathetic response or impairment of conscious level), but we draw a distinction to emphasise that the principal 'purpose' of migraine is to pre-empt and prevent harm, rather than to wait for that harm to actually happen.

3.3. The 'dark room' paradox

Regarding the active inference frameworks, the 'dark room' question has been often been posed (Baltieri and Buckley, 2023). That is, if an organism's overarching goal is to minimise *uncertainty* (largely by reducing prediction error), why it does not just retreat to a dark room and stay inactive, as these are surely the most effective ways of minimising external and internal uncertainty. The accepted answer, broadly speaking, is that these behaviours only minimise uncertainty in the short term. Longer term uncertainties remain: locating sources of food, evasion of threats, dealing with changing seasons, social interactions, and other higher-order behaviours. In our account of migraine, the dark room question is answered through allostasis, which permits stability and planning over larger-scale and longer-term situational changes beyond the organism's immediate vicinity; however, instances of allostatic inaccuracy necessitate a temporary return to small-sca le/short-term dark room behaviour, literally manifesting as the individual having a migraine attack wanting to be in a dark room.

3.4. Migraine and sensory attenuation

The gain/precision control mechanisms underpinning migraine can be considered within the wider framework of *sensory attenuation*, (Idei et al., 2022) thus allowing parallels and overlaps to be drawn with a variety of mental and physical health conditions (Pareés et al., 2014; Oestreich et al., 2015). Sensory attenuation is the process by which the precision of self-generated sensory signals is reduced. In normal functioning, its consequences include not being able to tickle oneself. A common psychopathological consequence of deficient sensory attenuation (in a very different context) is auditory verbal hallucinations in schizophrenia (Shergill et al., 2005). In allostasis, sensory attenuation prompts the resolution of IPE through autonomic reflexes and volitional actions, and reduces perceptual awareness of self-generated changes. In migraine, the indiscriminate broad gain increases on interoceptive and related signals can be considered a loss of sensory attenuation, forcing resolution of IPE through updating of interoceptive models. Because all of migraine's respective interoceptive and exteroceptive signals are, to some extent, the consequences of current or past allostatic and/or locomotor actions, migraine is a state where the sensory consequences of one's own actions are not attenuated because they are not predicted with sufficient accuracy. Loss of sensory attenuation fits particularly well with the typical feature of migraine symptoms being immediately exacerbated during physical activity.

3.5. Peak onset of migraine in adolescence

Whilst migraine does occur in children — often with prominent gastrointestinal features and lesser headache — the peak onset is adolescence. Here, we briefly consider why that might be. Firstly, and not specific to our model, migraine is clearly triggered by changing physiological (and environmental) states of some kind, and adolescence is the time in life with the highest rate of such changes, including sex hormones, circadian rhythms, rapid growth, changing personal identity and social behaviours and self-awareness. More specific to our model, we have considered migraine as a response occurring in systems capable of ignoring certain parts of the environment whilst attending to others (via selective attention). It is this context sensitivity, and particularly the ability to attenuate sensory signals, that allows IPE to persist and accumulate below the radar of conscious awareness sufficiently to present a high chance of migraine episodes occurring. Furthermore, the increased complexity (i.e. unpredictability) of the environment and social interactions — that characterise adolescent and working-age adult life — place additional pressure on allostatic responses. In children, it may be the case that lesser ability to attenuate interoceptive signals means that IPE reaches conscious awareness sooner, perhaps leading to a lower threshold for experiencing somatic symptoms, but a reduced propensity for IPE to trigger full-blown migraine attacks. By analogy, systems — such as those in allostasis — have been likened to learner vs. experienced drivers; (Clark, 2023) learner drivers lack the well-developed predictive systems relating to driving, and face a high rate of prediction errors in response to various events, even those which more advanced drivers would have predicted. Conversely, experienced drivers experience relative few prediction errors, as they anticipate most events and situations. However, rare and unpredictable events are readily noticed by learner drivers, whilst experienced are worse at registering these rare events, and are subject to much higher levels of surprise when they do. Similarly, we argue that the context sensitivity of allostatic systems is successful at limiting everyday errors effectively, but has 'blind spots' that allow large errors to occasionally occur, and that migraine is a key consequence of such occurrences.

3.6. Heterogeneous migraine phenomenology and migraine aura

Migraine does not necessarily have to feature increased gain across every interoceptive and exteroceptive modality, and subcortical gain control mechanisms probably still have some topographic and modality specificity. Therefore, the specific range and balance of clinical symptoms within a particular individual or episode may depend on a combination of nuances of the particular neuroanatomical and neuromodulatory systems being activated, and the particular type of IPE and wider circumstances triggering the episode. Put another way, it may depend on the network of inter-modal connections between the specific IPEs involved, which in turn determines the perceptual space over which gain/precision is increased and sensory attenuation is reduced.

Around 20% of migraine sufferers experience aura, which is characterised by a spreading wave of positive percepts (an extra sensation,

such as flashing zig-zag lights migrating across the visual field) followed by negative focal neurological symptoms (a decrease in sensation, such as blindness), thought to be caused by *cortical spreading depolarisation* followed by *spreading depression*. In our model, migraine aura represents the same type of physiological control mechanism as outlined in our description above, but operating in a different neuroanatomical feedback loop; instead of the positive feedback loop first occurring between IPE in subcortical structures and the gain control centres that increase their precision, it initially plays out between prediction error in sensory cortex and modulatory centres. In either case (migraine or aura), the underlying process is progressive amplification of persistent IPE, leading to a positive feedback cycle which further increases IPE, eventually reaching a cliff edge, and triggering a wave of cortical spreading depolarisation/depression.

4. Part 3: neurobiology of migraine

We have explained, in the preceding sections, the principles of allostatic regulation and its need for tiered failsafe regulatory systems, and described how these align with the clinical phases of migraine. In this section, we outline a putative biological implementation of these allostatic processes (Fig. 3) and explain how it accords with evidence of the neural correlates of migraine.

4.1. Functional neuroanatomy

The most striking and consistent change in brain activity with migraine is hyperactivity in the hypothalamus (Stankewitz et al., 2021; Denuelle et al., 2007; Maniyar et al., 2014). This builds up in the premonitory phase, then remains high during the migraine attack. We interpret these changes as the progressive accumulation of IPE at the intermediate level, with the hypothalamus the key centre for most allostatic modalities. The posterior insula, encompassing the primary interoceptive cortex, (Barrett and Simmons, 2015) shows a different temporal pattern, (Stankewitz et al., 2021) with increasing functional connectivity with the hypothalamus throughout the premonitory phase, but a drop at the onset of the migraine attack. Anterior insula is a key regulatory hub in control of allostasis, (Kleckner et al., 2017) interoception, (Wang et al., 2019) salience evaluation (Uddin, 2014) and autonomic control, (Menon and Uddin, 2010) including regulating related prediction error responses, (Geuter et al., 2017; Allen et al., 2016) and therefore the likely key centre responsible for multimodal predictions necessary to integrate and govern these diverse functions, alongside anterior cingulate cortex which assumes similar roles. Whilst not observed to be over- or under-active during migraine episodes, anterior insula also shows similarly altered functional connectivity profiles (Borsook et al., 2016; Tso et al., 2015; Coppola et al., 2018). Anterior cingulate cortex does show increasing activity prior to and during migraine attacks, (Karsan et al., 2018) and likely reflects increasing levels of prediction error. Increased connectivity is indicative of increased message passing between these areas, including increased precision of ascending hypothalamic prediction errors reaching cortex and/or changing predictions descending to the hypothalamic level. These are present during the premonitory phase, as part of the drive to address allostatic needs by prompting appropriate volitional behaviour. The migraine attack, conversely, is characterised by relative loss of higher cortical control over allostasis (i.e. a shift towards hypothalamically-driven homeostasis), which is reflected in hypothalamic hyperactivity that is relatively uncorrelated with insula and cingulate cortex activity. Spontaneous hyperactivity during migraine episodes is also seen in thalamus and brainstem areas, (Maniyar et al., 2014; Coppola et al., 2016; Weiller et al., 1995) indicative of broadly increased precision/gain at this intermediate level of sensory processing which we argue is a key process underlying of migraine.

4.2. Central neuromodulators

Interictally (i.e. between episodes), people prone to frequent migraines show abnormal physiological responses to external stimulation, which accompany clinical symptoms such as hyperosmia and photophobia (Judit A. et al., 2000). These have been characterised for vision, in which there is a failure of the normal decrement of responses to repetitive stimulation, and in the auditory modality in which there is lack of the usual attenuation of response magnitudes to louder sounds. These phenomena are most often interpreted as a deficit in the central action of serotonin, though other neuromodulators such as dopamine also affect this kind of response habituation (De Keyser et al., 2021). These abnormalities normalise in the premonitory phase and remain normal (or can overshoot) in the migraine attack phase. We interpret this as indicative of serotonergic hypofunction interictally, with a shift towards normal or hyperfunction before and during migraine attacks. Whilst a unifying role for serotonin in sensory processing has not been established, we posit that it may promote the updating of perceptual predictions based on sensory input, perhaps in part due to the drive to increased sensory precision resulting from prediction errors.

Increased attenuation of sensory responses during migraine attacks could also in part be due to reduced dopaminergic action occurring at that time. It is notable that migraineurs are hypersensitive to dopamine administration interictally, leading to symptoms characteristic of the premonitory phase (DaSilva et al., 2017; Akerman and Goadsby, 2016). Whilst dopamine release may rise in the run up to a migraine attack, central dopamine release has been found to fall during the attack itself (DaSilva et al., 2017). Falling dopamine might therefore be a cliff-edge phenomenon, producing the transition between the premonitory and attack phases, which are otherwise largely indistinguishable based on subcortical activity and indicators of serotonergic function.

Other neuromodulators whose levels or activities might acutely drop to commence the attack phase are noradrenaline and/or acetylcholine. Both of these have an action in maintaining attentional focus, and the sharpness (or specificity) of sensory inputs, (Moran et al., 2014; Slater et al., 2022; Jacob and Nienborg, 2018; Dahl et al., 2020; Hasselmo, 2006; Sarter et al., 2001) and therefore help to balance much of the broadly increased sensory gain during the premonitory phase. A release from this inhibition could catalyse the migraine attack. Noradrenaline as a determinant of attack timing would seem advantageous, as its level would be maintained during periods of acute stress or threat, and the migraine attack provoked by its subsequent fall would therefore be timed to coincide with the end of that period, when it would be safest to have a period of behavioural withdrawal. We note that noradrenaline reuptake inhibitory are sometimes effective as migraine prophylactics.

4.3. Peripheral neuromodulators

An alternative, or additional, explanation to acutely falling central monoaminergic activity is that the migraine attack itself is triggered when precision or gain increases reach the peripheral level. Abnormalities of the peripheral serotonin system have been identified in migraineurs, though blanket increases or decreases are controversial. Additionally, the utility of antidopaminergic medications in treating the pain and autonomic stasis of migraine episodes is hard to explain based on its central action, but would fit with suppressing dopamine's peripheral actions.

Serotonin is also a factor in influencing the release of CGRP, which in recent years has taken centre stage as the key player in in mediating the nociception and other sensitivities characterising migraine episodes, (Wattiez et al., 2020) and is also similarly broadly distributed across sensory organs (Mai et al., 2014; Blixt et al., 2017; Le Prell et al., 2021b). We note that whilst the triptans, which are serotonin 1b/d agonists, are useful for acute migraine therapy, they are thought to act through inhibition of peripheral CGRP (see below) and furthermore the centrally acting selective serotonin reuptake inhibitors (SSRIs) have little clinical

benefit in migraine prophylaxis. CGRP rises during spontaneous migraine episodes, administering it causes migraine episodes, and blocking its action prevents and treats migraine episodes. Our model is consistent with this 'final common pathway' position of CGRP, and might suggest that at a systems level its role is increasing the precision of unresolved IPE at the peripheral level in a topographically and temporally broad manner.

4.4. Migraine aura

Aura occurs in a significant minority of migraineurs, and is believed to be the result of *cortical spreading depolarisation/depression* (CSD), though this has only been observed in animals. Interictally, people prone to migraine have an increase in visual *centre-surround suppression*, (Battista et al., 2011) which is a manifestation of the inhibition (or attenuation of excitation) that occurs when large areas of visual cortex are stimulated together, along with a wider range of visual integration deficits such as detection of coherent motion across multiple visual elements (Battista et al., 2010). Whilst it has not been studied how surround suppression changes in the premonitory and attack phases of migraine, it is possible that surround suppression falls acutely, if it has been persistently overactive to compensate for increased gain at lower levels. An acute loss of inhibition in an area of cortex already subject to prolonged excessive input might therefore catalyse the onset of spontaneous depolarisation, initiating migraine aura. Once commenced, there are a variety of routes via which aura can rapidly trigger other aspects of a migraine attack, including through generating further prediction errors that drive migraine, through direct activation of the trigeminovascular system, and/or through loss of cortical inhibition of intermediate level prediction errors.

5. Part 4: migraine features explained by our model

5.1. The 'benefits' of migraine

Whilst previous models have tended to characterise migraine as solely an undesirable or unavoidable flaw or limitation of our sensory systems to which certain individuals are predisposed, our model highlights several benefits of both underlying migraine biology, and of the migraine attack itself, including why it is evolutionarily conserved at a higher rate than should be expected for any tendency that is solely a 'disorder', and also the benefit at a population level of having different individual migraine propensities.

5.2. Evolutionarily conserved differences in propensity to migraine

As IPE is an advance predictor of allostatic failure, it is not a perfect signal, but rather is subject to limitations based on its sensitivity and specificity. The resultant rate of false negatives (unanticipated instances of allostatic failure) and false positives (migraine episodes unnecessarily triggered) depends also on the threshold of IPE at which migraine episodes are triggered. This may be largely genetically determined, and at a population level it seems advantageous to have individuals with a range of thresholds, so as to mitigate the risks of a whole group succumbing to the same physical threat or harm, or all simultaneously withdrawing (potentially unnecessarily) from a particular situation. We also speculate whether aspects of modern life (e.g. artificial lights, chaotic sleep-wake rhythms and multiple competing attentional demands) are more likely to push the brain to boundaries of allostatic control than encountered through most of human evolution.

5.3. Cyclical and chronic migraine

Whilst many migraineurs have sporadic episodes, in some patient groups migraine has been characterised as a spontaneously cyclical brain disorder (Gallardo et al., 2022). This may well show a degree of correspondence with a clinical category termed *high-frequency episodic migraine* (i.e. between 8 and 14 headache days per month related to migraine), but we refer here more to the apparently spontaneously-occurring (as opposed to 'triggered') onset of episodes rather than necessarily frequency of these per se. Furthermore, a significant minority of patients experience *chronic migraine*, with headache or overt migraine occurring on the majority of days, in many cases with a persistent constant background headache. We outline in this section both how cyclical and chronic migraine can emerge from sporadic episodes.

5.3.1. Cyclical migraine

As we have discussed, certain brain responses, such as habituation to repetitive external stimulation, show differing behaviour approaching/during episodes compared to interictally. If similar patterns of brain responses to internal stimulation occur (which has not been tested experimentally) then this could explain how migraines can become cyclical and spontaneous. During a migraine episode, interoceptive signals are experienced with particularly high intensity (due to increased gain at intermediate and low levels), and at a cortical level there is enhanced perception (updating of internal models based on sensory signals). This is effective in reducing IPE in the short-term through stabilising physiological states towards set levels. However, perhaps due to depletion of the key neuromodulators, following the episode the opposite pattern may occur, where there is reduced intermediate and low-level gain, and reduced perception (i.e. prediction updating) at a cortical level (with interictally observed sensory habituation deficits indicating this reduced perception). This effectively causes a state of interoceptive hyposensitivity, allowing IPE to accumulate due to less accurate allostatic models and reduced high-level awareness of errors. If neuromodulatory control of interoception is restored to normal levels without excessive levels of IPE occurring then the system returns to its baseline state; however, if IPE are allowed to accumulate sufficiently then, as gain control returns to normal levels, IPE is already over the threshold for another migraine episode to occur. Thus, rather than operating around a stable mean level of gain control on interoception, the system oscillates between states of interoceptive hypersensitivity (i.e. migraine) and hyposensitivity. Whilst the optimal long-term operating mode would be enduring allostasis, where this is not achievable based on available allostatic models, the best possible alternative becomes this cyclical form of physiological regulation, where flexible behavioural and volitional goals are prioritised most of the time, but are not compatible with maintaining allostatic accuracy over long timescales, resulting in discrete periods of enforced relative homeostasis to restore allostatic accuracy and achieve a similar net effect.

5.3.2. Chronic migraine

In certain circumstances, the organism's particular combination of physiology, allostatic models and external environment do not permit unrestricted volitional activity for much, or any, of the time. This could be due to unusual stressors such as physical illness or a hostile external environment. However, in other cases, all that is required out of the ordinary is sufficient breakdown of accurate allostatic models; if a situation is reached where all courses of action are associated with high levels of irreducible uncertainty, then the optimal response becomes to limit the amount of action allowed per se. In chronic migraine, therefore, persistent or very frequent low-grade migraine symptoms can be considered a 'throttle' on the amount of activity or stimulation permitted to the organism, acting to contain IPE to safe, albeit still elevated and aversive, levels. Once there has been persistence of the migraine state for a sufficient period of time, the very fact that migraine processes are relied upon to resolve IPE, rather than accurate learned associations between physiological causes and effects, degrades the accuracy of allostatic models, perpetuating the chronic migraine state. As such, sensory attenuation is further reduced because changes are perceived as less self-generated. Furthermore, the positive feedback

cycle between increased IPE and increased precision on that IPE continues at a moderate persistent level (termed *central sensitisation*), as the elevated IPE has become irreducible. This account is compatible with accounts of chronic migraine based on excessive *allostatic load*, (Borsook et al., 2012) which is typically understood as the cumulative consequences of elevated baseline stress levels on an organism's physiological systems. Taking 'stress' to specifically indicate IPE, and 'baseline' to refer to the irreducible component, then 'allostatic load' is synonymous with the consequences of irreducible error. Given that we have argued that the role of migraine can be understood as causing a transient increase in IPE in order to facilitate a subsequent lasting reduction (i.e. it involves increasing stress in order to reduce stress), it is easy to see that if the subsequent reduction does not follow (for instance, if IPE is already down to its irreducible level) then migraine may become continuously triggered simply on account of the stress that the migraine itself creates.

5.4. Free energy and thermodynamic energy

Active inference is typically expressed using the *free energy principle* of the brain (Friston et al., 2006), which is inspired by the concept of *free energy* in physics, but refers to variational free energy in the informational rather than thermodynamic sense. *Efficiency* is simply the minimisation of free energy. There are alternative formulations of free energy (all formally identical but with complementary interpretations), of which the most useful one here is that *free energy* equals *complexity* minus *accuracy* (or, *complexity* plus *inaccuracy*). *Inaccuracy* is simply prediction error, whilst *complexity* reflects the degrees of freedom used up in providing an accurate account of data (i.e. the cost of updating prior beliefs when processing sensory evidence). Crucially, there is a thermodynamic cost associated with the requisite belief updating, which means that variational and thermodynamic free energy share the same minima (Sengupta et al., 2013). In short, the distinction between variational and thermodynamic free energy need not necessarily exist in the context of allostatic regulation.

The decomposition of free energy into accuracy and complexity speaks to the level of hierarchical control of physiology; higher-level (goal-directed or allostatic) functioning is associated with high complexity, which is only licensed when accompanied by high accuracy (i.e. low levels of IPE at lower hierarchical levels). Conversely, low-level homeostatic responses are engaged when the complexity cost of a high-level allostatic exceeds the increase in accuracy it affords.

The degree of activity of a particular brain area is directly proportional to the computations it is conducting, which in turn depend on the amount of informational free energy (or prediction error) it is having to resolve. This computational activity requires physical energy in the thermodynamic sense, which is therefore strongly correlated to informational free energy. It is possible that the parallel ends there, or that physical energy (e.g. ATP availability) imposes a limit on brain activity, and that reaching or exceeding this limit acts as a physical trigger of migraine attacks, as the culmination of excessive informational free energy from unresolved IPE. For instance, in the case of migraine aura, the initial loss of cortical level inhibition, as postulated above, could result from local neuroenergetic failure, manifesting initially as loss of local inhibition, followed typically by loss of excitation (resulting in the positive and negative symptoms of migraine aura, respectively). Outside the context of migraine aura, overloading the capacity of key brain areas to resolve prediction errors could act as a cliff-edge phenomenon leading to rapid escalation of IPE, and/or interoceptive sensing of the local neuroenergetic deficit could constitute another source of IPE to trigger the onset of migraine.

5.5. Migraine triggers vs. premonitory symptoms

An area of ongoing controversy in migraine is distinguishing migraine triggers from early symptoms of migraine (Karsan et al., 2021). For instance, patient reports of migraine episodes being preceded by exposure to strong light could reasonably be interpreted as evidence that light acts as a migraine trigger, or alternatively that photophobia is an early symptom of migraine. There is some evidence that the same modalities can feature as both triggers and early symptoms in the same individuals (Casanova et al., 2022). In our account of migraine, this dichotomy disappears, since specific modalities are not only able to act as both triggers *and* early symptoms, but are actually expected to behave in this way. We have proposed that the initiating event for migraine is prediction error within one or more specific modalities, leading to enhanced gain/precision on those modalities (i.e. a positive feedback cycle) which subsequently spread cross-modally. Therefore, it follows that an individual's sensory modalities most susceptible to forming these positive feedback cycles are both those in which prediction errors generate migraine episodes, and in which premonitory gain increases are most strongly experienced.

5.6. Migraine and interoception

A key insight from this account of migraine is the fundamental importance of interoception, as an afferent limb of allostasis, which may determine individuals' proneness to migraine episodes, and serve as a non-pharmacological avenue for migraine prevention; migraines could be prevented by improving interoceptive abilities, applying existing interoceptive abilities more, and/or by reducing the demands placed on interoceptive monitoring systems.

Interoception is often divided into three domains (Garfinkel et al., 2015): *interoceptive sensibility*, the subjective sense of how strongly interoceptive signals are perceived; *interoceptive accuracy*, the objective ability to correctly perceive interoceptive signals (with counting of heartbeats being the most commonly assessed measure); *interoceptive awareness*, the metacognitive correspondence between self-perceived and objectively determined interoceptive accuracy.

Whilst there are likely a host of other genetic and other influences on individuals' triggers, thresholds, frequencies and clinical features of migraine, we posit that these interoceptive traits may be important in determining migraine frequency. Interoceptive sensibility might be positively correlated to migraine frequency, if it indicates higher gain or precision on IPE, leading to more instances of levels of IPE crossing the threshold for triggering migraine. Alternatively, it could be negatively correlated to migraine frequency, if greater conscious perception of bodily states (i.e. at a cortical level) means that allostatic needs are addressed at an earlier stage, preventing the progressive build-up of IPE at lower hierarchical levels. As a further possibility, greater interoceptive accuracy might help to prevent migraines, by reducing IPE themselves through the formation of more accurate allostatic predictions. Finally, there might be an even more specific link, with a further interoceptive ability which we newly propose, interoceptive forecasting (i.e. accuracy of expectations about future internal bodily states), being protective against migraine episodes. Females have significantly lower interoceptive accuracy than males (Prentice and Murphy, 2022) (though, this does depend on the interoceptive modality and task), which provides one possible explanation or contributor to the three-fold higher prevalence of migraine in females than males. Surprisingly, to our knowledge, no studies have examined interoception in relation to migraine, therefore these possible relationships are presently speculative, but are easily amenable to future research.

Therapeutically, if migraine is associated with interoceptive deficits, then interoceptive training might be effective in helping to prevent migraine episodes. This fits in the increasingly popular framework of considering migraine not as a purely biomedical disorder, but a condition that is intertwined with a wider biopsychosocial network (Rosignoli et al., 2022). Training interoceptive accuracy via synchronisation with auditory tones has shown benefits in anxiety states, (Sugawara et al., 2020) and such approaches might help in migraine if deficits in interoceptive accuracy were to be found. Additionally, if migraine were associated simply with a lack of monitoring of interoceptive signals then

more straightforward strategies could include regular prompts to monitor one's internal state. This approach has similarities to mindfulness, for which a handful of small studies have shown some improvements in secondary measures related to migraine and overall symptom burden, but not in reducing the number of migraine attacks (Wells et al., 2020). Mindful awareness in body-oriented therapy (MABT) is an example of a more nuanced and individualised psychotherapeutic framework for facilitating interoceptive awareness and its integration with self and state of health, including identifying, accessing and appraising interoceptive sensations, (Price and Hooven, 2018) though this has not been applied to migraine. Wider interoceptive manipulations have been proposed, including MABT, breathing manipulation vagal nerve stimulation (VNS) and combined approaches (Weng et al., 2021). VNS has been applied for migraine prevention in multiple trials, with auricular application particularly showing some effect in reducing migraine days (Song et al., 2023). If the efficacy of VNS is due in part to its effect on interoceptive inference then identifying its specific mechanisms might help to develop more effective treatment approaches involving VNS, and/or to find other ways of achieving similar interoceptive changes. These issues have been discussed elsewhere from an active inference perspective (Ainley et al., 2016; Corcoran et al., 2020; Duquette, 2017; Fotopoulou and Tsakiris, 2017; Peters et al., 2017).

These possible future therapeutic avenues are consistent with, and build upon, existing clinical advice for patients to: 1) Live life more on the 'straight and narrow', reducing interoceptive prediction errors; 2) Gradually build up 'tolerance', i.e. predictive capacity. The latter should be done outside of the migraine phase itself, reconciling how exercise, for example, is both a trigger, exacerbator and a preventative.

5.7. Psychological links

Links between psychopathology and migraine are well-established, for instance with anxiety (Karimi et al., 2021) and past emotional trauma (Brennenstuhl and Fuller-Thomson, 2015) both increasing future migraine risk. Mechanistic explanations have included stress, muscle tension and/or serotonergic deficiency as common risk factors for, or consequences of, both conditions. However, we propose a more direct causal link based on this account of migraine. *Embodied* models of emotion propose that affective sensations are perceived as visceral sensations in the body, and rely on interoception for their correct identification and processing. The spatial mapping of emotions in the body has been characterised, (Nummenmaa et al., 2014) and there is also evidence that interoceptive training can improve symptoms of anxiety (Sugawara et al., 2020). We propose three alternative or complementary accounts of how interoception might be the mediator or common factor in the link between anxiety and migraine. 1) The *somatic error theory* of anxiety (De Preester and Manos, 2018) proposes that the initiating anxiety signal is a mismatch between predicted and sensed bodily states (i.e. IPE), which may result in unpleasant perceptions, prompting negative reactions and learned associations. Elevated levels of IPE might therefore drive both anxiety and migraine. 2) The unpleasant interoceptive signals associated with certain psychopathologies can lead to a compensatory direction of attention (i.e. gain or precision) away from interoceptive modalities, thereby creating a deficit in interoceptive accuracy or awareness, (Schaan et al., 2019) which allows greater accumulation of consciously undetected IPE that go on to trigger migraines. 3) Trait anxiety has been shown to associate with a reduced ability to mobilise the anterior cingulate cortex to attenuate surprising or potentially threatening task-irrelevant distractor stimuli (Bishop, 2009; Bishop et al., 2004); in our framework, this equates to allowing diverse and multimodal sensory prediction errors to persist unchecked at a cortical level, thus driving their resolution through subcortical gain increases. Note that none of these accounts necessarily implies that the increased tendency to migraine is always bad, as lowering the threshold for withdrawal behaviour when faced with potential threat or harm might be a way of 'learning' from previous trauma. However, in excess, the resultant migraines can be the cause of further suffering, distress and anxiety.

5.8. Pharmacotherapy for migraine prevention

Our model does not highlight previously unknown pharmacotherapeutic actions of existing preventative agents, but does provide a common framework within which to consider their levels and types of action. The three main classes of oral prophylaxis are antidepressants, anticonvulsants and antihypertensives, and injectable treatments act at peripheral nerves or synapses. Whilst we have highlighted evidence for a role of serotonin in migraine, selective serotonin reuptake inhibitors (SSRIs) have only a weak prophylactic effect, whereas serotonin and noradrenaline reuptake inhibitors (SNRIs) have a stronger effect, highlighting the importance of both neuromodulator systems. We have argued that these neuromodulators are key players in controlling the hierarchical level of precision/gain, and it therefore stands to reason that stabilisation of their levels would protect against switching into migraine states. Beta blockers and angiotensin receptor blockers both reduce sympathetic nervous system activity, and we have argued that changes in autonomic tone may constitute a form of IPE in their own right, as well as modulating the processing of other sensations and actions: acting in a wider and more context sensitive way across a range of IPE. Furthermore, we speculate that high sympathetic tone allows IPE to accumulate, and the ensuing fall abruptly removes the stabilisation that delays the migraine episode. Therefore, limiting peaks and stabilising levels of sympathetic activity should help prevent migraine episodes.

Anticonvulsants have neuronal membrane stabilising properties, which might limit neuronal responses, effectively reducing the level of IPE that they are able to encode. Finally, and importantly, blocking peripheral nerve activity (e.g. with botulinum toxin, nerve blocks or anti-CGRP monoclonal antibodies) blocks, what we argue is, the final and common stage in the migraine process: namely, the transmission of precision/gain increases to the periphery, and the ensuing noxious hypersensitivity. This may be, one the one hand, the approach that is effective in the highest proportion of cases, as it targets a final common pathway. It is also one that has perhaps the least effect in addressing the wider systems behaviour underlying migraine, and may therefore have a more limited ability to achieve sustained remission once therapy is withdrawn, except in helping break a cycle of persistent peripheral hypersensitisation.

Behavioural measures commonly employed by migraineurs, such as avoiding external stimulation or wearing dark glasses to reduce light intensity, can also be considered as having a similar effect to peripheral nerve activity blockade, by attenuating sensory input. However, the duration of benefit of these is likely to be low, due to ensuing central compensation.

5.9. Placebo responses

As placebo responses essentially result from predictions of improved symptoms, we consider here the implications of our model of migraine — as a disorder of predictive processing — in understanding placebo effects. We first consider that there are known mediators of placebo analgesia, (Benedetti et al., 2005) principally activation of the endogenous opioid system, which has similar effects to exogenously administered opioids, including abolition with opiate blockers such as naloxone. Furthermore, a range of other neuroendocrine and immune actions can be prompted by cue-based expectations, provided they have been previously conditioned with a physical inducer of those actions, e.g. a medication. With this in mind, placebo effects in migraine could act as placebo analgesia, or simulate the actions of a variety of endogenous or exogenous processes. More specifically to predictive processing, placebo effects have been explained in at least three forms relevant to our model (Pagnini et al., 2023). Firstly, placebo effects can be considered to constitute high-level priors, which generate top-down predictions (e.g.

of non-migraine states) that shape perception and action in accordance with these priors. Secondly, prior beliefs shape the way in which our brains sample sensory evidence (attending to, or increasing the precision on, sensory inputs that are relevant to confirming those beliefs, and ignoring those that are contradictory, i.e. via sensory attenuation), meaning that expectations of particular migraine-related symptoms improving would lead to reduced responsiveness to sensory inputs related to those symptoms. Finally, mindful attentiveness can be considered a form of placebo effect, in which sensory signals (including interoceptive ones) are attended to without bias as to their implications or desirability. The ensuing removal of negative associations with interoceptive signals might allow these to be monitored more accurately — and their sources more correctly inferred — than in disordered states of interoceptive processing associated with an excessive tendency towards migraine.

5.10. *Relationship with other disorders of self-regulation*

Our model of migraine sits well within allostatic and active inference frameworks alongside a variety of other common symptoms and disorders, which are also shown to have epidemiological associations with migraine. These include fibromyalgia, (Vij et al., 2015) chronic fatigue, (Lau et al., 2015) chronic widespread pain, (Stuginski-Barbosa et al., 2012) irritable bowel syndrome (IBS), (Wongtrakul et al., 2022) postural orthostatic tachycardia syndrome (POTS) (VanderPluym et al., 2018) and functional neurological disorder (FND) (Arbabi et al., 2022).

The first, general observation, is that in general these disorders are characterised by the excessively intense, spontaneous, frequent or persistent occurrence of symptoms which in a more limited and context-dependent setting are clearly advantageous to the individual. For instance: acute pain is vital for preventing the occurrence or exacerbation of tissue injury, whilst chronic pain is distressing and disabling; acute fatigue encourages rest and recovery to facilitate optimised functioning over longer timescales, whilst chronic fatigue is disabling; acute gastrointestinal irritation is an important part of purging toxins and infections, whilst IBS is unpleasant and impairs functioning. Our model is the first to place migraine into this scheme, demonstrating the benefits to the individual of having migraine as a protective response in certain situations, whilst recognising the potential for migraine to be excessive, or become a self-sustaining disorder in its own right.

We then consider why having one such symptom occurring as part of a disordered state is associated with increased risk of other symptoms entering similarly disordered states. Whilst a comprehensive account would require a series of papers in its own right, we highlight some general associating principles here. Firstly, there are shared risk factors in the form of inherited sensitivity traits, past adverse events, physical health, current life stressors and quality of restorative processes such as sleep. These conditions also share common symptoms, in the form of increased noxious sensitivity and/or reduced voluntary action, and may share underlying contributing mechanisms, such as a failure of sensory attenuation. Additionally, the adverse symptomatology of one condition likely acts as an additional stressor towards the precipitation of other disordered symptom states. Furthermore - akin to our claim in migraine relating to Ashby's principle of requisite variety - other related symptom states also act as variety attenuators, in terms of simplifying the individual's interactions with their environment, prompted by an inability

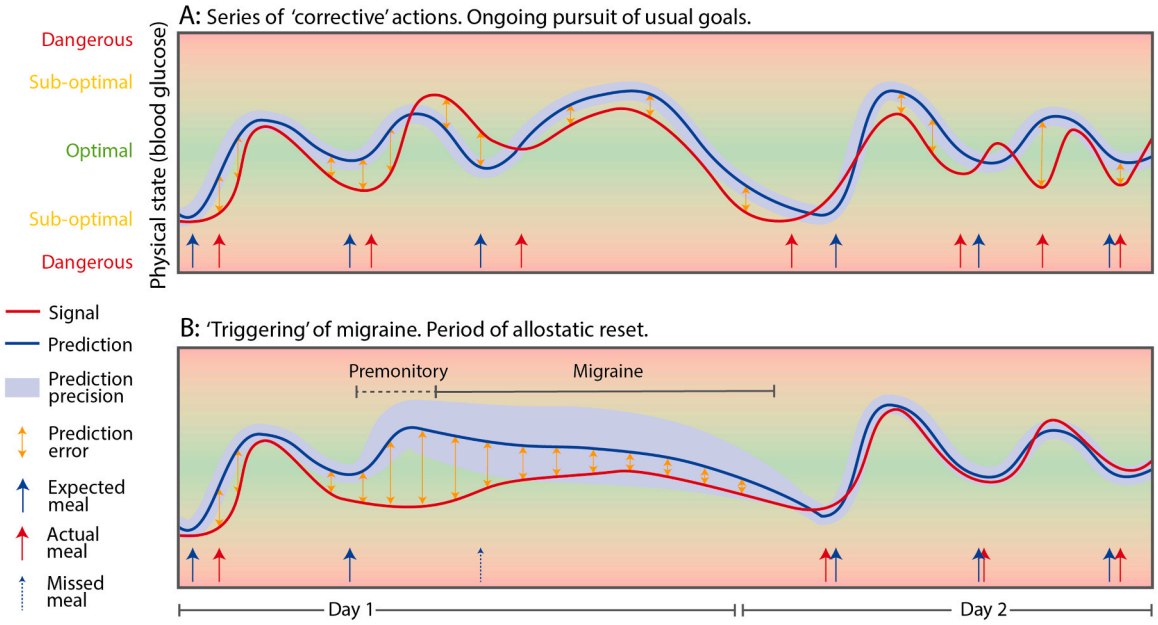

Fig. 4. Example predicted and actual time courses of an indicative physical variable (blood glucose), and their regulation with and without migraine. The body can function efficiently across a range of physical states (red curves), which can include time-limited excursions into sub-optimal states (colour gradient) if these are predicted (blue curves) with sufficient accuracy (precision of predictions indicated in light blue, represented as their inverse, i.e. variance). The two main panels illustrate different mechanisms of resolving prediction error (orange arrows), in a scenario similar to that described in Box 2, where an individual has been late with breakfast, eaten something more sugary than usual, and subsequently been late with lunch. A: If migraine does not occur, or the individual has a high migraine threshold, they react to prediction errors through corrective action, but from a constantly changing state, which can make it difficult to realign their state with their prediction. In this example, the individual continues working, eats a late lunch, by which time they are hungrier, and once again eat something more sugary, and this time larger. They are then not hungry at their usual evening meal time, and eat a smaller snack later. They are then hungry overnight, and wake early for breakfast. Being tired and out of their usual rhythm, they then eat a series of smaller snacks, which generate a variable and unstable pattern of ongoing prediction errors. B: If a migraine is triggered by the elevated prediction error, neuromodulatory changes render prediction error precision high, leading to withdrawal behaviour and loss of appetite, and predicted precision low, leading to the predicted state drifting towards the actual state. Prediction errors are resolved slower, and with the downside of temporary aversive symptoms and functional limitation, but the stable convergence of predicted and sensed states allows subsequent restoration of predictable routines and predicted accuracy. For simplicity, only one physical variable has been considered, and changing of predictions in light of prediction error has not been illustrated except in migraine. Incorporating these complexities would allow even greater fluctuating prediction errors than those seen in A, which lead to increased allostatic load, reduced efficiency, and a greater chance of entering dangerous physical states.

to adequately respond to an unpredictable situation. In doing so in a repetitive or persistent way, they may likewise reduce the individual's response variety in the longer term, increasing the probability of further such symptom states occurring in future. Within active inference frameworks, all such symptoms are aiming to reduce the uncertainty faced by the individual across certain systems, scales and timeframes, but become disordered when their occurrence creates a net increase in uncertainty over larger scales or timeframes.

6. Part 5: testable hypotheses

The main advance here is the overall framework describing the systems-level causes and consequences of migraine. We have linked this to specific putative neurobiological processes as far as present evidence allows, with a degree of speculation for areas presently lacking conclusive evidence. As such, it is inevitable that some aspects of the claims made herein will be inaccurate. The key question is whether the overall described behaviour of allostatic systems is as we propose. We suggest here a number of testable hypotheses that might support, refute or refine these claims.

6.1. Computational modelling

Ideally, a family of computational models of allostasis should be created, based on competing hypotheses, and fitted to empirical behavioural and/or physiological data. This is possible, but, given the breadth and complexity of the systems involved, seems some way off. However, a simplified proof-of-principle model seems within reach, based on a limited number of sensory modalities and hierarchical levels, and the two key types of gain control (high-level and specific, vs. low-level and broad).

6.1.1. Interoceptive evoked response studies

As our claims can be viewed as a form of sensory attenuation acting broadly on interoceptive modalities, these should be testable using interoceptive evoked response paradigms, where we would predict equivalent findings to those seen with exteroceptive stimulation, including loss of repetition suppression, and loss of differentiation between 'standard' and 'deviant' responses in oddball paradigms. Furthermore, these changes should evolve longitudinally over the migraine cycle in line with our hypotheses. Such studies are more technically challenging than auditory or visual stimulation, but are nonetheless possible.

6.1.2. Dynamic causal modelling (DCM)

As a middle ground between computational models and measured brain responses, DCM studies can compare alternative models or hypotheses based on their relative performance in explaining observed patterns of measured brain activity. In the case of our hypotheses, DCM studies of interoceptive and/or exteroceptive brain responses over the migraine cycle could characterise these in terms of underlying hierarchical gain control parameters.

6.1.3. Cross-modal gain

One of our central claims is that the premonitory phase and migraine attack are provoked by prolonged interoceptive or exteroceptive stimulation, and characterised by increased sensory gain both within and across sensory modalities. This presents a clear testable hypothesis that frequent migraineurs manifest increased gain in multiple sensory modalities, following repetitive stimulation in one modality, compared to controls.

6.1.4. Interoceptive traits and states

We have highlighted several potential interoceptive deficits that might associate with increased migraine frequency, which can easily be tested. These include increased or reduced interoceptive sensibility, reduced interoceptive accuracy, and/or a specific deficit in interoceptive forecasting. As well as linking these to migraine frequency, these measures can be tracked longitudinally over the migraine cycle to better establish cause and effect relationships.

6.1.5. Predictable triggers

If our claims are correct, then migraine triggers exert their effect insofar as they generate prediction errors. This might be evaluated empirically, for instance by exposing migraineurs to equivalent exteroceptive or interoceptive triggers with varying degrees of predictability. Additionally, helping migraineurs to better predict triggers, and their interoceptive consequences, might mediate the benefits of lifestyle interventions such as regular exercise, or even form the basis of an explicit therapeutic approach.

7. Conclusions

Based on recent advances in the understanding of allostatic systems, and their operation according to principles of active inference, we highlight their inherent propensity for compound and catastrophic errors, necessitating an early warning system which, we argue, uses interoceptive prediction error as a signal for possible impending allostatic failure. We show how the behaviour of such a failsafe mechanism, mediated by an increase in broadly-projecting subcortical gain systems, concords with the triggers, clinical features and neural correlates of migraine. In doing so, we present a formal framework in which migraine is a consequence of an adaptive and beneficial process (a 'defence' rather than an 'attack'), and show how interoception may be highly relevant in individuals with frequent migraines, and a novel avenue for research and treatment. Validation, refinement and exploitation of our model may be accomplished through examining the numerous testable hypotheses to which it immediately leads.

Competing interests

The authors report no competing interests.

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