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Review

Integrated neuroimmune processing of threat, injury, and illness: An ecological framework mapping social alienation onto lifetime health vulnerability

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ABSTRACT

Social alienation is a pre-eminent ecological threat for humans. In clinical and social care settings its impact is acknowledged in conditions as diverse as severe mood disturbance, chronic pain, and metabolic non-communicable diseases. An integrated psychoneuroimmune perspective shows how threat, injury, healing, and recovery follow through as a continuous process, but accepted cultural and clinical paradigms separating mental from physical illness provide little common ground on which to analyse and apply this continuum in practice. By reviewing the ecological relationships between emotional threat, tissue dyshomeostasis and injury, infection, pain, and mood this article explores not only how primeval somatic responses underpin the evolutionary foundations of depression and somatisation, but also links them to escalating physical non-communicable disease through archived socioeconomic adversity (allostatic load). Social alienation (in the absence of trauma) may prime and activate this ancient repertoire in which sensitised responses lay the foundation for persistent maladaptive states of aversive sensory misinterpretation, behavioural avoidance, anhedonia, and neuroinflammation presenting as widespread non-nociceptive pain, non-pain somatisation, and severe depression. The ecological perspective illuminates perverse clinical presentations, shows how some approaches to care may facilitate self-reinforcement in maladaptive syndromes, and offers pointers for inclusive rehabilitative clinical and social care.

1. Introduction

This article had its origins in a clinician's search for a comprehensive understanding of pain which persists after any triggering injury has ceased. That search rapidly showed how different non-nociceptive pain is from acute pain, and how similar it is (from a psychoneuroimmunological perspective) to mood disturbance following emotional trauma and social alienation such as shame, depression, anxiety/post-traumatic stress disorder (PTSD), and grief. This article with sister articles in preparation seeks to integrate and validate key aspects of this accumulating knowledge linking emotional distress to somatic symptoms and *vice versa*, with the final objective to communicate this emerging science to colleagues in clinical and social care practice. The overarching lesson from this project is that understanding maladaptive physical-with-emotional illness requires much more than a simple gene-environment model of causation. Genes contribute predisposition, and contemporary environment introduces the tapestry of potential stressful triggers, but the embodiment of experience through archived neural and immune learning (from pre-conception onwards) is the key source of vulnerability to complex persisting pain and mood disorders – the soil of experience into which the seed of threat, injury, and illness falls. This early history may explain perverse motivations leading to inhibited recovery often unrecognised by those who develop maladaptive illnesses.

There are four main themes from the project elaborated in this review. Firstly, how neural and immune function is intimately integrated. Secondly, how the concept of self is central in trauma and recovery, and how self-image and self-efficacy are founded in interoceptive and proprioceptive surveillance of successful or unsuccessful ecological engagement. Thirdly, how experience is archived in implicit neural and immune memory, resulting in the embodiment of emotion and cognition from trauma through recovery. Fourthly, how threat has preceded and predicted injury, starvation, and illness throughout evolutionary time leading to a continuous psychoneuroimmune response repertoire from threat (perceived emotionally) through injury and illness (perceived physically), to recovery (motivated emotionally and executed physically). In this ecological continuum, early avoidance (from fear, pain, heightened risk-awareness, and anhedonia) is gradually displaced through the motivational shifts associated with healing, reward re-

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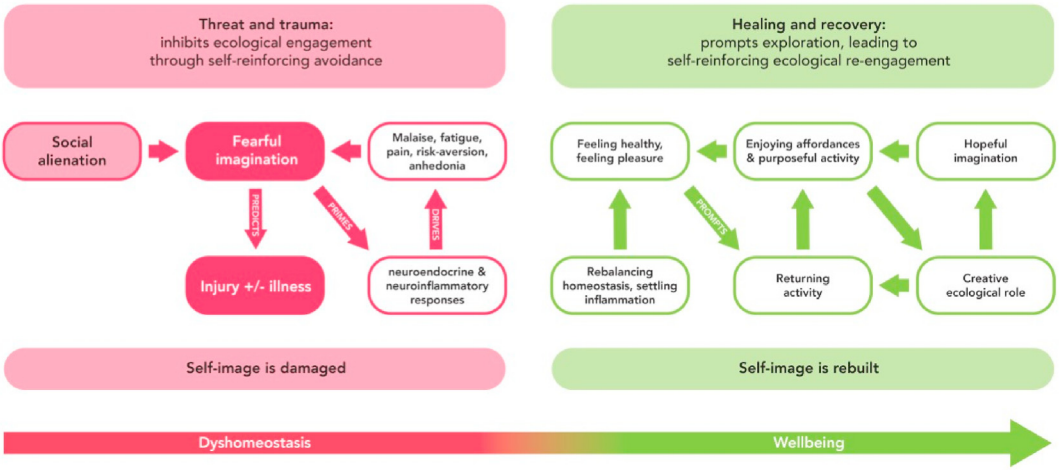

Fig. 1. Neuroimmune motivational influence on ecological engagement: a continuum from fearful threat/injury/illness (dyshomeostasis) through avoidance and anhedonia to creative re-engagement with a hopefully imagined future (recovering wellbeing). Note the potential for reinforcement both within the trauma response (maladaptive) and during recovery (adaptive).

adjustment, risk-reassessment, exploration, purposeful activity and cognitive reappraisal, to hopeful ecological re-engagement (summarised in Fig. 1).

2. Neuroimmune learning: predicting and anticipating threat, illness, and injury

Neuroimmune learning is the process whereby experience is imprinted (through synaptic plasticity and immunocyte adaptation, sometimes with epigenetic reinforcement) to guide short- and medium-term metabolism and behaviour change, and for long-term protection. Salient experience is emphasised in accessible (explicit) memory, but all neural and immune surveillance will feed into the background implicit record for ongoing life management. The term allostasis, an iteration of the concept of homeostasis, describes how neuroimmune surveillance accumulates predictive data and adjusts physiological/behavioural parameters in anticipation of system imbalance (Schulkin and Sterling 2019). Initially applied to metabolism at the organism level, it is also relevant to interpersonal and societal disharmony (Saxbe et al., 2020). If stress and resulting homeostatic imbalance persist, more permanent adjustments reflecting the optimum response in the new circumstances are made to mitigate ongoing impacts of the stressor. Such allostatic adjustments are archived, contributing to predictive life management (Clark 2013; Seth 2013) through a cumulative record of biological stress and the organism's adaptive responses. This archive embodies resulting homeostatic tension against the ecological ideal, and future encounters with the triggering contexts may activate any neuroimmune arousal "remembered" from those contexts. Such sensitised triggering of neuroendocrine and neuroinflammatory responses (termed allostatic load, the long-term legacy of sustained threat and adversity, Fig. 2) introduces vulnerability to mental and physical illness and early death through inflammatory as well as metabolic activation (Hertzman and Boyce 2010; Rohleder 2014; Frank et al., 2019; Santini et al., 2021). Neuroimmune flexibility is greatest in childhood and adolescence, and these developmental periods are critical in laying the foundations for such vulnerability, but also in building resilience to mitigate those effects through social and emotional support (Fisher et al., 2016; Bellis et al., 2018; Ungar and Theron 2019).

As adaptive responses, both the synaptic and immune components of the integrated neuroimmune response to trauma are flexible – as healing and recovery follows injury or infection, both are updated through ongoing interoceptive/proprioceptive surveillance. Physical injury illustrates the complex and dynamic nature of trauma's neuroimmune impact. It provokes an immediate "fast pain" nociceptive response,

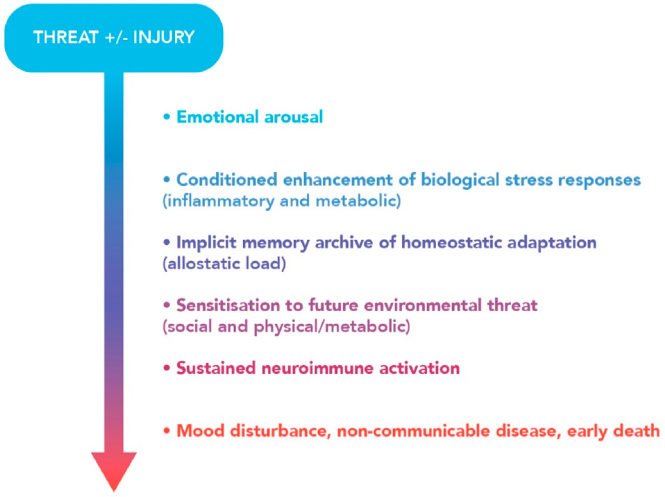

Fig. 2. Allostatic load archived following threat and adversity leads to cumulative neuroinflammatory impact on physical and mental health.

typically arising from high-threshold mechanoreceptors demanding defensive action through its characteristic salience. But as the inflammatory components of tissue damage build, a second neural with immune response often termed "slow pain" develops based on chemosensitive- (C-) fibres facilitating mechanoreceptor signalling and generating ongoing tenderness and pain on movement, in part through neuroimmune crosstalk (Chavan et al., 2017; Maruyama 2021). The early "slow pain" response includes altered synaptic thresholds and connectivity through the dorsal horn of the spinal cord and brain stem, but dyshomeostasis-derived neural plasticity permeates centrally leading to a complex and dynamic synaptic imprint introducing affective-motivational and cognitive-behavioural influence in addition to the sensory-discriminative awareness of the site of damage (Melzack 1968; Harvey 1987; Harte et al., 2018).

From an evolutionary perspective, "fast pain" warns of threatened and/or actual tissue damage and motivates avoidance – it shares an exteroceptive orientation with other systems monitoring threat from the physical and social environment such as vision and hearing. "Slow pain" has an internal orientation as a specialised form of interoception with which it shares unmyelinated neuronal characteristics, ascending neural pathways, and central termination in insular and cingulate cortices (Damasio and Carvalho 2013). Together, background

(interoceptive-homeostatic) and foreground (nociceptive-salient) sensory flow provides surveillance of tissue health, guiding physiological management of dyshomeostasis but also building emotional states motivating behavioural responses, epitomising the embodiment of emotion and cognition (Craig 2003; Medford and Critchley 2010; Seth 2013).

Rest and recuperation following severe injury is a fundamental biological necessity, and anhedonia has been crafted by evolution to support pain and fatigue in demotivating activity - by reducing the predicted reward from exploratory activity, anhedonia facilitates ecological disengagement (Borsook et al., 2016; Ferenczi et al., 2016). As physical injury's exteroceptive repertoire sensitises to environmental threat like anxiety, its interoceptive repertoire generates motivational features of depression in support of tissue healing. These associations between pain and mood are well recognised (Simons et al., 2015) but are commonly discriminated into distinct mental and physical processes, attributing causal direction between them using the traditional paradigm. A psychoneuroimmune interpretation provides a more parsimonious explanation – pain and mood are synergistic components of an ancient integrated repertoire responding to threat with injury. Distinct exteroceptive vs. interoceptive orientations can be extrapolated to emotional "injuries" such as shame and grief. Shame is initially exteroceptive, acutely nociceptive to the threat of social alienation. If socially reinforced it may become more inward-looking, demanding reflection on the individual's social position, in which case it may lead to neuroimmune inflammatory responses seen in other sustained mood disturbance (Rohleder et al., 2008; Slavich and Irwin 2014). On the other hand, grief is internally focused from the point of loss to facilitate self-care. It may also self-reinforce maladaptively as "complicated grief" through metabolic and inflammatory features characteristic of major depressive disorder (O'Connor 2012).

3. The dynamic influence of archived experience

To examine the complexity of these processes, consider the effects of a significant human limb injury such as ankle fracture. As its neural imprint permeates centrally, it modulates signals from multiple modalities, interpretating the experience within context. Note how our culturally embedded conceptual paradigm discriminates as "mental" some processes (shown in italics) that are central in adaptive "physical" recovery:

- Following peripheral C-fibre activation synaptic plasticity modulates transmission of mechanoreceptor signalling - touch becomes tenderness, movement becomes stiffness. The neural injury imprint is the incorporation of these synaptic adaptations in implicit memory. Professor Antonio Damasio's concept of interoceptive imprinting implies a baseline archive (the "master interoceptive map") which acts as a reference template against which injury- or illness-induced synaptic change sets up homeostatic tension, prompting and guiding healing by generating and resolving prediction errors ((Damasio 2010) page 190 et seq. and see (Clark 2013)).
- To facilitate healing the injured limb is unloaded through altered movement protocols in pre-motor and motor cortices networking with cerebellum.
- The early salient nature of the signal is set in the amygdala (Veinante et al., 2013).
- Prefrontal cortex (PFC) attention is influenced by amygdala-driven salience which it may accept or overrule according to strategic imperatives (Salzman and Fusi 2010).
- Interpretation of somatic surveillance (insula) and generation of injury-relevant behaviour (cingulate cortex) is biased according to the PFC-controlled strategic agenda (Medford and Critchley 2010).
- *PFC-basal ganglia networking shifts the balance of behaviour from exploratory (ecological default state) to risk-averse* (see (Addicott et al., 2017) for analysis of dynamic naturalistic response to risk).
- *Negative bias in reward-related processes networked through the lateral habenula may result in global anhedonia experienced as lowered mood* (Shelton et al., 2012; Fakhoury 2017).

But injury surveillance is necessarily dynamic - as it follows metabolic processes through healing, it shifts motivational direction for recovery (Fig. 3).

- Interoceptive surveillance of tissue healing integrates with proprioceptive surveillance of normalising movement embodying progress by updating injury mapping.
- As this data flow remodels self-image (working self-memory (Conway and Pleydell-Pearce 2000)) and self-efficacy, it prompts the expression of recovery through ecologically valued activities (Jensen et al., 2003; Benight and Bandura 2004).
- As neuroimmune feedback demonstrates return of a healthy efficacious self, it prompts cognitive/behavioural re-imagining of the post-injury future (Markus and Nurius 1986) leading to ecologically valued self-reinforcing behaviours.

4. Adaptive vs. maladaptive recovery and the central role of fear

During adaptive recovery from physical injury, salient interpretation of nociceptive signalling as fearful pain gradually reduces while interoceptive data flow within which it is integrated continues, largely unconsciously. This reflects the dynamic nature of the injury imprint as it initially biases system sensitivity and connectivity throughout the neural hierarchy, then adaptively prompts return to the pre-injury state in each affected domain. Top-down influence may facilitate or inhibit how the

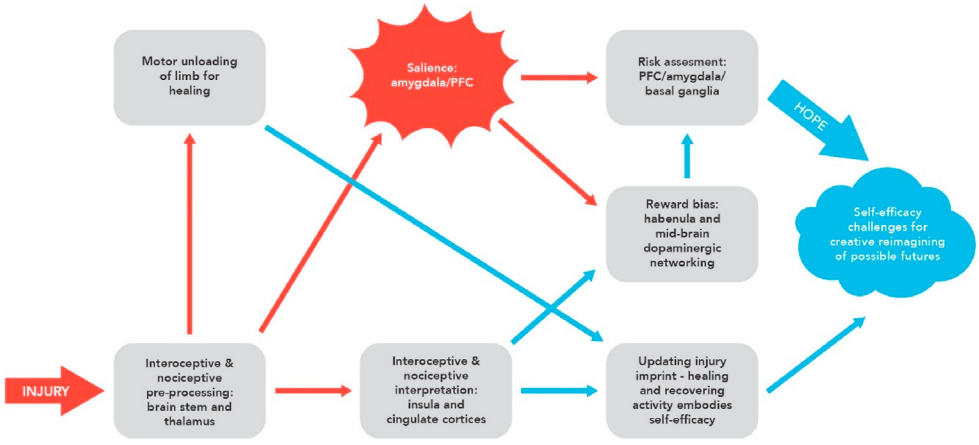

Fig. 3. Adaptive response to threat and injury. Early networking of bottom-up signalling following physical injury aversively influences central motivational bias (red arrows). As tissues heal and proprioceptive flow normalises, homeostatic rebalancing rebuilds the default state of adaptive hopeful self-efficacy, facilitating recovery top-down by resetting caution (blue arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Text box
Affordances (after (Withagen et al., 2017)).

The term 'affordance' was coined by the American psychologist James Gibson (1904–1979) for the neural outcome of an opportunity offered to an organism by its ecological niche ((Gibson 1979) chapter 8). The environment 'affords' the benefit, for example nutritious fruit or a key developmental trigger, beckoning the individual to interact. This process is strictly ecological - the organism's genetic priming, adapted by developmental experience, engages it with the affordance through neural reward. It is within the interaction that affordances are activated – a primed organism is automatically attracted to the affordance before understanding its potential or calculating how it will engage (Withagen, Araújo, and de Poel 2017).

injury imprint is updated. For example, hopeful health and social beliefs will positively bias sensory interpretation (Rhudy and Meagher 2001; Dunn 2012), and high self-efficacy will motivate innate exploratory behaviour (Jensen et al., 2003; Benight and Bandura 2004). Resulting engagement with environmental affordances will adaptively reinforce ecologically valued activity through neurochemical reward (see Fig. 3 above and text box on affordances).

On the other hand, fearful health and social beliefs will sustain adverse perceptual bias, promoting conditioned reinforcement of salient nociceptive flow (Mathews and MacLeod 2005; Hartley and Phelps 2012), inhibiting exploratory drive with maladaptive self-reinforcing avoidance (Vlaeyen and Linton 2000) (Fig. 4).

It is important to recognise how substantial a neural imprint can become when healing is arrested in maladaptive self-reinforcement, accumulating adversely perceived surveillance into the allostatic archive (McEwen et al., 2016). In chronic pain syndromes, neuroimaging shows both functional and structural changes in key areas relevant to slow pain processing (Cauda et al., 2014), similar to changes predisposing to persisting mood disturbance following childhood trauma (Opel et al., 2019). However, although this imprint is pervasive and powerful, it is dynamic and malleable, and changes persisting following severe threat (PTSD) and tissue injury (maladaptive chronic pain) can reverse with effective therapy (Thomaes et al., 2014; Shpaner et al., 2014), particularly in the flexible nervous system of childhood (Erpelding et al., 2016).

One key additional question must be addressed – why does adversity (perceived emotionally) consistently trigger neuroinflammatory responses targeted at physical protection? In "evolutionary times", emotional threat through predation or conflict would reliably predict physical injury. As a result (this developing evidence argues) biological stress perceived emotionally as salient threat not only sets in motion autonomic "fight or flight" defence responses prioritising cardiorespiratory capacity and lining up energy resources, but also anticipates trauma by priming neuroimmune responses preparing for injury and infection (Rohleder 2014; Frank et al., 2019). Corticosteroid (CS) mobilisation (initiated from the hypothalamus) has been considered a proxy biomarker for emotional threat, but its major contribution (with other neuroimmune modulators) is homeostatic buffering of the physical effects of an adverse environment - tissue damage, inflammation, and

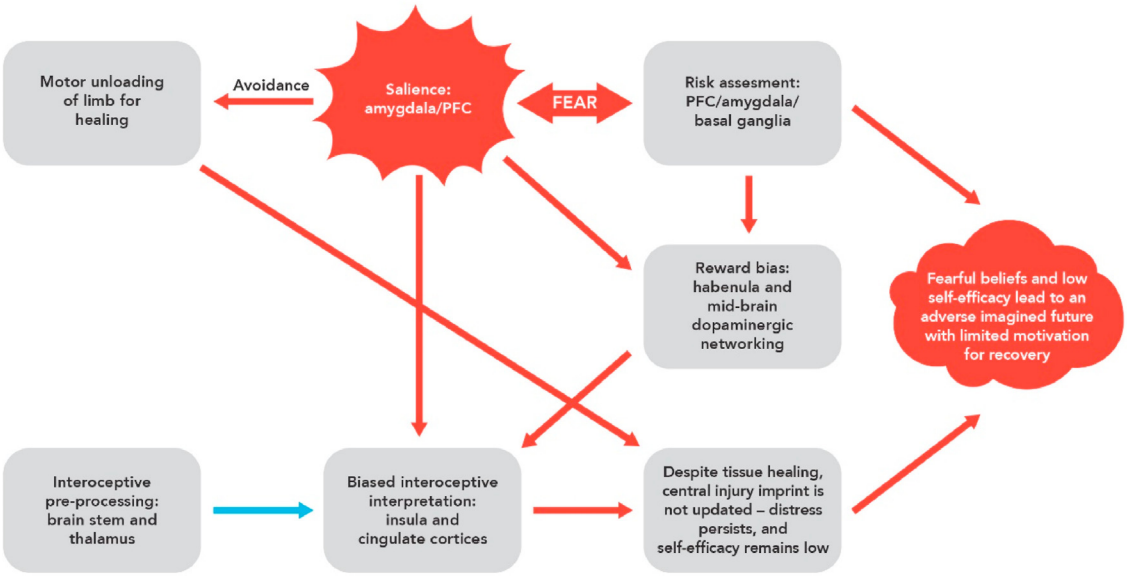

Fig. 4. Maladaptive response to threat and injury. In adaptive recovery (Fig. 3) motivation is primarily generated bottom-up as healing and movement update the injury imprint, rebuilding self-efficacy and prompting recovery behaviours. In maladaptive fear-led states, a self-reinforcing aversive set builds between prefrontal cortical beliefs and amygdala-based salience, leading to top-down biasing of many functions: ongoing interpretation of sensory flow in the insula/cingulate cortices is adverse; reward responses are attenuated; risk-awareness is heightened; movement is sensitised to an avoidance default through conditioning; distress self-reinforces; limited motivation can be sourced from the fearful imagined future.

starvation (Caratti et al., 2018). This review argues that social alienation alone is sufficient emotional threat to trigger this primeval integrated repertoire at our socially highly vulnerable stage of evolution (Meredith et al., 2008; Eisenberger 2012; Walker and McGlone 2013).

By setting out the evolutionary foundations of a system integrating neuroimmune responses to threat and injury/infection and seamlessly guiding recovery, this review points to negative motivational influences that help to explain some maladaptive syndromes of pain and somatisation, and positive ones that may be recruited during recovery. It also lays a foundation for clinical practice that supports more personalised care and potentially allows more accurate prediction of lifetime healthcare needs (Gluckman et al., 2009; Halfon et al., 2014; Nijs et al., 2021).

5. Immune-neural integration and body-mind crosstalk

Persisting non-nociceptive pain is associated with mood depression, and major depressive disorder is accompanied by enhanced pain experience (Robinson et al., 2009). The culturally accepted paradigm through which these observations are usually interpreted implies that persisting pain causes sadness leading to depression, and depressed mood sensitises neural networks to pain. Accumulating evidence suggests otherwise, that pain sensitisation and depressed mood evolved as synergistic outputs of a seamlessly integrated system handling threat and injury (Walker et al., 2014). Immune and neural processes collaborate in ancient repertoires of interoceptive surveillance across the spectrum of threat responses and defensive behaviours (Blalock and Smith 2007; Marin and Kipnis 2013). Although cytokines are better recognised as infection-related immune signals, they are released from injured and dyshomeostatic tissue, inducing sickness behaviours of fatigue and depressed mood through direct effects on the brain (Hart 1988; Watkins and Maier 2000; Dantzer et al., 2014; Shattuck and Muehlenbein 2015). In tandem, neural mechanisms contribute to bi-directional communication around microbial surveillance (Jakob et al., 2020). The immune system is fully integrated in organism maturation and homeostasis (Chavan et al., 2017; Morimoto and Nakajima 2019); engages in adaptive neural learning (Yirmiya and Goshen 2011); responds to non-injurious physical activity (Pedersen 2019; Duggal et al., 2019) as well as tissue damage/dyshomeostasis; and collaborates in guiding tissue healing following trauma/illness (Rankin and Artis 2018; Aloysius et al., 2021). Immune and neural memory both contribute to epigenetic archiving (Sun et al., 2014).

Immune-to-neural signalling biases social as well as somatic perception, motivating behaviour by altering amygdala-based saliency to exteroceptive stimuli. For example, microbiota-derived signalling modulates emotion, mood, and social decision-making (Cowan et al., 2018), and experimental induction of immune activation leads to anhedonia and feelings of social isolation (Eisenberger and Moieni 2020). This developing psychoneuroimmune understanding illuminates the somatic foundations of mental wellbeing, clarifying mechanisms for the host defence group of hypotheses in which depression is viewed as part of a complex neuro-humoral-immune response to threatened tissue integrity and dyshomeostasis, particularly implicating infection (Shattuck and Muehlenbein 2015; Miller and Raison 2016). Kynurenine metabolism impacting glutamate-dependant neurotransmission is a key biochemical link between immune activation and mood (Dantzer 2017). The mechanisms whereby such responses may be maladaptively reinforced in building clinical depression and non-nociceptive pain are also becoming clearer as lifestyle- and adversity-associated neuroimmune activation introduces vulnerability through allostatic load (Danese and McEwen 2012; Shonkoff et al., 2012; Dhabhar 2014; Cole 2019).

6. Escalating responses following complex injury – an ecological perspective on severe mood depression

Neuroimmune injury/illness responses influence recovery at many levels, unloading damaged tissues, co-ordinating healing, and demotivating risky behaviours. The early motivational impacts (for example fear, pain, fatigue) will dynamically adapt during recovery, but what if healing is delayed, or infection complicates tissue repair? Consider the situation of a non-primate social mammal, a female wolf for example, which receives a major wound to her flank while hunting with the pack. During the chase, she will have felt little inhibitory pain, but as she follows the pack home she will be limping and barely able to keep up. Nociceptive signalling warns that damage has been done and cautions her against vigorous activity – she will not be able to work with the pack but continues to support her cubs. However, if infection develops in the wound, rest and self-care will be essential for timely recovery, and the neuroimmune influence from her injury will initially escalate from inhibition of movement by pain to the higher-level inhibition of behaviour through fatigue, undermining initiation of purposeful activity. However, behavioural inhibition from fatigue (in humans at least) is only experienced as "advisory" – it would not countermand primeval ecological imperatives to care for offspring and respond to social interaction. If the wound does not heal at this stage, ecological affordances must be rendered less inviting by negatively biasing reward responses – anhedonia (Slavich and Irwin 2014; Borsook et al., 2016).

Escalation of the neuroimmune threat/injury repertoire from pain through fatigue to anhedonia illustrates pursuit of a common strategic agenda working across the physical-mental divide and recognisable in the loss of pleasure (loss of appetites) in human depression. Furthermore, defaulting from ecologically demanded imperatives requires an adaptive shift in self-image away from cooperative socially motivated action to uncooperative social isolation. This review hypothesises that self-stigmatisation is a predictable neuroimmune outcome from disabling injury to the self, resulting from but also reinforcing social withdrawal. Self-image will be demeaned by a reduced sense of value in the injured and disabled body perceived in interoceptive and proprioceptive surveillance. For a social animal, as this surveillance reports default from culturally valued priorities, self-stigmatisation may be internally generated, subsequently reinforced by alienating peer feedback, laying the foundations for the loss of self-worth seen in severe depression (discussed further below). This developing framework argues that if injury is severe enough, only by introducing such escalating imperatives for rest will the neuroimmune response sufficiently undermine the wolf's innate motivations (caring for offspring and contributing to shared hunting and parenting) and offer the possibility of healing (Fig. 5). The risk that her cubs may starve fits with the evolutionary perspective - if the wolf dies, they will die anyway.

There is one further evolutionary perspective necessary to explain the persistence of physical and emotional distress after threat and injuring has ceased. In challenging evolutionary times, the neuroimmune systems of humans' evolutionary ancestors "learned" to respond to threat and injury through rapid wind-up sustained by reinforcing (positive) feedback. In order to downregulate such responses, balancing (negative) feedback must build as an output from the system, as surveillance indicates that an effective response is underway ((Meadows 2008) pages 27–30 and 153–5). Considering the injured wolf, her neuroimmune responses to tissue damage and wound infection will be built on such wind-up, generating a rapidly escalating imprint inhibiting active behaviour through pain, fatigue, anhedonia, and social self-alienation as necessary. If there is no healing of her wound and no resolution of her infection there will be no return to ecologically necessary and neurally predicted activity, no balancing feedback, and no opportunity to overwrite the injury imprint which will continue to self-reinforce through fear and avoidance. More importantly, there could have been no evolutionary pressure for the development of responses to buffer an organism during terminal stages of severe injury or infection, because it would not survive to pass relevant genes to later generations. In fearful maladaptive syndromes such as persisting pain, major depression, and severe somatisation, conditioned avoidance prevents the ecological re-engagement which would provide balancing feedback, and self-sustaining reinforcement is the result.

Fig. 5. Neuroimmune influence of threat and injury on behaviour.

7. The fundamental importance of self in trauma and recovery

Integrated mind-body responses are pervasive within human experience of illness - self is the fundamental unit expressing itself in these responses, epitomising the organism's physical and mental integration. Physical injury may profoundly affect self-image, not only as the physical alterations and functional handicaps it brings impact social roles and relationships, but also as the felt effects of trauma influence mood and motivation. The evidence reviewed so far shows how injury's nociceptive/interoceptive imprint permeates the central nervous system, inducing complex biases in sensory interpretation which generate aversion to active movement, sensitise to risk in usual behaviours, build distress, undermine wellbeing, and reduce interest in ecological interaction. The evidence argues that self-stigmatisation also facilitates healing from severe threat and/or injury by undermining self-efficacy to further limit activity. All these adaptations must be integrated into working self-image as they push for behavioural influence in shifting motivation away from exploratory activity. As adaptive recovery begins and progresses, surveillance feedback (interoceptive and proprioceptive) must shift the balance back towards a "whole and healthy" self-image across all adapted networks.

A social mammal such as a wolf must have a well-developed sense of self, kin, and others, but considering its limited imaginative capacity, its self-image must be largely experienced through bodily awareness and peer feedback. Although we think of self-image and self-efficacy as mental phenomena, developing understanding shows that their neural states are founded in awareness of the body through interoceptive and proprioceptive sensory flow (Medford and Critchley 2010; Seth 2013; Delafield-Butt and Trevarthen 2015; Frewen et al., 2020). Self-image is built in a self-memory system integrated within autobiographical memory which is relatively stable over time, but a more dynamic "working" self-image is strongly adaptive to emotive feedback from engagement with the social and physical environment (Conway and Pleydell-Pearce 2000; Mikels and Reuter-Lorenz 2019). Self-efficacy is the expression of self-image in ecological interaction, and perceived self-efficacy is fundamental to recovery from all traumas, large or small (Benight and Bandura 2004; Schonfeld et al., 2016).

The expression of injured self-image is a major contributor to post injury disability, over and above the contribution of any physical impairment, as self-motivated recovery is dependent on an individual's perception that he is well matched to the challenges of his ecological space. Self-efficacy is the degree of "fit" between perceived ability (closely tied to self-image) and the imagined difficulties presented by any contemplated activity, and can be considered to derive neurally from interoceptive/proprioceptive surveillance describing the current health and competence of the body, matched against exteroceptive feedback not only of the current context, but archived from previous engagement (successful or not) in similar challenges. In practice, if an individual believes herself sufficiently healthy and competent for the task, she will commence it with hope, but sickness behaviours such as fatigue and depression undermine ecological engagement by undermining self-efficacy.

This review proposes further that the neural foundations of low self-worth (self-stigmatisation), a core feature of human depression, evolved as a component of the complex injury repertoire of social mammals to facilitate ecological disengagement, and have been incorporated into the ecological fabric of our lives by cultural as well as genetic influence. Following mental as well as physical trauma, social engagement is undermined and self-worth is demeaned by internal neuroimmune influence including low perceived social value (Will et al., 2020) which may be repaired by ecological re-engagement through physical activity (Liu et al., 2015). Behaviour which defaults from culturally mandated ecological imperatives such as caring for family, community members, and shared resources may lead to stigmatisation and ostracism, in which case feedback from peers is commonly internalised, strengthening negative self-image and self-stigmatisation, and reinforcing social avoidance (Abiri et al., 2016).

A sense of self-efficacy is critical to recovery from any trauma, but loss of self-worth undermining ecological engagement is its opposite - as post-injury self-stigmatisation undermines self-worth to promote healing, it introduces existential risk for the individual. The erosion of self-worth through this primeval neuroimmune repertoire fundamentally threatens survival, evidenced in the high suicide mortality from severe depression and chronic pain (Hassett et al., 2014). As an internally generated state (albeit reinforced by external feedback) self-worth must be rebuilt within the neural self, and in the face of the composite physical, emotional, and cognitive inhibitions of a maladaptive trauma response, such self-care will require effortful attention. This ecological

imperative may underly the increasing importance attributed to self-forgiveness in the psychological literature (Hall and Fincham 2005) – in severe depression, self-forgiveness reduces suicidal ideation and self-harm (Cleare et al., 2019).

7.1. Injured self and injured mood

Professor Georg Northoff and distinguished colleagues highlight the contribution of bodily perception to the motivational state of depression, reflected in enhanced neural activity in the insula (Northoff et al., 2011). These authors emphasise a fundamental shift in the balance of sensory attention in depression from exteroceptive social responsiveness to interoceptive self-preoccupation (Fig. 6). In their model, they position evolutionarily recent prefrontal cortical (PFC) processing as mediating between these two orientations, enabling the strategic agenda to shift motivational focus from ecological engagement towards self-care, energy conservation, and reflection, including through the generation of anhedonia and self-directed negative emotion. The mediating areas include ventromedial and dorsomedial PFC active in emotion modulation for social interaction, and the precuneus, a key node in self-reference, self-other differentiation, and the mentalising network (Murray et al., 2015).

Although socially relevant PFC functions are considered of recent evolutionary origin, they are built on the ancient brain with which they maintain intimate connectivity for motivational influence, and from which they source conscious experience ((Damasio 2010) chapter 8, "Building a conscious mind"). Northoff and colleagues' conceptual model of depression's neural generation differs from many others in emphasising input from the body, rather than from the environment, as the driver for adjusting motivational sensitivities and biases. This current review argues that it is injured self-image, specifically self-worth, that shifts the organism away from default exploratory behaviour to ruminative self-protection; and it is healing self-image which returns the organism towards exploratory behaviour through recovering self-efficacy. Stigmatisation of self is a major additional step in this primeval injury repertoire – it builds inertia into any recovery behaviours, presenting an existential threat which may lead to death.

The neuroimaging-derived data that Northoff and colleagues highlight translates to the female wolf's situation in pointing to foundations of depressed mood in physical injury. The orientating shift of focus from external environment to handling the massively enhanced interoceptive/nociceptive data flow from severe tissue damage and infection is predictable, leading to the aversive motivational state stemming directly from this injured-body-derived data. If adaptive healing is possible, the motivational direction will gradually reset, facilitating recovery neurochemically as strategic attention opens up to ecological opportunities. The mediating role of PFC/precuneus can be viewed as pragmatically shifting the balance in reward/punishment-responsiveness following injury away from the inviting influence of external events (anhedonia), committing processing resources internally to healing, and prompting ruminative re-appraisal to explore possible futures as strategically necessary.

Sensitisation of somatic responses following threat alone (perceived emotionally) as it anticipates the risk of physical injury (or illness in our modern health-conscious environment) is predicted by this integrated understanding of self. This review argues that this ancient neuroimmune repertoire promoting interoceptive attentional focus may be triggered solely by emotional/social threat, linked as it may be with imprinted somatic neuroinflammatory activation with life-long implications (Shonkoff et al., 2012; Slavich and Irwin 2014; Frank et al., 2019; Cole 2019). It also plays out in non-pain somatisation (Farb et al., 2015; Perez et al., 2015; Beutel et al., 2019), including syndromes which commonly associate with mood depression such as chronic fatigue, irritable bowel, and anxiety-related breathlessness/panic disorder among many others.

8. The ecological value of social affiliation, and the implications of alienation

This project's long-term objective is to integrate and present to clinical and social care professionals an understanding of the neurobiology of

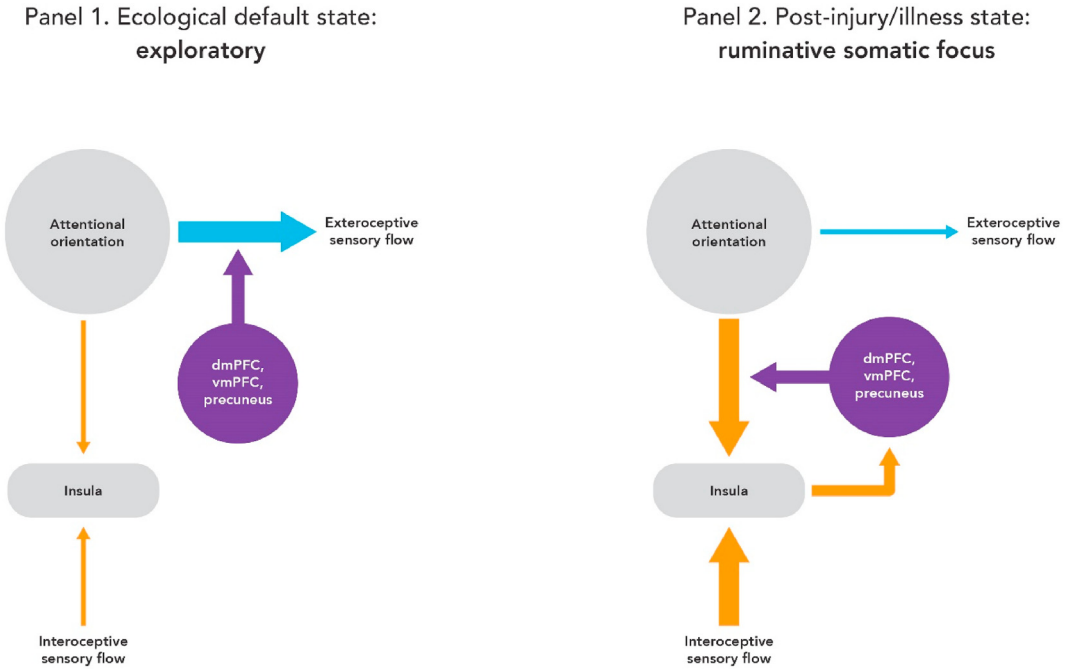

Fig. 6. Severe illness/injury shifts attentional focus internally to facilitate healing and self-care. Switching is probably driven by interoceptive/nociceptive flow through the insula (Northoff et al., 2011).
Panel 1. Ecological default state: exploratory. Exteroceptive attention derives motivational influence from environmental affordances.
Panel 2. Post-injury/illness state: ruminative somatic awareness. Interoceptive attention derives motivational influence from damaged tissue and/or metabolic dyshomeostasis.

distress and disability resulting from threat, illness, and injury. A pillar of the conceptual framework is that humans are fundamentally a social species, with familiar expressions of the distress of social alienation presenting as anxiety, depression, shame, and grief, but also in the alienation of youth (persistent unemployment, addiction, imprisonment (Marmot 2018)) and of old age (loneliness (Holt-Lunstad 2018)). Social affiliation is the key source of emotional wellbeing for individuals who are in an ecologically "good space", and from the perspective of evolutionary neurobiology social alienation is the pre-eminent threat to emotional wellbeing. Human social co-dependence developed as our evolutionary ancestors were forced to settle into larger communities through risk of predation and conflict (Dunbar 2012; Walker and McGlone 2013) - when our neuroimmune reflexes were being crafted by evolution, social alienation threatened death.

The current epidemic of opioid overprescribing associated with chronic pain offers evolutionary insight into mechanisms translating the impacts of social alienation into persisting distress. The endorphin system established its central position in primate-human social evolution as it generated wellbeing to facilitate group affiliation under threat. Social alienation can be considered a state of endorphin deficiency, as therapeutic opioids very effectively mitigate the distress of social alienation - resulting wellbeing will lead to increasing demand for the drug quite apart from any effect on associated physical pain (Gulliford 2020).

8.1. Social/emotional adversity affects physical as well as mental health

Through the integrated threat-illness-injury system, allostatic load arising fromsocial disadvantage in childhood may sensitise responses to future mental traumabut also to metabolic disturbance and physical injury, triggering persisting maladaptive mental and physical illness in dose-responsive ways that affect lifetimewellbeing and survival (Santini et al., 2021); persisting non-nociceptive pain can beincluded with depression and anxiety in the outcomes from early and ongoingsocial adversity (Mills et al., 2019). Illnesses linked with the neuroimmune activations of social adversity are the main contributors to the world-wide escalation of non-communicable disease, considered one of the greatest public health challenges in this and coming generations (Mendenhall et al., 2017). From an ecological perspective, emotional distress leading to mood and behaviour change is the key dyshomeostatic outcome from social alienation and adversity. The developing framework invokes a causal relationship whereby social/emotional threat embodies vulnerability to both mental and physical illness by sensitising neuroimmune responses to subsequent hardship and distress (Stapelberg et al., 2015; Kuhlman et al., 2017; Cole 2019). Resulting allostatic load drives a systemic immune inflammatory response with long-term biological impacts and health consequences (Danese and McEwen 2012; Rohleder 2014; Slavich and Irwin 2014; Nusslock and Miller 2016; Muscatell et al., 2016). To simply illustrate this mechanism in a clinical context, in adolescents with intermittent depression and a history of childhood adversity, blood-borne inflammatory activity predicts relapse (Miller and Cole 2012). This is a lifelong causal relationship - the concept of frailty in older people is now being framed as greater vulnerability to accumulating impacts of aging due to homeostatic inflexibility (Rockwood and Howlett 2018). Allostatic load linked to social distress mediates this vulnerability, as measures of frailty directly correlate with social isolation and loneliness (Davies et al., 2021).

The brain components of this neuroinflammatory response stem from resident immune (microglial) cells (Mondelli et al., 2017; Frank et al., 2019) which have a central role in brain homeostasis as well as contributing to neural remodelling following threat and trauma (Yirmiya and Goshen 2011; Marin and Kipnis 2013). Brain microglial activity correlates with severity and duration of major depressive disorder implying cumulative allostatic activation (Setiawan et al., 2018). Microglial cells also contribute to non-nociceptive pain following maladaptive response to physical injury - negative affect in patients with chronic pain correlates with brain microglial activation and with change in functional connectivity between the pregenual anterior cingulate cortex and areas of the prefrontal cortex (Albrecht et al., 2019), a network linked to ruminative self-focus, supporting similar neuroimmune impact in non-nociceptive pain as in depression.

For humans as essentially social beings by evolution, the anticipated neuroimmune ideal is to be socially and emotionally embedded in family and community (Meredith et al., 2008; Walker and McGlone 2013), but in recent generations, socioeconomic inequality has generated an increasing sense of alienation among sections of the population. Analysis of societal data shows that it is the degree of inequality within a population that correlates most closely with effects on physical health ((Wilkinson and Pickett 2009) chapters 2 and 3) and see also (Tobias 2017)). Human empathic sensitivity to inequality has a long evolutionary history (Decety and Yoder 2017) and together this evidence argues that it is the emotional distress of being left behind more than the physical effects of any state of absolute poverty that predominantly contributes to the underlying allostatic archive.

Social inequality has been paralleled by plateauing in overall life expectancy and widening disparity in societal health and mortality (Woolf and Schoomaker 2019; Marmot et al., 2020). It is manifest in physical non-communicable diseases (Kivimäki et al., 2020); maternal as well as infant mortality (Bornstein et al., 2020); morbidity and mortality from pain and its opioid treatment (Gulliford 2020); and self-injury and suicide (Rockett et al., 2021). Stigmatisation and discrimination (for example on grounds of race) make an important contribution to the allostatic load from alienation (Geronimus et al., 2006; Bailey et al., 2017), for example by increasing central sensitisation to pain (Mathur et al., 2016; Harte et al., 2018). Furthermore, the foundations of greater inflammatory responses to Covid-19 infection and associated mortality within Black, Asian, and minority ethnic (BAME) communities in the current pandemic may lie in the same allostatic archive - they are only partly explained by genetic factors, with socioeconomic inequality and discrimination through structural racism separately increasing vulnerability (Lo et al., 2021; Parpia et al., 2021).

Social alienation interacts with alienation from our co-evolved physical environment, appearing to predispose to physical inactivity, allergy, and poor-quality diet with its associated altered gut microbiome and obesity. Resulting metabolic disharmony introduces another broad source of allostatic load which is similarly archived in implicit neuroimmune memory, drives an inflammatory response, harms both mental and physical health, and leads to early death (Dawson et al., 2016; Ding et al., 2016). Emotional-with-immune resilience is impaired through the ecological alienation of our clean and risk-averse modern lifestyle - in relation to allergy, sequential iterations of the hygiene hypothesis recognise the health benefits from environmental exposure to microorganisms in childhood (Bloomfield et al., 2016); similarly the concept of "steeling" implies developmental benefit from controlled risk exposure in early childhood (Rutter 2012).

Endnote

Our neuroimmune heritage is little changed from when our ancestors were hunter-gatherers facing regular conflict and predation ((Harari 2015) page 45 et seq). This review argues that contemporary mood depression triggered by emotional trauma and social alienation is built (like chronic pain) on primeval responses to physical injury with the same risk of self-reinforcement, and that only by acknowledging how physical and emotional threat and injury are served seamlessly by a single neuroimmune system can the complex impacts of mental-with-physical stress on health and illness be fully understood. Lifecourse health development models 'have synthesized research from biological, behavioural and social science disciplines, [and] defined health development as a dynamic process that begins before conception and continues throughout the lifespan', highlighting the heavy toll of both physical and mental illness resulting from early socioeconomic adversity and emotional trauma ((Halfon et al., 2014) and see also (Gluckman et al., 2009)).

Recovery from severe trauma is contingent on sourcing sufficient motivation within the ecological niche, motivation which may need to push back against imprinted neural inhibition of pain and fear reinforced by loss of exploratory drive through anhedonia and self-stigmatisation. If self-efficacy is insufficient to source that motivation, if fearful beliefs eclipse hope, and if others provide an individual with daily needs without his effort, the imprint is likely to persist and be reinforced daily by conditioned contexts. Responses to physical and/or mental distress may then self-reinforce through avoidance of the activities which could overwrite those conditioned responses, and a persistent maladaptive state of aversive multimodal sensory misinterpretation, behavioural avoidance, and anhedonia may result.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100349.

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