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Review article

A neuroinflammatory compulsivity model of anorexia nervosa (NICAN)

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1. Introduction

Anorexia nervosa (AN) is an eating disorder often highly resistant to treatment, characterised by restrictive eating and/or compensatory behaviours such as purging or excessive exercising, leading to low body weight and dysregulated appetite. The recovery rate is low for those with AN in standard treatment, including cognitive behavioural therapy (CBT), enhanced-CBT, and anti-depressant medication, and risk of relapse is high (Muratore, Attia, 2021; Monteleone et al., 2022; Dalle Grave et al., 2023) estimated at around an annual global rate of 50% (Steinhausen, 2002; Frostad et al., 2022). Moreover, longitudinal studies show that for those with over twenty years lived experience of AN, recovery rate is only 40–63% (Eddy et al., 2017; Fichter et al., 2017). And for the last five years in the UK (2017–2022), an alarming 84% rise in AN admissions to the National Health Service was reported (Royal College of Psychiatrists, 2022), a rise echoed around the world, especially in high-income countries (Zipfel et al., 2022). Given this alarming rise, some clinicians are dividing opinion by suggesting palliative care and medically assisted death for treatment resistant AN (Royal College of Psychiatrists, 2023). Considering the dangerous nature of AN and heightened risk of death, new approaches are urgently needed to examine novel neurobiological mechanisms maintaining the disorder that may improve global treatment resistance.

People with AN experience an intense fear of weight gain, as well as a disturbed sense of their own body (American Psychiatric Association, 2013). Restrictive eating and low body weight can lead to many physical complications such as hypotension, bradycardia, hypothermia, amenorrhea, and reduced bone density. Due to both the physical consequences of starvation and an increased incidence of suicide, patients with AN have the highest co-morbidity and mortality rate of any psychiatric disorder (Edakubo and Fushimi, 2020, American Psychiatric Association, 2013; Tauro et al., 2022). Besides physical complications, AN is associated with executive functioning impairments (Dias-Marsa et al., 2023) that maintain the *stuckness* of the disorder - often presenting prior to onset and persisting after weight recovery - such as cognitive inflexibility and lack of central coherence, broadly representing a rigid, perfectionistic, threat-sensitive, and detail-oriented mindset (Dann et al., 2021; Stedal et al., 2021). Deficits have been shown in cognitive tests of attention, long-term memory, working memory and processing speed (Stedal et al., 2021; Dahlen et al., 2022). Furthermore, cognitive deficits contribute to emotional dysregulation, alexithymia and disturbed social processing, as well as an intolerance of uncertainty, corresponding to a rise in AN cases since the pandemic and other global threats, including climate change (Cooper et al., 2022; Zipfel et al., 2022; Lin et al., 2021; Walinski et al., 2023; Tauro et al., 2022; McAdams et al., 2022; Mariani et al., 2022). Moreover, often-abrupt transition from child/adolescent to adult eating disorder services can add to uncertainty threats that may exacerbate the disorder (Dalle Grave et al., 2023). Threat perceptions and cognitive deficits heighten the risk of psychiatric comorbidities in AN, with anxiety and depression being the most common (Stedal et al., 2021; Dahlen et al., 2022; Muratore, Attia, 2021; Huang et al., 2022).

Reduced brain structure (e.g. volume, cortical thickness) and dysfunction in prefrontal and subcortical regions are often reported in

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AN (Seitz et al., 2016; Zhong et al., 2023), but the underlying mechanisms of these observations are poorly understood. Some have proposed that changes in prefrontal and basal ganglia processes in addiction, defined as a chronic, relapsing disorder associated with compulsivity and repetitive behaviours despite adverse consequences (Goldstein and Volkow, 2011) correspond to addictive processes of incessant food restriction and starvation in AN (O'Hara et al., 2015). Moreover, inflammatory processes play an important role in several psychiatric diseases, including addictions (Yuan et al., 2019; Chen et al., 2022) and there is increasing evidence that AN is one of these pro-inflammatory psychiatric disorders (Dalton et al., 2018; Solmi et al., 2015). As such, it raises the possibility that neuroinflammation – and not only malnutrition – is an underlying mechanism of reduced/altered brain structure and function in AN, contributing to the compulsive maintenance, relapse, and treatment resistance of the condition.

Against this background, the present article examines evidence for a neuroinflammatory compulsivity model of AN (NICAN), whereby increased cytokines cross the blood-brain barrier, altering brain structure and function underlying compulsive food restriction. Reduced food intake is suggested to alter the allostatic load – the adaptation of homeostatic set-points (McEwan, 2000) – for hunger and satiety. We propose that the level of food restriction occurs in a stepwise mechanism (alternating between sensitisation and habituation) to negatively reinforce the rewarding effects of fasting that temporarily reduces pro-inflammatory cytokines and anxiety in the presence of perceived, pervasive threats. The model will provide a novel platform upon which to explore and test disorder mechanisms and new treatment options that target pro-inflammatory processes and cognitions, and reduce threat perceptions that increase anxiety. New knowledge acquired by testing this model may enhance existing therapies, especially for chronic treatment resistant individuals.

It is hypothesised that anti-inflammatory approaches (e.g., supplements, Mediterranean-style diets) combined with neurocognitive interventions (cognitive behavioural therapy, cognitive training) that improve brain function in networks disrupted by cytokines, will reduce relapse rates by lowering inflammation and anxiety associated with threat perceptions, which will in turn improve cognitive deficits for people with treatment resistant AN. To address aspects of the model, the following article will review mechanisms of peripheral and neuroinflammation, animal models, homeostasis, allostasis and compulsive, learned behaviours associated with AN.

2. Peripheral inflammation

Inflammation is a crucial part of the body's immune system, particularly during times of perceived threat (e.g., internal pathogens, external stressors), and is regulated by a complex network of cellular signalling pathways. A hypothesis for the involvement of peripheral inflammation in AN begins with the cell surface toll-like receptors (TLRs) that bind with bacteria or bacterial byproducts such as lipopolysaccharide (LPS) during gut dysbiosis (Bambury et al., 2018). TLRs can be found on the surface of macrophages, neutrophils and dendrites, and binding of bacterial products activates canonical inflammatory processes and transcription factors such as nuclear factor kappa beta (NF-kB), which upregulates the production of various glycoproteins.

One important class of small glycoproteins are called cytokines. Cytokines are pro- or anti-inflammatory signalling molecules involved in the peripheral and central nervous system (P/CNS). Two inflammatory pathways involve cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), both are enzymes that convert arachidonic acid (AA) into different types of inflammatory mediators (He et al., 2020; Chen et al., 2022; Gilbert et al., 2021). The COX pathway – inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) – leads to the production of cytokines called prostaglandins, associated with acute inflammation and pain. Conversely, the 5-LOX pathway produces cytokines called leukotrienes that contribute to the inflammatory response associated with chronic inflammation (Brooks, 2018; Butler et al., 2021; He et al., 2020).

Several meta-analyses in patients with AN report increased peripheral inflammation, including leutotrienes (Solmi et al., 2015; Dalton et al., 2018; Breithaupt et al., 2023). Compared to healthy controls, people with AN have elevated 5-LOX leukotrienes that are upregulated by signalling molecules such as NF-kB and released from endothelial cells, monocytes, macrophages, T cells, fibroblasts, hepatocytes: interleukin 1beta (IL-1β), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) (Solmi et al., 2015; Dalton et al., 2018; Brooks, 2018; Caso et al., 2020; Butler et al., 2021). IL-1β has a wide array of functions in the inflammatory process, such as regulating body temperature and fever via interaction with the hypothalamus (Matsuwaki et al., 2014). IL-1β links the immune system and metabolism due to its effect not only on immune cells, but also insulin producing cells in the pancreas (Collier et al., 2021). In addition, IL-1β modulates hormonal activity affecting feeding behaviour and the stress response known as the hypothalamic-pituitary-adrenal (HPA) axis (de Baat et al., 2023). IL-6 stimulates B-cells and is associated with inflammatory diseases (e.g., arthritis), increasing lipolysis and glucose production in the liver, as a reaction to low energy levels, and increasing satiety by influencing leptin levels (Han et al., 2019). IL-6 reduces food intake in mice and may have similar effects in humans (de Baat et al., 2023). TNF-α was originally associated with toxic effects on tumour cells but also has metabolic effects, such as reducing food intake and modulating lipogenesis and ketogenesis in longer periods of food deprivation (de Baat et al., 2023). For a schematic diagram of peripheral inflammatory processes in AN, see Fig. 1.

3. Neuroinflammation

Neuroinflammation is the inflammatory response of the CNS (Butler et al., 2021; Capuron and Miller, 2011; Chen et al., 2022; Chen and Zou, 2022; Dalton et al., 2018) that may involve cytokines and LPS, an immunogenic particle on the membrane of some bacteria. The CNS has its own immune response cells – microglia and astrocytes – which help to maintain brain homeostasis (Garland et al., 2022). Some suggest that chronic inflammation contributes to a *'leaky gut-leaky brain syndrome'* (Obrenovich, 2018; De Vincenzo et al., 2023). A *leaky gut* refers to dysfunction of the intestinal epithelial barrier and increased permeability leading to bacteria and toxic digestive metabolites such as LPS and cytokines 'leaking' into the bloodstream. A *leaky brain* refers to an increased permeability of the blood-brain-barrier (BBB), allowing cytokines and other toxins to cross more easily into neural regions. Within the leaky gut hypothesis, LPS might play a role as a potent inflammogen that leaks through other peripheral regions and into the CNS, causing systemic inflammation and increased gut-brain porosity (Herpertz-Dahlmann et al., 2017). Interest in the 'gut-brain axis' has risen in the last few years (Li et al., 2023), and gut-brain disorders are common in eating disorders (Atkins et al., 2023). Within this axis the arcuate nucleus of the hypothalamus is referred to as the 'first-order neural nuclei' in humoral regulatory pathways, given its rich blood supply and porous BBB within the third ventricle, enabling neurons to receive peripheral appetite regulatory signals more easily (Wen et al., 2019).

Cytokines like IL-1β, IL-6 and TNF-α act as signals from the peripheral immune system and cross the BBB to the CNS to initiate behaviours that may facilitate a faster recovery (Capuron et al., 2020). Crossing the BBB through the humoral pathway to affect the brain directly gives these cytokines an ability to increase pro-survival behaviours governed by the CNS (Dalton et al., 2018; Chen et al., 2022; Butler et al., 2021; Capuron and Miller, 2011). Peripheral cytokines also affect the CNS through changes in signalling from afferent peripheral nerves known as the neural pathway (Capuron and Miller, 2011). The first line of CNS cytokine defence is the facilitation and infiltration of peripherally activated monocytes, known as the cellular pathway. Once pro-inflammatory cytokines reach the brain via the humoral, neural or

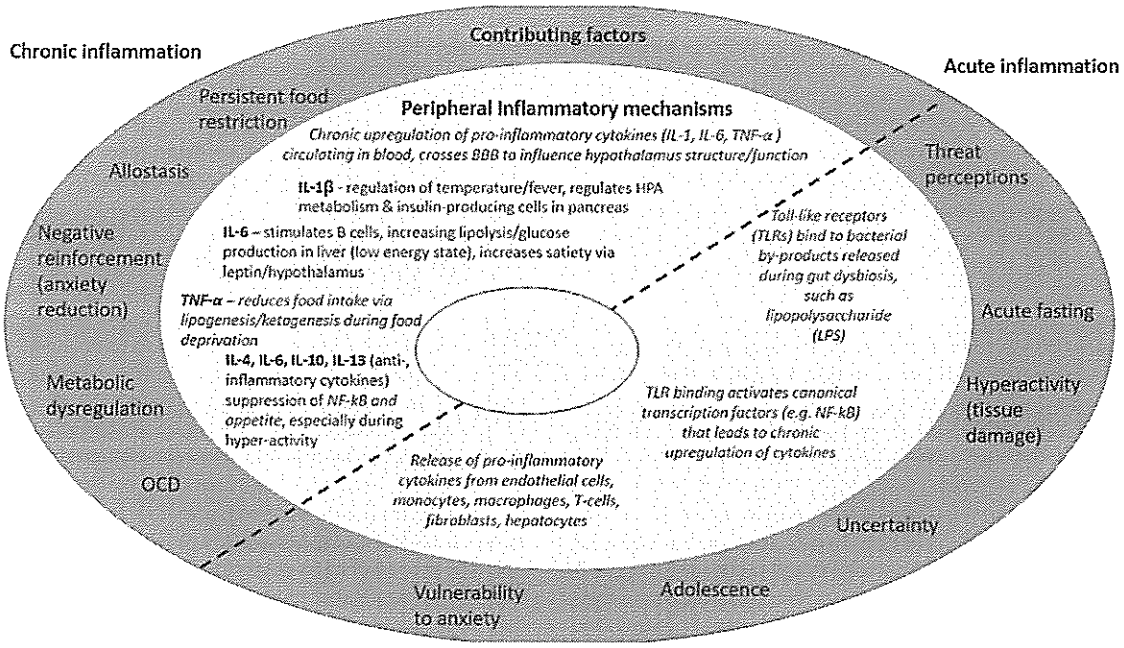

Fig. 1. A schematic diagram of peripheral inflammatory processes in AN.

cellular pathways they can affect behaviour by altering neurotransmitter signalling and metabolism, neuroendocrine functions, neuroplasticity and overall brain structure and function, especially if cytokine release is chronic (Capuron and Miller, 2011; Butler et al., 2021).

The CNS is significantly protected from a heightened immune response when the BBB maintains its integrity (e.g., not subject to a leaky gut-brain axis), which prevents most inflammatory molecules from entering the brain. However, cytokines such as interleukins are small and even without a leaky gut-brain axis can cross the BBB, altering the metabolism (synthesis, release, uptake) of several neurotransmitter systems, including dopamine, serotonin, noradrenalin (Miller et al., 2013). When pro-inflammatory cytokines cross the BBB they can elevate the experience of anxiety, depression, and memory deficits (Reichenberg et al., 2001). Neuroinflammation may involve chronic influx of pro-inflammatory molecules that influence brain structure and function, which may be neurotoxic if activated by a chronically unhealthy lifestyle, including elevated and prolonged stress and the perception of threat in one's immediate environment, unhealthy food consumption (type, amount), metabolic syndrome, infection, traumatic injury, toxic metabolites, and autoimmunity (Muscat and Barrientos, 2020; Butler, 2021).

4. Animal models of neuroinflammation in AN

There are approximately eighteen known animal models of AN to date, and almost all (bar two studies with monkeys) are rodent (rats and mice) models (Scharner and Stengel, 2021); the most well-known are the activity-based anorexia (ABA), dehydration induced anorexia (DIA), lipopolysaccharide (LPS) and *anx/anx* murine models. The main findings of these models described below have contributed much to our knowledge of the underlying pathophysiology and neural correlates of AN, with possible connections to neuroinflammation.

4.1. ABA model

The ABA murine model is the most widely used animal model of AN (Scharner and Stengel,2021) and involves scheduled food restriction and free access to a running wheel resulting in weight loss and hyperactivity, mimicking some (not all) of the phenomena of AN (Hall and Hanford, 1954; Routtenberg and Kuznesof, 1967). Studies of the ABA mouse model show increased inflammatory markers – specifically arachidonic acid (AA)-derived eicosanoids in corticolimbic regions of the mouse brain (Collu et al., 2020). In particular, significantly increased levels of AA and LOX-derived eicosanoids in the hypothalamus, alongside significantly decreased levels of AA and COX/LOX-derived eicosanoids in the caudate, amygdala, and hippocampus (Collu et al., 2020). The finding of altered levels of eicosanoids – one of the most abundant poly-unsaturated fatty acids (PUFAs) in the CNS - in the ABA model is pertinent, because other studies have shown that PUFAs induce food restriction in rats by impairing hypothalamic leptin signalling (Cheng et al., 2015). In addition, the ABA model has demonstrated that TLR4 – one of the toll-like receptors that bind with bacteria and bacterial products - is upregulated in colonic epithelial cells and intestinal macrophages, leading to upregulation of mucosal cytokines prior to hypothalamic and IL1 changes (Belmonte et al., 2016). Interestingly, this study also showed a mediating role for TLRs, as TLR-knockout mice were more susceptible to ABA model mortality (Belmonte et al., 2016). Finally, a recent review of animal studies using the ABA model (Frintrop et al., 2022) shows that microglia and astrocytes play an important role in hypothalamic activity related to feeding behaviours, especially involving reduced glial fibrillary acid protein (GFAP) density. Frintrop and colleagues further suggest that this could indicate reduced proliferation of astrocytic precursor cells, apoptosis/necrosis of astrocytes, decreased mRNA expression, and an inhibition of GFAP protein synthesis in the ABA model of AN. Together, these ABA model studies link hyperactivity and food restriction – two core aspects – to neuroinflammatory processes in AN.

4.2. DIA model

Similarly, the DIA murine model (Reyes-Haro et al., 2015) links AN to neuroinflammation, involving reduced food intake and avoidance of food despite its availability, which appears to ameliorate hyperosmolaemia (higher blood concentrations of sodium, glucose and other substances). Studies using this model have demonstrated increased microglia density in the medial and orbital PFC, correlating with disrupted glutamate-glutamine homeostasis, the redox state and neurodegeneration in young female rats (Reyes-Ortiga et al., 2020). Moreover, Reyes-Ortiga and colleagues reported that the pro-inflammatory environment in microglia was associated with elevated levels of TNF- α, IL-6

and IL-1β. Similarly, the DIA has demonstrated reduced GFAP cell density and increased intermediate filaments vimentin and nestin (reactive astrocytes) in the rat hippocampus and reduced astrocyte density in the rat corpus callosum (Reyes-Haro et al., 2015, 2016). Such data further links reduced grey and white matter volume to neuroinflammation in AN rather than malnutrition per se. Thus, the DIA model highlights the role of glial cells – particularly in the hippocampus, PFC, and major white matter pathways – in a neuroinflammatory environment in AN.

4.3. LPS model

The LPS model of AN – LPS being an immunogenic particle on the membrane of some bacteria - shows how lipid metabolism is crucial to the immune response during infection with bacteria and bacterial products. Bacterial infection can alter body metabolism, including heightened glucose, fat and protein levels (McGuinness, 2005), and inflammation via LPS collaborates with IL-1β, TNF-α, and PUFAs to influence lipid metabolism in liver, muscle and adipose tissue (Glass and Olefsky, 2012). Cell surface TLRs bind with bacteria or bacterial by-products such as LPS during gut dysbiosis (Bambury et al., 2018), and TLR4 is upregulated in colonic epithelial cells and intestinal macrophages during an ABA model study, leading to upregulation of mucosal cytokines prior to hypothalamic and IL1 changes (Belmonte et al., 2016). With this in mind, Yang et al., (2022) injected LPS into TLR4 knockout and wild-type mice to measure inflammation and lipid metabolism, finding that short-term sustained inflammation induced by LPS leads to tolerable anorexia. In addition, leptin appears to be a mediator of LPS-induced anorexia and fever via an IL-1β, dependent mechanism in the hypothalamus (Sachot et al., 2004). The evidence suggests that LPS-induced AN depends on central – rather than peripheral – inflammatory signals (Wisse et al., 2007). For example, disruption of TLR4s in mice leads to AN-resistance during LPS injection, whereas wild-type signal transduction activated by TLR4s or IL-1β maintains LPS-mediated induction of hypothalamic mRNA encoding for IL-1beta and TNF-α (Wisse et al., 2007). Thus, the LPS model of AN links dysregulated metabolism via infection and a central nervous system inflammatory response, especially in the hypothalamus, to the development and maintenance of weight loss in AN.

4.4. Anx/anx model

The *anx/anx* anorexic model is a mouse strain homozygous for the *anx* mutation, characterised by reduced body weight, hyperactivity including head weaving and body tremors, gait abnormalities and poor appetite (Maltais et al., 1984; Son et al., 1994; Broberger et al., 1997, 1998; Jahng et al., 1998). The model demonstrates neurodegeneration in the hypothalamus, as well as altered neuropeptides such as neuropeptide Y (NPY) and serotonergic hyper-innervation related to anxiety, dysregulated appetite and feeding behaviour in the arcuate nucleus of the hypothalamus (the first order nucleus of the humoral pathway) (Butler et al., 2021). Similar studies have linked neuroinflammation and AN by showing how pro-inflammatory cytokines like IL-1β, IL-6 and TNF-α are associated with decreased feeding and body weight through interactions with hypothalamic structure and signalling as well as altered neuropeptides and increased leptin signalling (Butler et al., 2021; Collu et al., 2020). In addition, Lindfors et al. (2015) examined glucose tolerance with the *anx/anx* model, and demonstrated increased concentrations of circulating fatty acids in serum and increased macrophages in islet cells, suggesting increased inflammation.

In summary, considering the animal models combined, the ABA, DIA, LPS and *anx/anx* suggest a central role for the hypothalamus (arcuate nucleus, closest to the most porous aspect of the BBB) interacting with peripheral immune responses in AN. For example, in terms of food restriction and hyperactivity in the ABA model, colonic epithelial cells and intestinal macrophages have upregulated TLRs that bind with bacterial products (e.g. LPS) in peripheral processes prior to leptin-signal disruption in the hypothalamus. Moreover, inflammatory processes in the hypothalamus involve microglia and astrocytes, especially in terms of reduced glial fibrillary acid protein (GFAP) density. Reduced GFAP density could indicate reduced proliferation of astrocytic precursor cells, apoptosis/necrosis of astrocytes, decreased mRNA expression, and an inhibition of protein synthesis. In the DIA model, the PFC is additionally implicated in AN which may exacerbate executive dysfunction underlying cognitive ruminations, specifically increased microglial density correlating with elevated TNF- α, IL-6 and IL-1β, along with disrupted glutamate-glutamine homeostasis. Furthermore, the DIA model links reduced GFAP and reactive astrocytes to disrupted hippocampal cell function. Considering the LPS model – a bacterial by-product that binds to TLRs in the central and peripheral system –links are proposed during inflammation to elevated levels of IL-1β, TNF-α, and PUFAs that influence lipid metabolism in liver, muscle and adipose tissue. However, the difference between tolerated versus chronic AN in the LPS model seems to depend on a peripheral (e.g. binding to receptors in the mucosal endothelium) versus central nervous system (e.g. binding to receptors in the hypothalamus) role of TLR-LPS binding, respectively. The *anx/anx* model also implicates hypothalamic dysfunction, particularly involving neuropeptides and serotonergic hyper-innervation. Also, like other models, the *anx/anx* model demonstrates elevated IL-1β, IL-6, TNF-α, PUFAs and macrophage levels that disrupt leptin signalling in the hypothalamus. Thus, animal models have provided significant evidence linking structural and functional deficits to neuroinflammatory processes – particularly in the hypothalamus and connected corticolimbic regions – in AN.

5. Human neuroinflammation in AN

Communication between the immune system and the brain is an adaptive response to acute illness, but when inflammation becomes chronic, the effect on the CNS can become pathological. For example, studies show that neuroinflammation (activation of glia and cytokines) impairs the endothelium of the BBB amplifying the neuroimmune response (Takata et al., 2021), which is associated over time with decreased brain volume and altered functional connectivity (Chen et al., 2022). Amplified neuroinflammatory responses are associated with hippocampal dysfunction, in line with elevated glucocorticoids, sensitised microglia and memory impairments (Barrientos et al., 2015), which are also observed in AN patients (Chen et al., 2022). For example, in those with AN, memory impairments associated with hippocampal dysfunction are observed in immediate and delayed recall (Nikendei et al., 2011) and perseverative working memory deficits (Dann et al., 2023). These deficits may play a role in the development and persistence of the disorder, particularly core symptoms such as inflexible thinking. Moreover, reduced structure and altered function in prefrontal, insula, and occipital brain regions are observed in AN that correspond to these core cognitive deficits (Curzio et al., 2020; Su et al., 2021).

Similarly, neurotransmitter signalling is known to be affected by neuroinflammation (Capuron and Miller, 2011). For example, pro-inflammatory cytokines can disrupt the production of both serotonin and dopamine by inhibiting necessary cofactors (Dalton et al., 2018). Dysregulation of serotonin, dopamine and other neurotransmitters is observed in those with AN and these neurotransmitter systems work within corticolimbic circuits that are associated with the core pathophysiology of AN, including anxiety and cognitive deficits (Li et al., 2023; Södersten et al., 2016). Moreover, the hypothalamus is an area that is central to both neuroinflammation and the pathophysiology of AN, including disturbed appetite and the stress response. For example, neuroinflammation has been reported to affect hypothalamic connections related to feeding behaviours, and studies of the neuronal correlates of AN show both structural and functional alterations of the hypothalamus, with disturbed striatal connections and a decrease in glucose reactivity (Caso et al., 2020). Inflammation in the hypothalamus

is directly connected to disturbed feeding behaviour and decreased body weight (Caso et al., 2020; Butler et al., 2021; Breton et al., 2022). Moreover, pro-inflammatory cytokines increase activation of the hypothalamic-pituitary-adrenal (HPA) axis, the stress response hyperactive in AN (Dalton et al., 2018; Chen et al., 2022; Caso et al., 2020; Capuron and Miller, 2011).

The appetite suppressing effects of neuroinflammation bear a significant resemblance to the core pathology in AN, not limited to the hypothalamic processes (Dalton et al., 2018; Collu et al., 2020; de Baat et al., 2023). Studies administering pro-inflammatory cytokines both centrally and peripherally induce an anorexic response in both animals and humans (Dalton et al., 2018; Collu et al., 2020). This effect is suggested to be mediated by altered concentrations of appetite regulating hormones like histamine, ghrelin and neuropeptide Y, as well as increased leptin, a satiety hormone produced by adipose tissue (Dalton et al., 2018).

Beside the effects on feeding behaviours, neuroinflammation can affect a wide array of cognitive functions in various psychiatric conditions, including but not limited to learning, memory, mood, feeding behaviour, motivation, and alarm (Butler et al., 2021; Capuron and Miller, 2011; Dalton et al., 2018; Ioakimidis et al., 2011; Scangos et al., 2023). For example, depression and anxiety are associated with inflammatory processes in several studies (Collu et al., 2020; Howe, Lynch, 2022; Scangos et al., 2023; Sundberg et al., 2020). This is corroborated by an increased incidence of depression in patients with chronic inflammatory diseases (Dalton et al., 2018; Capuron and Miller, 2011; Dalton et al., 2020). Anxiety and depression may well be the subjective experience of chronic inflammation in the CNS via alterations to corticolimbic neurotransmitter functioning (Won and Kim, 2020; Scangos et al., 2023), as evidenced by elevated pro-inflammatory cytokines and correlating anxiety following bacterial LPS administration (Lasselin et al., 2021). Neuroinflammation has also been connected to other symptoms relevant to many psychiatric disorders, including AN, such as fatigue, general cognitive impairment, sleep disturbance and general disruptions to well-being (Chen et al., 2022; Capuron and Miller, 2011).

6. The role of compulsive physical hyperactivity and exercise in AN

As well as appetite restraint, one of the fundamental clinical symptoms at the onset of 40–60% of AN cases is hyperactivity (Davis, 1997). It can be seen as a strategy to lose weight, but animal models also suggest that hyperactivity reflects other complex biological mechanisms associated with appetite restraint and starvation (Kohl et al., 2004). Various models exist to expand on the potential mechanisms in humans, for example, hyperactivity can result in starvation in a self-maintenance cycle (Epling et al., 1983). Others (Le Grange and Eisler, 1993) suggest that hyperactivity (especially excessive long distance running) is a psychiatric comorbidity of AN akin to the anxiety-related obsessive compulsive disorder (OCD), or reward-driven addictive behaviour, or that hyperactivity is a subtype of AN (e.g. alongside binge-purge subtype). In general, high intensity exercise that results in weight loss influences PNS and CNS pro and anti-inflammatory processes.

6.1. PNS and CNS inflammatory processes of hyperactivity and exercise during onset, development and relapse in AN

In terms of PNS, during injury or perceived threat to the body (including excessive exercise and weight loss in AN that may damage tissue), chemical attractants (chemokines) are released from damaged tissue that attract cytokines (e.g., leukotrienes) to adhere to the endothelium of damaged sites (Baggiolini et al., 1997). This process plays an important role in response to disease and excessive exercise (Daniela et al., 2022). After chemokine release during excessive exercise, destruction of damaged tissue mediated by pro-inflammatory processes occurs, alongside promotion of tissue repair via anti-inflammatory cytokines (IL-4, IL-6, IL-10, IL-13), restricting inflammatory cytokine production (e.g., via suppression of nf-kb) and suppressing inflammatory cell activity (Daniela et al., 2022). These inflammatory responses also disrupt appetite, for example via circulating plasma IL-6, which correlate with active ghrelin and cortisol and is associated with appetite dysregulation after high intensity exercise in normal weight adolescent males (Hunschede et al., 2018). The anti-inflammatory cytokine IL-6 is also regarded as an *adipo-myokine* – a protein secreted from both skeletal muscle and adipose cells, that regulates muscle contraction and repair – and its role during excessive exercise in AN is significant (Raschke and Eckel, 2013) given that both IL-6 and leptin are released by adipose tissue and cross the BBB, altering hypothalamic appetitive and stress-related functions.

In terms of CNS processes, excessive exercise appears to be a versatile anti-inflammatory tool to control hypothalamic satiety signalling. For example, whereas obesity and a sedentary lifestyle are associated with fatty diets and an inflammatory response in hypothalamic astrocytes and microglia - which disrupts leptin signalling for satiety - extreme exercise alters adipose tissue density that also raises circulating anti-inflammatory signals (Ropelle et al., 2021). Moreover, rodents with inflammatory processes associated with traumatic brain injury show attenuation of short-term memory impairment and reduction of apoptotic processes in the hippocampus after high intensity exercise (Kim et al., 2010), suggesting that exercise enhances a neural anti-inflammatory response. In people with AN, IL-10 increases after physical exercise (Svendsen et al., 2014; Ribeiro et al., 2012; Helmark et al., 2010) which is also linked to hypohydration (Sawka, 1992). Elevated physical exercise despite low weight may also be a symptom of mobilisation of phylogenetically old systems in those vulnerable to develop AN, and a dysregulated neural response to starvation involving hypothalamic leptin signalling, known as *hypoleptinemia* (Hebebrand et al., 2003). However, more recently it is temperature regulation – another hypothalamic function - not leptin that seems to play a crucial role in hyperactivity in animal models of AN (Fraga et al., 2020).

6.2. Anxiety-reducing effects of exercise

Obsessionality is a core aspect of AN, and obsessive-compulsive behaviours, such as excessive and repetitive exercise are habits formed in some types of the disorder to cope with anxiety (Davis et al., 1998; Guarda et al., 2015). For example, a multiple regression analysis revealed that 64% of variance in physical activity in the acute phase of AN was explained by a synergistic relationship between food restriction and anxiety (Holtkamp et al., 2004). The authors further suggest that hyperactivity in AN is not only a repetitive, automatic and learned coping strategy for anxiety, but is also linked to starvation and hypoleptinemia, with interventions restricting exercise heightening anxiety (Holtkamp et al., 2004). In recent studies, the inclusion of supervised activity for those in treatment for AN appears to aid anxiety reduction, weight and body fat recovery, suggesting a link to anxiety-related processes (e.g. PNS and CNS pro and anti- inflammatory damage and repair respectively) that may drive weight loss (Marcos et al., 2021). Hyperactivity in AN may well be a learned response to the negatively reinforcing effects of anxiety reduction, based on an interplay between anti- and pro-inflammatory processes described above, which also influence appetitive processes in the hypothalamus.

6.3. Rewarding/addictive effects of exercise

Excessive exercise is associated with neural responses in dopamine reward and motivation circuitry involving the basal ganglia and prefrontal cortex, which also regulates mood (Cheval et al., 2018; Gorrell et al., 2022). In addition, engaging in regular exercise may increase impulsive 'automatic' responses including attentional bias to exercise and/or disorder-salient stimuli and triggering of positive affect, which

corresponds to activation in neural reward circuitry (Cheval et al., 2018). Others have studied various theories attempting to explain exercise dependence, including affect regulation, sympathetic arousal, β-endorphin, and the role of IL-6 in the link between the gut and brain in a novel 'cytokine hypothesis' (Hamer and Karageorghis, 2012).

The affect regulation hypothesis of exercise dependence broadly exerts that excessive exercise increases positive – and decreases negative – affect, and that abstinence can lead to depression and anxiety (Anshel, 1991, Rosa et al., 2004). The sympathetic arousal hypothesis (Thompson and Blanton, 1987) suggests that reduced catecholamine release during excessive exercise as an adaptive process increases efficiency of energy utilisation, which ultimately means that an individual needs to engage in greater levels of activity to maintain arousal. The β-endorphin hypothesis involves dysregulation and allostasis in neural processes of dopamine and endorphins in the brain reward circuitry contributing to positive and negative reinforcement during addictive processes (Koob and Le Moal, 2001) For example, aerobic exercise stimulates the release of β-endorphin and other endogenous opioid peptides that have analgesic qualities, and regular exercise can lead to opioid tolerance (Smith and Yancey, 2003).

In relation to the novel cytokine hypothesis, 'sickness behaviour', including depression, anxiety and psychological distress, has been linked to elevated peripheral IL-6 and comparable behaviours during withdrawal in those with exercise dependence (Hamer and Karageorghis, 2012). Peripheral measures (e.g. plasma) of pro-inflammatory cytokines, including TNFα and IL-1β, do not increase following excessive exercise, but IL-6 does (Hamer and Karageorghis, 2012). Exercise-induced IL-6 may enhance a reparative anti-inflammatory environment by promoting IL-1 receptor antagonist and IL-10 synthesis, while inhibiting TNF-α release (Steensberg et al., 2003). According to Hamer & Karageorghis' IL-6 model of excessive exercise dependence, a trigger (excessive exercise load, acute psychological stress, infection) may over- produce IL-6 leading to sickness behaviour and negative affect.

7. Homeostasis, allostasis and the allostatic load

Homeostasis is the term for the PNS/CNS maintenance and regulation of internal milieu variables for bodily constancy and stability in the presence of internal and external threats (e.g., pathogens, stressors, damaged tissue). For example, regulation and maintenance of a stable body temperature between 36.5 and 37.5 degrees Celsius enables the human body to survive in a wide variety of climates. When negative feedback occurs, e.g., when body temperature drops in a cold climate, automatic processes to generate heat (e.g., peripheral vasoconstriction, shivering) and behaviours (deliberate movement) raise the body temperature. The General Adaptation Syndrome (GAS: Selye, 1946) refers to biological adaptations in the body when threats and stressors are chronic.

Adaptation is a form of allostatic load, or *the price people pay for chronic stress* (McEwan, 1998). Allostasis is the altering of homeostatic set points (e.g., an evolutionarily set body temperature, an optimal daily calorie intake) to maintain equilibrium in the presence of changing, sometimes chronic, environmental demands. Relatedly, allostatic load is the extent to which natural homeostatic setpoints readjust in the presence of novel stressors that become chronic (e.g., adjusted daily calorie needs adjusted in times of chronic food scarcity or threat, or a more sedentary lifestyle than previously). For example, a person in recovery from chronic AN and very low weight cannot immediately eat normal amounts of food due to a form of allostatic load illustrated by *re-feeding syndrome*, (Mosuka et al., 2023) which may include muscle weakness, delirium, convulsions, cardiac arrest and even death if re-feeding is not introduced conservatively.

Environmental stressors may chronically activate cytokine release and contribute to allostatic load. In a person at risk of developing an eating disorder, stressors are notoriously ambiguous, mostly biopsychosocial, including threats associated with social status and hierarchy changes during puberty (Surbey, 1987; Pokhrel et al., 2010), and evolutionary, as in the sexual competition theory and prevention of sexual maturity (Abed and Ayton, 2022). Environmental stressors for a person with AN could also be related to heightened/perceived societal uncertainties (e.g., intolerance to uncertainty: Brown et al., 2017), as in the threats posed by the uncertain outcome of the Covid-19 pandemic, which elevated rates and exacerbated eating disorder symptoms, especially for those with AN (Zipfel et al., 2022).

According to Selye's GAS, the key is that stressors need only be *perceived* not *actual,* and in response to perceived stress, the CNS and PNS elicit specific inflammatory remedies as described in detail above. These include activation of the hypothalamic-pituitary-adrenal (HPA) axis via elevated cytokine release into the bloodstream that cross the BBB, increasing glucocorticoids (e.g., cortisol) suppressing non-essential systems such as appetite and reproduction (amenorrhea is a core symptom of AN), and adrenalin to increase activity in response to threat. Activation of cellular processes following a threat perception, such as transcription factors (e.g., the signalling molecule nf-kb) upregulate the production of 5-LOX cytokines, which enter the bloodstream and cross the BBB (for review see Brooks, 2018). The pro-inflammatory cytokines IL1, IL6 and TNF-α lead to long-term changes in the HPA to suppress appetite (Shinsyu et al., 2020), and alter neurotransmitter circuits in the brain, including dopaminergic, serotonergic, and noradrenergic, increasing the chronic experience of anxiety and depression, as well as memory and reward deficits (Reichenberg et al., 2001).

Acute, short-term anorexia that redirects metabolism away from feeding/digestion to reduce nutrition for potential pathogens in response to threat is beneficial to the organism, a point demonstrated in experimentally infected mice that are force-fed to control levels and subsequently die (Langhams and Hrupka, 2003). The appetite-suppression response works well when the stressor is temporary. However, for a person with AN who is at risk of starvation and related physical and psychological complications, perceived threat is chronic and difficult to diminish. Moreover, tolerance can develop to the effects of chronic appetite suppression, exerted by cytokines on hypothalamic appetite systems (Plata-Salamán, 1998). This may be key to the compulsive and addictive nature of food restraint, particularly treatment resistant AN (O'Hara et al., 2015), as well as the 'seeking' aspects of preoccupation with food, weight and body image (Halmi, 2013). Similarly, compulsivity and seeking are commonly observed in those with compulsive behaviours (Luscher et al., 2020).

8. Neuroinflammatory compulsivity model of anorexia nervosa (NICAN)

Evidence suggests that people with AN have increased levels of pro and anti-inflammatory cytokines (Dalton et al., 2018; Solmi et al., 2015; Brooks, 2018; Caso et al., 2020; Butler et al., 2021) and that cytokines underlie the experience of anxiety maintaining the disorder (Frank et al., 2023; Scangos et al., 2023). In the earlier stages of disorder, adolescents with AN have lower levels of pro-inflammatory cytokines such as IL-1β and IL-6, and higher levels of anti-inflammatory cytokines such as IL-10 (Ruiz Guerrero et al., 2022; Specht et al., 2022). This could indicate an early reward driven anti-inflammatory response in AN (Ruiz Guerrero et al., 2022). An anti-inflammatory pattern of early phase AN is in line with much of the research into intermittent fasting and calorie reduction, whereby short-term, deliberate calorie restriction reduces inflammation (Malinowski et al., 2019; Dwaib et al., 2021; Visioli et al., 2022), which may be negatively reinforcing due, in part, to anxiety-reducing effects (Berthelot et al., 2021).

AN commonly begins during adolescence when individuals are most vulnerable to anxiety disorders (Solmi et al., 2022; Slavich et al., 2020; Xie et al., 2021). AN is associated with high levels of anxiety for the duration of illness (Frank et al., 2023), and sometimes before illness onset as a predisposing factor (Lloyd et al., 2018). Propensity to

experience anxiety, potentially (epi)genetic (Mevorach et al., 2021), is linked to a pro-inflammatory state (Howe and Lynch, 2022; Sundberg et al., 2020; Lasselin et al., 2020) and inflammatory cytokines reduce appetite (Dalton et al., 2018; Chen et al., 2022; Capuron and Miller, 2011; Collu et al., 2020). Subsequent intermittent fasting mitigates the pro-inflammatory effects, lowering cytokine levels and anxiety (Malinowski et al., 2019; Dwaib et al., 2021; Visioli et al., 2022). Moreover, models of AN incorporating mechanisms in OCD – of using ritualistic, compulsive behaviour – highlight the anxiety-provoking role of obsessional thoughts (Steinglass and Walsh, 2006).

Therefore, maintenance of AN may be a learned response associated with an initial controlled reduction of food intake that is experienced as a self-medicating way to reduce pro-inflammatory cytokines and anxiety (and gain a sense of control over negative emotions). The anti-inflammatory effects of short-term fasting (Malinowski et al., 2019; Dwaib et al., 2021; Visioli et al., 2022), may explain why restrictive eating provides a temporary relief from anxiety in response to pervasive perceived threat (until habituation via allostasis occurs). The behaviour of restrictive eating may become negatively reinforced by the lessening of anxiety, as per a classical and operant conditioning model (Kirsch et al., 2004). This idea is supported by experimental results showing induction of food avoidance and a fear response to high calorie food in healthy subjects with the use of conditioning paradigms (Spix et al., 2023a,b). However, for a person with AN, the anti-inflammatory effects of fasting are likely short-term in the presence of continued threat perception and allostasis during chronic reduced food intake. As such, tolerance likely ensues, pro-inflammatory cytokines increase again, and greater food restriction is needed to gain the same suppression of cytokine levels (Golonka et al., 2020) (see Fig. 2). By this point, self-starvation as a response to anxiety – eventually independent of the anxiety-reducing outcome – is rigidly and implicitly conditioned in brain memory systems that are in addition debilitated by the neurotoxic effects of neuroinflammation.

8.1. Learning mechanisms and perseverance behaviours despite adverse consequences

Habitual and goal-driven behaviour despite adverse consequences

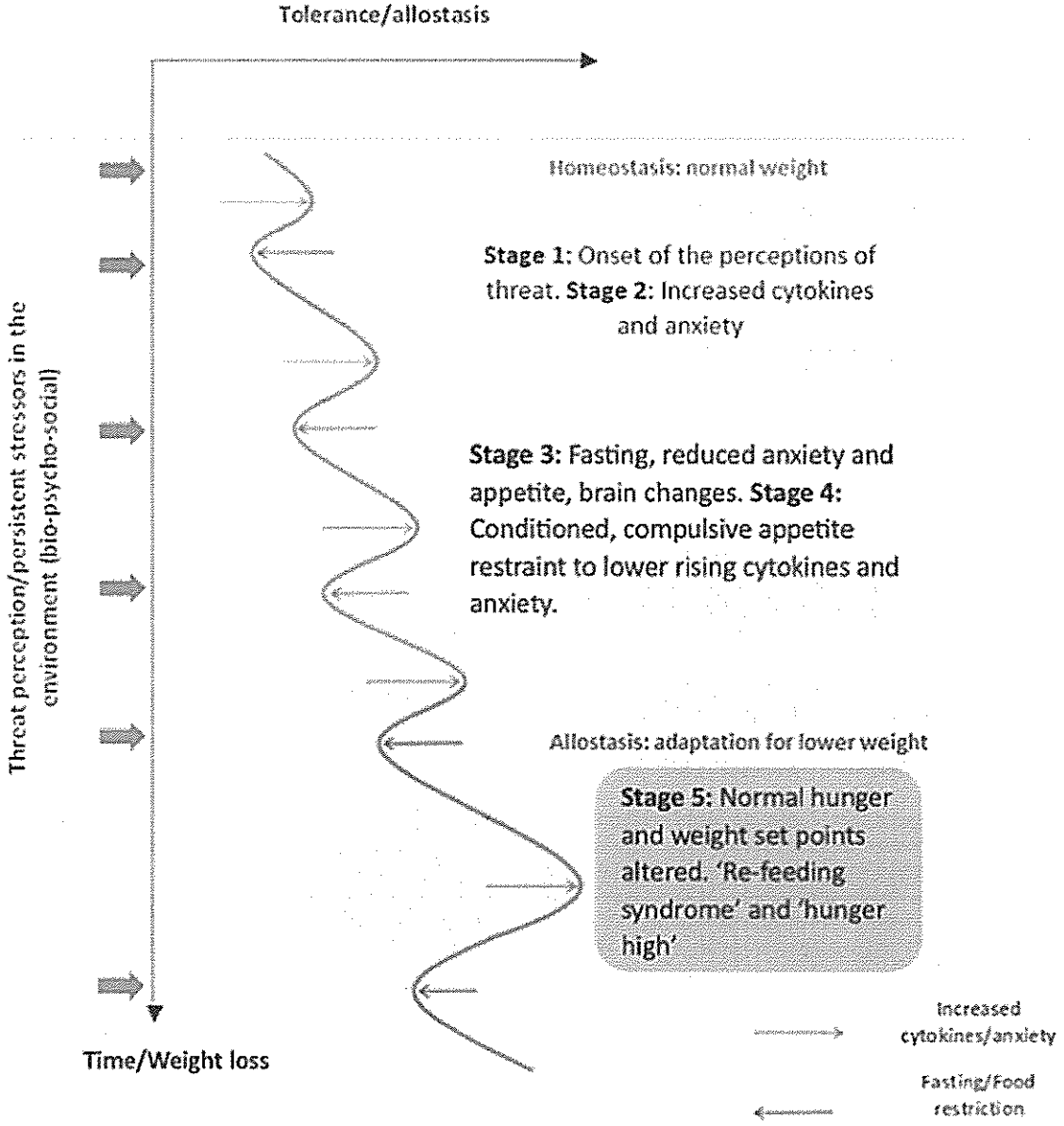

Fig. 2. A schematic diagram of the NICAN model.

may be a learned response to anxiety reduction, similar to OCD (Steinglass and Walsh, 2006). For example, '*compulsions are repetitive, purposeful actions that are usually intended to neutralise or reduce anxiety raised by obsessions [e.g. about threat and safety fears]...and are highly ritualised and stereotyped behaviours*' (Steinglass and Walsh, 2006). The learned aspect of OCD-like behaviours in AN (e.g. body checking, preoccupation with food, weight and shape) are implicit, or procedural, occurring outside of conscious awareness (Steinglass and Walsh, 2006). This type of learning involves three stages; learning a response to a stimulus (operant conditioning, or controlled learning); response-outcome learning (positive or negative reinforcement following the behaviour); and classical conditioning, where an implicit association occurs between a behaviour and desired outcome. With these stages in mind, once behaviour is learned and reinforced, it can become divorced from the initial outcome (Dickinson, 1985), and may be rigidly repeated despite its initial benefits, especially under threatening or uncertain conditions.

In conditions of uncertainty (e.g. pervasive, ambiguous threats), humans may learn to use their behaviour as a measure of information (*'behaviour-as-information effect'* Pittig et al., 2020*)*, and rigidly learned safety behaviours can be interpreted as the presence of persistent threat. As such, it has been demonstrated that avoidance, restrictive eating and body checking are forms of rigidly adopted safety behaviours that exacerbate fear and anxiety in AN (Spix et al., 2023a,b). People prone to develop AN (e.g. those vulnerable to anxiety, excessive safety behaviours and threat perceptions), are susceptible to such rigid habit formation, wherein reinforced behaviours are difficult to reverse and become automatic, even under conditions of adversity (Uniacke et al., 2018), such as the physical – sometimes mortal – consequences of starvation. Interestingly, such rigid habit formation is associated with corticolimbic neural circuits that are susceptible to damage during chronic neuroinflammation, coinciding with a heightened experience anxiety and threat sensitivity (Scangos et al., 2023).

Relating learning mechanisms and implicit perseverance behaviours despite adverse consequences to the NICAN model, a crucial aspect is the compulsive, downward spiral the disorder follows (Koob and Le Moal, 2001; Everitt, 2014). Neural reward processes are hijacked by disorder-specific stimuli to rigidly and automatically maintain food restriction in AN (O'Hara et al., 2015; O'Hara et al., 2016; Giunti et al., 2023; Monteleone et al., 2018; Beeler and Burghardt, 2021), which also mimics the compulsive and seeking behaviours in those with addictive behaviours (Luscher et al., 2020). As the disorder progresses down through the weight loss spiral, cues related to restrictive eating (e.g., obsessional preoccupations with body, shape, weight, food and eating) strengthen the associations with successful appetite suppression and negative reinforcement as an anxiety reduction, becoming more rewarding than natural rewards, leading to the pursuit of these stimuli (O'Hara et al., 2015; O'Hara et al., 2016). In line with this, a clinical trial shows that cue-induced natural reward responses in AN patients are significantly reduced after dopamine depletion, suggesting that dopamine plays a crucial role in aberrant reward signalling (O'Hara et al., 2016).

Moreover, evidence suggests that dopamine signalling follows a similar repetitive inverse-U pattern as inflammatory markers potentially do in AN (see Fig. 2), in that while dopamine is increased in the early, positive-reinforcement driven stage of illness, it is reduced in later stages as habituation and negative reinforcement (anxiety reduction) occurs (Beeler and Burghardt, 2021). Dopamine dysregulation not only supports an early reward driven phase in response to disorder-specific cues, but might also contribute to the maintenance of rigid, repetitive, motivated behaviours that become independent of the initial outcome (Beeler and Burghardt, 2021.

). As the disorder progresses, long-term starvation and neuroinflammation decreases dopamine signalling (transmission, receptor densities, transporters etc), and alterations in corticolimbic circuits that are damaged by chronic neuroimflammation (Scangos et al., 2023). These alterations are associated with anxiety and threat perception, and contribute to negative reinforcement (starvation to reduce anxiety), cognitive inflexibility and difficulties in learning new behaviours (Beeler and Burghardt, 2021). However, more longitudinal studies are needed to confirm the chronic pattern of dopamine and cytokine levels in AN (Breithaupt et al., 2023; Dalton et al., 2020).

9. Discussion

The central tenet of the proposed NICAN model is that people become 'stuck' in a downward, 5-staged spiral of compulsive, increasingly severe appetite restraint, as a negative reinforcement response to the neuroinflammatory cytokine and anxiety reducing effects of fasting. This notion is akin to an existing spiral model explaining neural mechanisms of compulsivity posed by others (Koob and Le Moal, 2001; Everitt, 2014), see Fig. 3 for an adapted version of the model by Everitt (2014). This spiral model describes how initial voluntary behaviour in those vulnerable to develop compulsive behaviours (e.g., drug seeking, intermittent fasting) transitions to a loss of control and the emergence of habitual, inflexible behaviour (compulsive drug use or starvation) and repeated relapses.

9.1. Five stages of the NICAN

Using a staging marker for illness progression in AN is a clinical approach suggested by others to improve treatment interventions (McGorry et al., 2014). In the first stage of the proposed model, in those vulnerable to perceive novel environmental threats, stressors are elevated - typically, but not exclusively - in adolescence. During the second stage, chronic threat perception and safety behaviours activate transcription factors such as nf-kb that elevate the production and release into the bloodstream of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-a). These leukocytes cross the BBB, especially the most porous barrier in the brain, in the third ventricle, chronically influencing the structure and function of the hypothalamus (e.g., the arcuate nucleus), activating the HPA axis for a prolonged experience of stress and anxiety. Other brain regions are also affected (particularly in the corticolimbic circuitry), including the hippocampus and prefrontal cortex, which may embed learned responses in rigid, repetitive, obsessional cognitions. During the third stage, appetite is reduced via HPA processes, as are cytokine levels and anxiety. The memory (both implicit and explicit) of the effects of appetite restraint on reducing anxiety is consolidated in hippocampal systems (the structure and function of which are also influenced by chronic cytokine release). In the fourth stage, memory systems re-activate the conditioned behaviour of reduced feeding in the presence of continued perceived threats to remedy the re-elevation of cytokines and anxiety. In this fourth stage, conditioned responses recreate only partially (due to allostasis) the anxiety-reducing effects of appetite suppression that was experienced during the second stage of cytokine release, when the threats were novel. In the model's final, most dangerous stage, chronic, conditioned appetite restraint adapts homeostatic set points for hunger and satiety (allostasis/allostatic load) creating a 're-feeding syndrome' and 'hunger high', with tolerance reducing the impact of appetite restraint on anxiety and cytokine reduction. As such, greater levels of appetite restraint (coinciding with dangerously low weight and related consequences) are employed to recreate the rigidly learned negative reinforcement that anxiety/cytokine-reduction affords. The behaviour (appetite restraint) is independent of initial anxiety reduction at this most fatal stage. This stepwise 'downward spiral' NICAN model captures the chronic, compulsive, increasingly severe, yet rewarding (e.g., to lower anxiety) food restriction that has been learned, despite adverse consequences. Such behaviours are commonly observed in treatment resistant AN and in people with other compulsive behaviours (Koob and Le Moal, 2001; Everitt, 2014), who also present with elevated cytokines and anxiety (Dalton et al., 2018; Yuan et al., 2019; Chen et al., 2022). See Fig. 4.

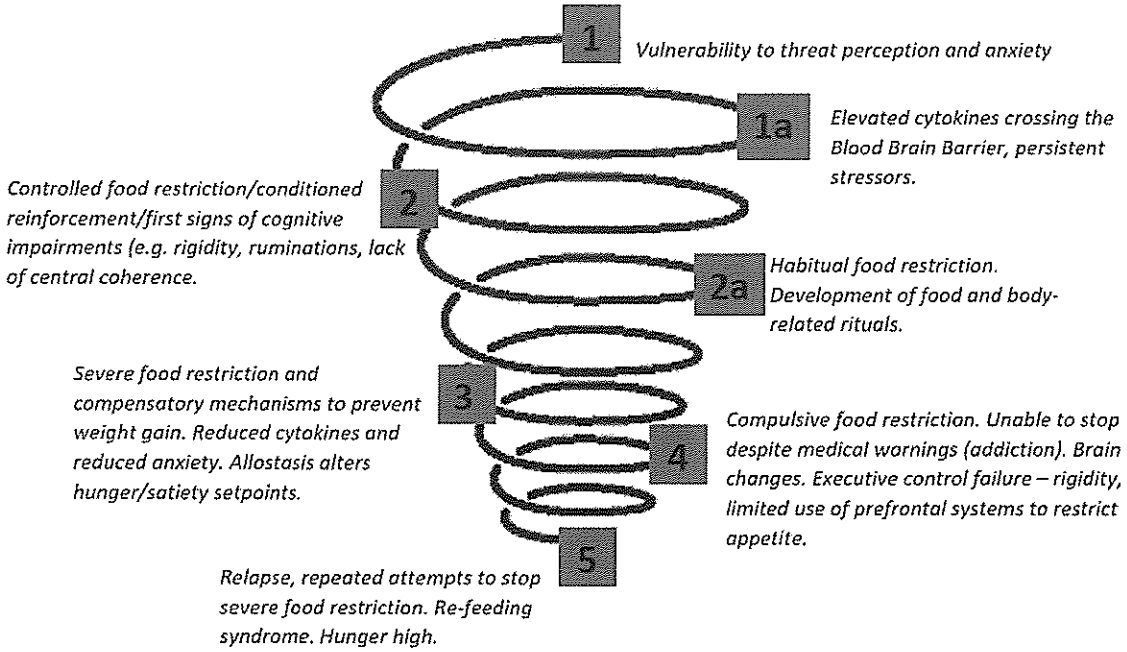

Fig. 3. The NICAN model as a spiral, representing the descent into compulsive appetite restriction (adapted from Everitt (2014)).

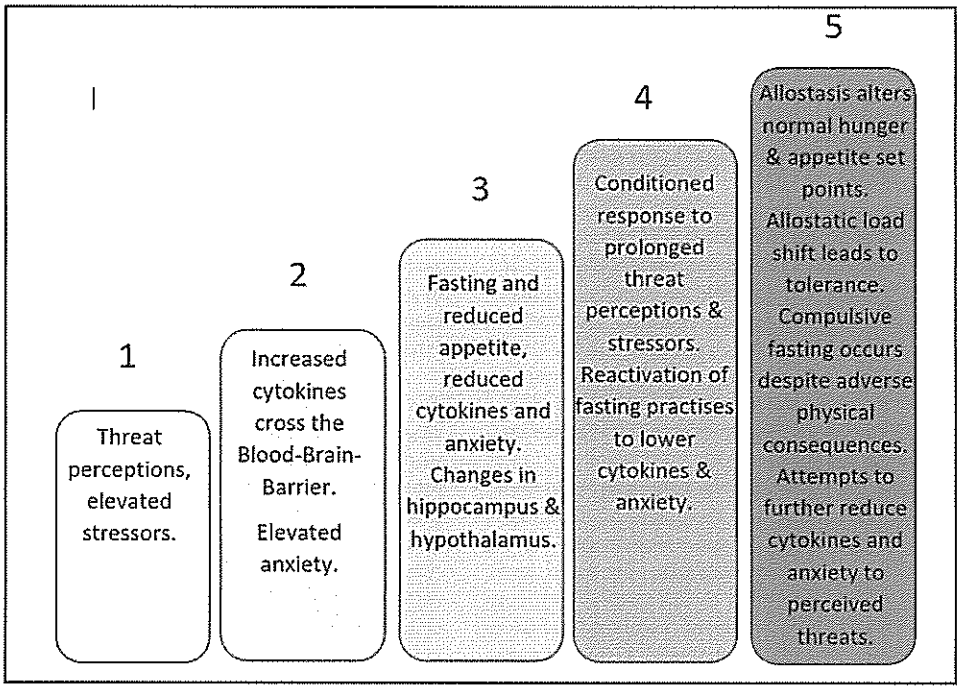

Fig. 4. Five stages of the NICAN model.

9.2. Limitations to the model

Despite supportive evidence from human and animal studies there are limitations of the proposed model. Firstly, it is difficult to measure threat perceptions that increase stressors, cytokine levels and anxiety - a key driver and the first stage of the model. For example, perceived threats could be intangible and changeable, including social, sexual (maturation) and general affective factors. Self-report measures for these do exist, for example the Threat Perception Measure for social threats (Cottrell et al., 2010) and the Tanner Stages for a Sexual Maturity Rating (Emmanueal and Boker, 2023), along with measures of affect regulation, such as the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983). However, these rely on subjective accounts prone to bias, particularly in adolescents who may experience difficulty in expressing what feels threatening to them, due to underdeveloped pre-frontal networks required for affect expression and executive functioning (Caballero et al., 2016). Threat perceptions may also influence behaviour without conscious awareness (Sun et al., 2021). To circumvent the biases of conscious self-report measures, implicit/non-conscious cognitive tasks could be used to gauge levels of threat perception in those at risk of AN, such as the Posner cueing task (Sun et al., 2021), subliminal or supraliminal tasks such as Priming

Tasks (Smith et al., 2014; Soussignan et al., 2010) or the Threat and Food Stroop tasks (Cao et al., 2023; Stott et al., 2021).

In the second and third stages of the model, it is not clear which cytokines cross the BBB in AN, and the mechanisms by which pro- and anti-inflammatory molecules influence brain structure and function. It appears that cytokines alter the metabolism (synthesis, release, uptake) of various neurotransmitter systems implicated in AN (Miller et al., 2013), which may also alter receptor densities. Animal models (e.g., the *anx/anx* knockout phenotype: Siegfried et al., 2003) and receptor density studies in AN (Frank et al., 2005; Yoshizawa et al., 2008) corroborate this idea, especially for dopamine and histamine receptor densities. However, more investigations are needed to better understand the mechanisms of neuroinflammation in the symptomatology of AN.

The model's fourth stage suggests that anxiety decreases related to cytokine reduction negatively reinforces food intake restriction, a concept evidenced through the Opponent Process Theory of Addiction (Koob and Le Moal, 2008) and in the excessive stress response involving the HPA in AN (Dalton et al., 2018; Chen et al., 2022; Caso et al., 2020; Capuron and Miller, 2011). However, the link between elevation of specific cytokines and anxiety is unclear (Costello et al., 2018), and the role of neuroinflammation in AN is an under-explored area, with publications to date quantifying peripheral cytokine levels in eating disorders (Solmi et al., 2015; Dalton et al., 2018; Breithaupt et al., 2023) rather than understanding the mechanisms. Some progress has been made linking neuroinflammatory mechanisms to compulsive behaviours (hyperactivity, starvation), for example, glial activation and neuroadaptations, with anti-inflammatory approaches to alter neural mechanisms being proposed (Kohno et al., 2019) that may be considered for AN.

Finally, it is not clear how allostasis and tolerance contribute, at the neuroinflammatory level, to the persistent harmful food restriction and compensatory behaviours observed in those with AN. Some studies of those with ED have examined peripheral cytokine levels longitudinally according to a recent meta-analysis (Dalton et al., 2018), but the data were not available in the meta-analysis to confirm longitudinal changes. Thus, it is still unclear whether a stepwise pattern of cytokine levels occurs, proposed by the present model, as duration of AN persists, but using cytokines as a marker for illness progression and clinical staging is an approach suggested by others to improve clinical intervention (McGorry et al., 2014). In terms of allostasis and allostatic load as a model to explain the potential stepwise pattern of dysregulated neural reward systems in AN, others have also proposed this idea (Halmi, 2009). However, no studies have yet linked allostasis, allostatic load and neuroinflammatory compulsive processes in AN.

Thus, data is currently lacking to support the ideas presented here, but again, allostasis, neuroinflammation and disrupted dopamine systems have been linked in compulsive behaviours elsewhere (George et al., 2012; Beeler, Burghardt, 2021), which, as already discussed, have been identified in the symptomatology of AN (O'Hara et al., 2015). It could be that an initial positive reinforcement involving elevated dopamine motivates the learning of self-starvation and weight loss as a solution to enhance positive affect. But in chronic illness a switch is proposed towards habitual negative reinforcement via increasingly severe appetite restraint and hyperactivity that reduces pro-inflammatory cytokines and elevates anti-inflammatory cytokines. We propose this evokes a temporary stepwise reduction (and allostatic elevation) of anxiety that drives the maintenance and relapse in AN.

9.3. Implications of the NICAN model

The model stimulates more research linking neural mechanisms in AN and compulsive behaviour (O'Hara et al., 2015, 2016; Everitt, 2014), the aim of which is to improve current treatments (e.g., CBT, pharmacological interventions). This may prove fruitful to prevent the development, maintenance, and relapse of AN, to reduce the alarming rise in eating disorders (Muratore, Attia, 2021; Frostad et al., 2022; Monteleone et al., 2022; Royal College of Psychiatrists, 2022; Zipfel et al., 2022), and to prevent palliative care and medically assisted dying for treatment-resistant cases (Royal College of Psychiatry, 2023). Neural similarities exist between AN and compulsive behaviours, in terms of elevated neuroinflammation (Kohno et al., 2019; Solmi et al., 2015; Dalton et al., 2018), along with two separate neural mechanisms of hypervigilant executive functions and obstinate compulsive behaviours that continue despite adverse consequences (Goldstein and Volkow, 2011; Yuan et al., 2019; Luscher et al., 2020; Chen et al., 2022; Breithaupt et al., 2023). A meta-analysis of structural brain imaging studies in AN patients revealed subcortical reduced volume in regions affected by inflammatory processes described above, including hippocampus and other basal ganglia regions, as well as cortical regions including prefrontal and parietal (Walton et al., 2022). The most recent structural brain imaging study in AN additionally reveals, like earlier work by our group (Brooks et al., 2011), that prefrontal and insula regional volume is larger in AN (Tose et al., 2024), suggesting that a rumination process (e.g. repetitive restraint cognitions linked to anxiety) limits normal age-related brain volume reduction observed in age-matched non-eating disorder groups (Brooks et al., 2011). Heterogeneity of functional neuroimaging methods stimulate need for more definitive studies regarding neural dysfunction in AN (Bracke et al., 2023), although excessive prefrontal cortex involvement including the cingulate cortex (Su et al., 2021) may reflect excessive threat perception predicted by the present model.

Neuroimaging studies are required to link specific inflammatory markers to compulsivity symptoms in AN. It is only in the last decade that researchers have begun to examine levels – not mechanisms - of neuroinflammatory markers in AN (Solmi et al., 2015; Dalton et al., 2018; Breithaupt et al., 2023) despite investigation of neuroinflammation in other psychiatric disorders (Yuan et al., 2019; Chen et al., 2022). Longitudinal studies charting the chronicity of cytokine levels in people with AN and other eating disorders would aid the endeavour to understand neuroinflammatory mechanisms (Dalton et al., 2020) and test the hypotheses of the present model. If it can be demonstrated that weight fluctuations during the illness course coincide with fluctuating cytokine and anxiety levels, this would be the first step to corroborate a neuroinflammatory compulsivity mechanism in AN. More specifically, the model will be supported if different stages of food intake restriction are linked to variations in cytokine levels.

The model predicts that threat perception is the initial driver of elevated cytokines, anxiety, and subsequent compulsive appetite restraint (e.g. cognitive ruminations involving PFC-related neural networks), but it is not clear what causes perception of threat. Perceived threat for a person who develops AN is notoriously ambiguous, and could include bio-psycho-social fears related to sexual maturity, social norms, global anxieties (e.g., climate, pandemic), etc. (Surbey, 1987; Abed and Ayton, 2022; Brown et al., 2017; Zipfel et al.,2022). As such, a better measure of threat perception (not *actual threats,* as in adverse childhood experiences) is needed for adolescents and adults to gauge vulnerability to develop an eating disorder. For instance, the 10-item Threat Perception Measure (Cottrell et al., 2010) examines perception of threat posed by target social groups (e.g., LGBTQ+, immigrants etc.), and is not broad enough to gauge all potential perceived threats in those with AN. Thus, the development of an eating disorder specific threat perception scale would be helpful to further test the hypotheses proposed by the present model through linking elevation of cytokines to levels of threat perception.

9.4. Implications to improve treatment and relapse for AN

The hypotheses proposed by the NICAN model suggest at least four approaches that could be incorporated into existing treatments, for further development and exploration to improvement relapse rates. The first is to reduce threat perceptions with specialised CBT. The second is to strengthen/repair neural architecture with cognitive training, to

enhance the holding in mind of competing, complex cognitions that challenge rigid, limited, threat perceptions. The third is to advocate for a Mediterranean style diet rich in anti-inflammatory nutrients as part of recovery programmes. The fourth is to conduct experimental investigations testing the efficacy of a course (e.g., six months) anti-inflammatory nutraceuticals and/or phytoceuticals for reducing elevated cytokines and improving neural structure and function. Each of these approaches will be briefly described below.

9.5. Reducing Threat Perceptions with Specialised CBT

Individualised CBT approaches for AN began with Bemis' work focusing on challenging core beliefs about body shape and weight, linked to perfectionism, asceticism, and difficulties in affect regulation, with treatment success dominated by weight restoration rather than chronic cognitive dysfunction (Dalle Grave et al., 2016). Other CBT approaches include Enhanced-CBT, systemic, family-centred (e.g., MANTRA: 'Maudsley model of anorexia nervosa treatment for adults') and pre-CBT steps such as Cognitive Remediation Therapy, and attentional bias modification (Tchanturia and Davies, 2010; Dalle Grave et al., 2016, 2023; Schmidt et al., 2019; Mercado et al., 2020). While CBT-type approaches achieve some success for some cases, the relapse rates are still rising (Muratore and Attia, 2021; Monteleone et al., 2022; Frostad et al., 2022; Zipfel et al., 2022; Royal College of Psychiatrists, 2022). While CBT-E has shown significant efficacy (Dalle Grave et al., 2023), it still focuses on weight restoration and clinical measures. However, if the above cognitive approaches were to also incorporate measures of neuroinflammation and threat perception, treatments may better predict improvements to anxiety and stress regulation, which this model predicts would reduce relapse post-treatment.

9.6. Strengthen/repair neural architecture

Cognitive training interventions purportedly alter neural structure and function, with neural level changes occurring prior to behavioural changes in those with addictions (Brooks et al., 2020). Brain imaging studies of working memory training demonstrate neuroplasticity associated with reduced function (related to improved neural efficacy) and enhanced myelination in frontostriatal and parietal regions (Brooks et al., 2020), brain regions which may be susceptible to neuroinflammation in AN as described above. A recent Delphi review by experts of cognitive training for addiction reveals that implicit biases, positive affect, arousal, executive functions, and social processing are key targets for training (Verdejo-Garcia et al., 2023). Adaptive working memory training in particular targets frontostriatal circuitry that is altered in AN and addictions (Brooks, 2016), and involves progressively difficult levels, whereby practice effects correspond to brain changes, improved impulse control and attention (Klingberg, 2010; Spencer-Smith & Klingberg, 2015). Improved affect regulation coincides with greater working memory capacity because more complex cognitions (e.g., conflicting viewpoints, goals for the future, alternative cognitions to challenge an aberrant sense of self) can be held in mind for longer, compared to those with a limited working memory capacity (Little et al., 2014). Thus, improving working memory neural networks purportedly damaged by neuroinflammation in AN may reduce perceptions of threat (which contribute to deficits in affect regulation and related cognitive deficits) enabling competing, complex cognitions to be held in mind simultaneously. This might be beneficial to a person in recovery from AN to prevent relapse, when pro-AN thoughts might otherwise 'win' over the holding in mind (and subsequent implementing) of healthier options. Future studies should test the feasibility and efficacy of working memory training to improve relapse in people with AN, whose working memory networks are likely damaged by neuroinflammation (linked to core cognitive deficits described above).

9.7. Mediterranean-style diet

A Mediterranean-style diet could be used as tool to combat inflammation and chronic diseases including AN (Solmi et al., 2015; Dalton et al., 2018; Tsigalou et al., 2020). Dietary patterns that increase serum IL-6 levels may accelerate cognitive dysfunction, pro-inflammatory cytokine production and neuronal apoptosis, according to the Whitehall II prospective cohort study (Ozawa et al., 2017). Evidence shows that the Mediterranean diet can prevent non-communicable chronic diseases and has been shown to reduce pro-inflammatory cytokines in humans (Casas et al., 2014). A recent large meta-analysis has revealed that a Mediterranean diet has a protective effect on the development of Axis I disorder symptoms, including eating disorders, but especially anxiety and depression (Madani et al., 2022). The first study of the link between Mediterranean diet and risk of eating disorders revealed that a Mediterranean diet reduced the risk of AN, particularly cereal and olive oil intake (Leone et al., 2018). Thus, utilising a Mediterranean-style diet during recovery from AN could reduce pro-inflammatory markers and may aid the repair of neural processes damaged by neuroinflammation.

9.8. Anti-inflammatory nutraceuticals and phytoceuticals

In a similar vein to the evidence that a Mediterranean-style diet reduces pro-inflammatory and enhances anti-inflammatory molecules, certain nutrient-based nutraceuticals and plant-based phytoceuticals, which can be taken as daily supplements, are purported to lower inflammation. These include omega-3 fatty acids (Kavyani et al., 2022), curcumin (Ferguson et al., 2021), zinc (Marreiro et al., 2017), Boswellia serrata resin (Brooks, 2018), Capsaicin (Fattori et al., 2016), and Cat's Claw (Sandoval et al., 2000). This approach to treating psychiatric disorders was recently addressed by the World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce (Sarris et al., 2022). While this approach to reducing inflammation in psychiatric disorders is in its infancy, the WFSBP and CANMAT taskforce gathered 31 leading academics and clinicians across 15 countries between 2019 and 2021 to inform on this approach. The taskforce revealed a range of nutraceuticals and phytoceuticals were given either a supportive recommendation or a provisional recommendation across a range of various psychiatric disorders. Thus, exploring the use of nutraceuticals and phytoceuticals in AN is another promising avenue to pursue.

The introduction of specialised CBT for reducing threat perception, cognitive training, Mediterranean-style diet, and anti-inflammatory nutraceuticals and phytoceuticals, in the context of clinically hospitalized treatment-resistant individuals may be challenging. However, given the alarming rise in relapse and admission rates for eating disorders globally, new adjuncts to existing treatments are worth exploring.

For example, CBT-based approaches are effective for long-term eating disorder symptom reduction in patient settings (Bowers and Ansher, 2008), and could incorporate group CBT demonstrating efficacy for reducing threat perception in anxiety disorders (Espejo et al., 2017). A brief 15-minute, increasingly difficult cognitive training intervention used by individuals on their own without need for trained clinicians such as 'CYa' working memory training (Brooks et al., 2016), could be incorporated into a daily in-patient treatment programme. The aim would be to strengthen neural processes that may be damaged by chronic neuroinflammation and malnutrition, which would augment the aims of existing treatments (e.g. neurocognitive restructuring). Removing barriers to implementing short computerised adaptive training into inpatient settings may involve ongoing commitment amongst patients and clinical staff (van Dam et al., 2022).

Re-feeding in those with resistant AN is one of the most challenging aspects of inpatient treatment. Hypophosphatemia is a commonly reported biochemical disturbance, including aberrant sodium and fluid balance, changes in glucose, protein, and fat metabolism, thiamine deficiency, hypokalemia, and hypomagnesemia as a result of hormonal

and metabolic changes (Bolhuis et al., 2024). Addressing these biochemical disturbances alongside weight restoration is key in refeeding programmes for AN. Thus, it is promising that a Mediterranean-style diet can significantly increase weight in adolescents with AN, including lean body mass, as well as intake of carbohydrates, lipids, mono-unsaturated fats and fibre alongside improvements in resting energy expenditure (Cinelli et al., 2023). Finally, the inclusion of a daily anti-inflammatory nutraceutical pill into inpatient procedures should be tolerable, especially nutraceuticals with a demonstrable safety record for psychiatric conditions corroborated by world leading experts from the WFSBP and CANMAT Taskforce. With careful clinical observation, especially for those severest cases with gut-related disorders (esophageal symptoms: globus and functional dysphagia, gastroduodenal symptoms: functional dyspepsia and nausea, and bowel symptoms: abdominal pain, bloating and constipation), daily ingestion of a nutraceutical anti-inflammatory is likely feasible for inclusion in existing interventions.

10. Conclusion

Based on recent studies into neuroinflammation and negative reinforcement in AN, a NICAN model is proposed that integrates altered inflammatory processes and inflammation/anxiety reduction to explain the development and maintenance of AN. Threat perception in the early development of AN is suggested to drive the disorder, followed by reinforcement processes associated with relentless food restriction. Learned behaviour is reinforced via operant conditioning that restrictive eating lowers inflammation, subjectively felt as a relief from anxiety. In the early stages of the proposed 5-stage, 'downward-spiral' model, dopamine and endogenous opioid signalling is increased and positively reinforces cues related to restrictive eating, while pro-inflammatory cytokine levels are decreased due to the anti-inflammatory short-term starvation effects. Over time however, as the allostatic load changes the amount of food that can be ingested, the pro-inflammatory cytokine levels increase and appetitive setpoints are altered.

Negative reinforcement of restrictive eating to reduce anxiety occurs and is compulsively repeated, further embedding these learned behaviours in hippocampal long term and implicit memory systems (which are also altered by cytokines). At this later stage, dopamine levels are lowered, and reward value switches to a negative reinforcement schedule (reduction of anxiety), while pro-inflammatory cytokines chronically increase in a stepwise manner. At the most dangerous final stage, reward is shifted to a 'hunger high' and the allostatic load following chronic starvation contributes to 're-feeding syndrome'. Additionally, in the final stage, lowered dopamine levels and neurodegenerative effects of neuroinflammation on the hippocampus may lead to cognitive inflexibility, habit formation, rigid thinking and difficulty to learn new behaviours. Compulsive repetition of the self-starving behaviours that were embedded during the positive reinforcement development phase make it difficult to break learned patterns of restrictive eating as a pleasurable response to lowering anxiety. It is proposed that the NICAN model will help to test these theories (e.g., longitudinal measures of cytokine and anxiety levels), to improve existing therapies and develop new interventions (CBT specialising in threat perception, cognitive training, Mediterranean-style diet, and anti-inflammatory nutraceuticals, for example), in order to lower the rising global rates of this often-fatal psychiatric disorder.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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