

INVITED REVIEW

Novel treatments for anorexia nervosa: Insights from neuroplasticity research

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Abstract

Objective: Treatment for anorexia nervosa (AN) remains challenging; there are no approved psychopharmacological interventions and psychotherapeutic strategies have variable efficacy. The investigation of evidence-based treatments has so far been compounded by an underdeveloped understanding into the neurobiological changes associated with the acute stages of AN. There is converging evidence of deficiencies in neuroplasticity in AN.

Method: This paper provides an overview of neuroimaging, neuropsychological, molecular and qualitative findings relating to neuroplasticity in AN, translating these findings to the identification of novel biological and psychotherapeutic strategies.

Results: Novel psychopharmacological approaches that may ameliorate deficiencies in neuroplasticity include medications such as ketamine, psilocybin and human recombinant leptin. Anti-inflammatory medications and brain-derived neurotrophic factor mimetics may emerge as potential treatments following further research. Psychotherapeutic strategies that may target neuroplastic deficiencies, as well as having wider effects on identity, include imagery rescripting, memory specificity training, cognitive remediation therapy, exposure therapies, narrative therapies, cultural interventions (e.g. music and arts therapies) and yoga/mindfulness-based interventions.

Conclusions: Treatments specifically targeted towards mitigating the neurobiological sequelae of AN are warranted, and emerging neurobiological and neuropsychological research utilising longitudinal designs and large sample sizes, as well as initial feasibility studies, are necessitated to bolster translational efforts.

KEYWORDS

anorexia nervosa, neuroplasticity, neuroprogression, psychopharmacology, psychotherapy

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Highlights

- There is converging evidence from neuroimaging, neuropsychological, molecular and qualitative research suggestive of altered neuroplasticity during the acute stages of anorexia nervosa (AN), which is also a trans-diagnostic feature across psychiatric disorders.
- Novel pharmacological treatments that are used for the treatment of other conditions in humans, and could be applied to target neuroplasticity in AN, include ketamine, psilocybin, human recombinant leptin and anti-inflammatory medications.
- Psychotherapeutic strategies that may target neuroplastic deficiencies in AN, some of which have already been investigated, include those targeting cognitive problems or biases (e.g. imagery rescripting, memory specificity training, cognitive remediation therapy (CRT)), fear (e.g. exposure-based therapies), stress (e.g. yoga/mindfulness-based interventions) and identity (e.g. narrative therapies, cultural interventions such as arts and music-based therapies).

1 | INTRODUCTION

Anorexia nervosa is a severe psychiatric illness characterised by an intense fear of weight gain, disturbances in body image and a restriction of energy intake, leading to significantly low body weight (American Psychiatric Association, 2014). It has one of the highest morbidities and mortalities of any psychiatric disorder with a standardized mortality ratio of ~5.2 (Himmerich et al., 2019). There are currently no licenced or approved biological treatments for AN (Himmerich et al., 2023), and psychological interventions, as well as weight restoration treatments, have variable efficacy (Murray et al., 2019; van den Berg et al., 2019). Early intervention can promote recovery, especially in adolescents. However, a longitudinal study conducted in the USA indicated remission of only a third at 9 years and two-thirds at a 22-year follow up (Eddy et al., 2017). Therefore, a large proportion of patients with AN go on to develop a protracted, or “severe-enduring” form of the illness, which is associated with a greater reduction in life expectancy (Strober, 2010) as well as more frequent presentation to specialist medical facilities, eating disorder (ED) services and hospital admission (Hay et al., 2012). This high proportion of protracted cases is attributable also to a paucity of evidence-based treatments, due to chronic underfunding of ED research (Murray et al., 2017; Schmidt et al., 2016), as well as inequalities in access to treatment (Downs, 2023). There is controversy on how to define severe-enduring AN (SE-AN), with most definitions placing illness duration and number of previously failed treatment attempts at the centre of diagnosis, but with differing criteria for the number of years of illness (e.g.

≥5, ≥7, ≥10 years) and number of failed treatment attempts (Broomfield et al., 2017). For the purposes of this article, the term SE-AN will broadly refer to cases whereby illness duration is seven or more years.

The precise neurobiology of AN remains elusive, and research investigating biomarkers, endophenotypes, and subsequently potential evidence-based treatment approaches is compounded by a lack of understanding into the “neuroprogressive” changes associated with the illness (Treasure et al., 2020). The term “neuroprogression” here refers to pathological alterations in brain structure across the course of illness in structural integrity (e.g. atrophy, volume), neuropsychological function and vulnerability to threat (e.g. stress, inflammation). One aspect of neuroprogression that is hypothesised to occur across psychiatric disorders is a reduction in neuroplasticity (Singh & Garg, 2014). Neuroplasticity is the ability of the nervous system to reorganise itself in its structure, function and connections (Fuchs & Flügge, 2014). Several mechanisms are involved, including the formation of new-born neurons (neurogenesis; occurring throughout the lifespan in areas such as the subgranular zone of the dentate gyrus in the hippocampus and the subventricular zone) and modifications of neuronal morphology, including axonal and dendritic arborisation and pruning, increases in spine density and synaptogenesis (Castrén & Hen, 2013). Neuroplasticity underlies recovery of the brain after insult or injury, as well as many cognitive processes including cognitive flexibility, memory and learning (Sagi et al., 2012; Su et al., 2016). Additionally, astrocytes and microglia act as support cells for neuroplastic processes, with astrocytes being involved in the regulation of synaptogenesis and

the balance between excitation/inhibition in neuronal networks, and microglia acting as the brain's immune cells, resculpting synapses and remodelling neuronal networks (see Dzyubenko and Hermann (2023) for a review).

Treatments that aim to enhance or modulate neuroplasticity have received interest in the field of psychiatry more broadly; it has been suggested that such treatments may provide a window of opportunity for behavioural and/or cognitive treatments to harness the state of increased neuroplasticity, in people with depressive disorders (Price & Duman, 2020; Wilkinson et al., 2019). The ineffectiveness of psychotherapies during the acute stages of AN may also be a result of neuroplastic deficits, including their sequelae such as cognitive difficulties that may both interfere with direct therapeutic engagement but also the ability to engage in daily life generally. This article aims to provide a brief overview of the neuro-morphological, molecular, and behavioural findings in AN that are likely related to neuroplastic alterations, before considering some potential pharmacological and psychological treatment approaches that may mitigate these alterations. We searched PubMed, Web of Science and American Psychiatric Association PsycInfo for articles regarding the psychopharmacological and psychotherapeutic treatment of AN and neuroplasticity following the step-by-step guidance for narrative reviews by Cronin et al. (2008). We included articles that were helpful to highlight new research streams and theoretical and conceptual aspects of the topic.

2 | NEUROINFLAMMATION AND NEUROPROTECTION

Neuroinflammation has been considered to play a role in neuroprogression. Therefore, neuroinflammatory molecules have been suggested as therapeutic targets in neurodegenerative diseases, and more recently in psychiatric disorders such as major depressive disorder (Troubat et al., 2021). Elevations in pro-inflammatory cytokines such as tumour necrosis factor (TNF)- α , interleukin (IL)-6 and IL-1 β , can contribute to brain cell atrophy (Lyman et al., 2014) and may provoke reductions in neuroplastic abilities (Hayley, 2014; Lecca et al., 2022). On the contrary, growth factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF)-1, vascular endothelial growth factor (VEGF), glial cell line-derived growth factor (GDNF), nerve growth factor (NGF) and fibroblast growth factor (FGF) may have neuroprotective and regenerative effects (Levy et al., 2018). BDNF in particular has an important role in the differentiation,

plasticity and survival of neurons (Calabrese et al., 2014). Additionally, the gut microbiome, through its connections to the brain, may modulate neuroplasticity and neurogenesis (Guzzetta, 2022; Möhle et al., 2016), perhaps through moderating BDNF expression in the hypothalamus and hippocampus (Cryan et al., 2019), or by contributing to immune responses and inflammatory states (Foster et al., 2021). Several reviews have highlighted the potential role of the gut microbiome in AN (Dhopatkar et al., 2022; Seitz et al., 2019).

A meta-analysis has reported that pro-inflammatory cytokines, such as TNF- α and IL-6, have been found to be elevated in individuals with AN during the acute stage, compared to healthy controls (Dalton et al., 2018). A normalisation of IL-6 has been observed following treatment, coinciding with improvements in ED symptoms, suggesting that increases in IL-6 may be a state marker for AN (Dalton et al., 2020). However, more recent studies have failed to replicate the findings (Keeler, Patsalos, et al., 2021; Nilsson et al., 2020; Specht et al., 2022). For example, one study did not find increased IL-6 in adults with AN, although there were differences between AN and controls in several other immune markers (Nilsson et al., 2020). A study by our group found lower concentrations of IL-6 in adults with AN compared to controls when controlling for age, ethnicity, smoking status and use of antidepressants, and nominally lower levels of TNF- α (Keeler, Patsalos, et al., 2021). Finally, a study in adolescents with AN found elevated levels of TNF- α at admission, but lower levels of IL-6 (Specht et al., 2022). More research is needed to clarify the role of inflammatory markers in AN and the presence of a potential inflammatory subgroup, given that a disproportionate number of cases above the 90th quantile of IL-6 measurements in one study were AN rather than controls (Nilsson et al., 2020).

The literature investigating growth factors and neurotrophins in AN has largely focused on the IGF family (in the context of growth hormone resistance and bone density), as well as BDNF (in the context of brain health) (Keeler, Robinson, et al., 2022). To date, three meta-analyses have confirmed a reduction in peripheral BDNF in the acute stages of AN (Brandys et al., 2011; Keeler, Robinson, et al., 2022; Shobeiri et al., 2022), which normalises after weight restoration (Keeler, Robinson, et al., 2022) and most likely represents a state effect of dietary restriction. Furthermore, one meta-analysis also found a decrease in IGF-1 in the acute stages and increases following treatment (Keeler, Robinson, et al., 2022). At present, there are insufficient studies to conclude whether other growth factors such as VEGF, GDNF, FGF or NGF are altered in AN (Keeler,

Robinson, et al., 2022) and more research needs to be conducted. Nevertheless, it appears that increasing BDNF may be a viable target for treatment in AN, in order to improve neuroplasticity, brain integrity and learning processes (Trinh et al., 2023). However, BDNF has anorexigenic properties, and one study in adolescents with AN found supranormal levels of BDNF at lengthy follow-up periods (i.e. 2.5 years) after weight restoration treatment (Borsdorf et al., 2021). Therefore, it has been suggested that increases in BDNF could be a risk factor for relapse, and caution should be made when investigating BDNF as a target for treatment in AN (Trinh et al., 2023).

3 | NEUROMORPHOLOGICAL CHANGES IN ANOREXIA NERVOSA

Structural brain changes have been observed in people with AN. A meta-analysis reported a global reduction in grey matter (GM) and white matter (WM) volume in adolescents and adults with AN (Seitz et al., 2016). The reduction in GM is greater in adolescents compared to adults (−8.4% vs. −3.1%), with a more similar reduction in WM between the two groups (−4.0% vs. −2.1%; (Seitz et al., 2016)). These findings have since been replicated in a study by the same group (Seitz et al., 2018). The meta-analysis also reported a persistent deficit in GM following short-term weight restoration (−3.6%) but not WM, although brain matter volume loss is generally regarded as largely reversible in people who have remitted from AN (Seitz et al., 2016).

At present, there is limited knowledge regarding the impact of SE-AN on brain volume. A global reduction in GM, WM and cortical thickness, of a comparable magnitude to the aforementioned meta-analysis, has been observed in a study of participants with approximately 16 years of illness (Mishima et al., 2021). In this study, brain volumes were positively associated with body mass index (BMI). The associations between brain volume and other clinical characteristics are unclear in AN (Fonville et al., 2014; Seitz et al., 2015), although some studies indicate that higher duration of illness and lowest lifetime weight are related to GM volume loss (Seitz et al., 2018).

Cortical thinning is greater in people with AN (approximately −6.4%; (Bahnsen et al., 2022)), in comparison to other psychiatric disorders, such as major depressive disorder (−0.2%; (Schmaal et al., 2017)), but smaller in comparison to neurodegenerative diseases, such as Alzheimer's disease (−12%; (Lerch et al., 2005)). These findings have recently been replicated by the Enhancing Neuro Imaging Genetics through Meta

Analysis consortium who, using a sample of 685 individuals with AN and 963 healthy controls, found that the cortical thickness reductions in AN are the greatest across the psychiatric disorders (Walton et al., 2022). In this study, it was found that the subcortical structures with the greatest reductions in volume included the thalamus, amygdala, hippocampus and putamen (Walton et al., 2022).

Whilst the neurobiological mechanisms underlying brain volume loss in the acute stages of AN remain unclear, King and colleagues reviewed potential hypotheses, which include: cellular effects of dehydration; apoptosis (i.e. programmed cell death of glial or neuronal cells); macro-nutrient and/or micronutrient deficiency; and the suppression of leptin, neurotrophins, and gonadal and thyroid hormones, as well as increased cortisol, leading to neuronal and/or glial remodelling (King et al., 2018). In this review, it is suggested that the latter hypothesis may be the most plausible explanation of neuromorphological changes in AN, which may constitute neuroprogressive alterations as an adaptation to malnutrition (King et al., 2018). Research from this group has shown increases in neuronal and glial damage markers (including neurofilament light [NF-L], tau protein and glial fibrillary acidic protein [GFAP]) in the acute stages of AN, indicative of neuronal and astroglial injury (Hellerhoff et al., 2021). Concentrations of these damage markers mostly normalise following partial (Hellerhoff et al., 2021) and long-term (Doose et al., 2022) weight recovery. A later study found that higher concentrations of NF-L, but not tau protein or GFAP, were associated with lower cortical thickness in regions including those in the bilateral temporal lobes, indicating that cortical thinning may result from axonal damage (Hellerhoff et al., 2023). The authors of this study speculate on the use of neuroprotective pharmacological agents to mitigate the effects of AN on the brain (Hellerhoff et al., 2023).

4 | NEUROPLASTICITY-RELATED COGNITIVE ALTERATIONS

Loss of brain matter integrity can have an impact on brain function (Seitz et al., 2016). Deficiencies in cognitive functions, such as flexible thinking, decision making, central coherence and general executive functioning (Adoue et al., 2015; Reville et al., 2016; Roberts et al., 2010; Stedal et al., 2012), have been consistently reported in people with AN. This has led to deficiencies of central coherence and cognitive flexibility, and altered social, emotional and reward processing, being considered as candidate cognitive endophenotypes of AN (Malcolm & Phillipou, 2021).

However, a recent meta-analysis on neuropsychological tasks in adults with AN indicated broader and non-specific deficiencies in cognition (Stedal et al., 2021). Notably, the most impacted domains were visuospatial abilities, verbal and non-verbal memory (Stedal et al., 2021). Both BMI and age played a role, with lower BMI and increased age being associated with greater cognitive deficiencies. It is interesting to note that another meta-analysis found no significant problems with overall cognitive functioning in young people (12–18 years) with AN, although a significant impact was still observed specifically for memory, working memory and visuospatial abilities (Stedal et al., 2022). At present, there is insufficient evidence to identify whether all cognitive sequelae of AN resolve following weight restoration, or can be considered as endophenotypes of AN, or result in “scarring”.

Memory remains an under researched area in AN, although difficulties in this area are well-recognised. In a qualitative study by our group that investigated the phenomenology of cognitive difficulties in AN, respondents acutely unwell with AN reported several specific memory difficulties reminiscent of problems with prospective and procedural memory (Keeler, Konyn, et al., 2022), which have not been investigated in detail in AN populations. However, poorer performance in logical memory has been associated with a greater likelihood for treatment dropout, indicating the clinical importance of recognising memory problems in individuals with AN (Terhoeven et al., 2022).

5 | SPECULATIVE EFFECTS OF REDUCED NEUROPLASTICITY ON MOOD, ANXIETY AND THE MAINTENANCE OF ANOREXIA NERVOSA

Areas of the brain that are implicated in AN such as the hippocampus (Keeler et al., 2020) are crucial for neuroplastic processes (e.g. memory, learning and cognitive flexibility), and have also been implicated in the regulation of mood and anxiety (Anacker & Hen, 2017). Indeed, anxiety and depressive disorders are present in ~50% of people with AN (Ulfvebrand et al., 2015), and are a negative prognostic factor (Franko et al., 2018), although early improvements in depression are associated with an improved prognosis (Kahn et al., 2020).

Qualitative evidence from people acutely unwell with AN and recovered from AN suggests that engaging in weight loss behaviours both mitigates depressive and

anxiety symptoms (in the initial stages) and exacerbates them (in the later stages) (Keeler, Konyn, et al., 2022). In addition, respondents reported both behavioural and cognitive rigidity, as well as problems with information processing, memory and learning, and a biased allocation of both their attention and their (limited) cognitive resources to AN-related stimuli or demands. The information processing and memory difficulties meant that tasks were more energy- and time-demanding, which together with a prioritisation of AN-related demands (e.g. performing well at work or in education, avoiding food-related social situations), meant that engagement in other personally-meaningful aspects of life was neglected. This had wider implications for their identity being centred around AN - with the nurturing of a non-AN identity identified as a key route out of AN by recovered respondents - as well as leading to social isolation, and increases in both AN and mood and anxiety-related symptomatology (Keeler, Konyn, et al., 2022). These findings highlight the phenomenological importance of neuroplasticity-related cognitive difficulties and their wider effects on the maintenance of AN, quality of life and identity.

6 | OVERVIEW OF NOVEL TREATMENTS

There are limited effective treatments for AN (Himmerich et al., 2023), particularly for individuals with SE-AN (Wonderlich et al., 2020). Weight restoration is an important first step, given the physical sequelae of low body weight on the brain and cognition. However, weight restoration can be particularly challenging for individuals with SE-AN.

A focus on improving quality of life and mood, rather than solely weight gain and improvements in ED psychopathology, may be a useful first approach (Touyz et al., 2013; Touyz & Hay, 2015). Comorbid anxiety/depression is often observed in people with AN, which may precede or succeed AN onset. However, antidepressants have limited efficacy in managing mood difficulties in people with AN, and novel approaches are necessitated.

People with AN often experience fear around food, with weight and shape concerns. Psychological therapies support them to learn new ways to manage these difficulties, although sufficient neuroplasticity is key to new learning. Novel treatments may facilitate neuroplasticity by targeting the barriers described in previous sections (Figure 1). Biological treatments aiming to normalise

BIOLOGICAL TREATMENTS

PSYCHOLOGICAL TREATMENTS

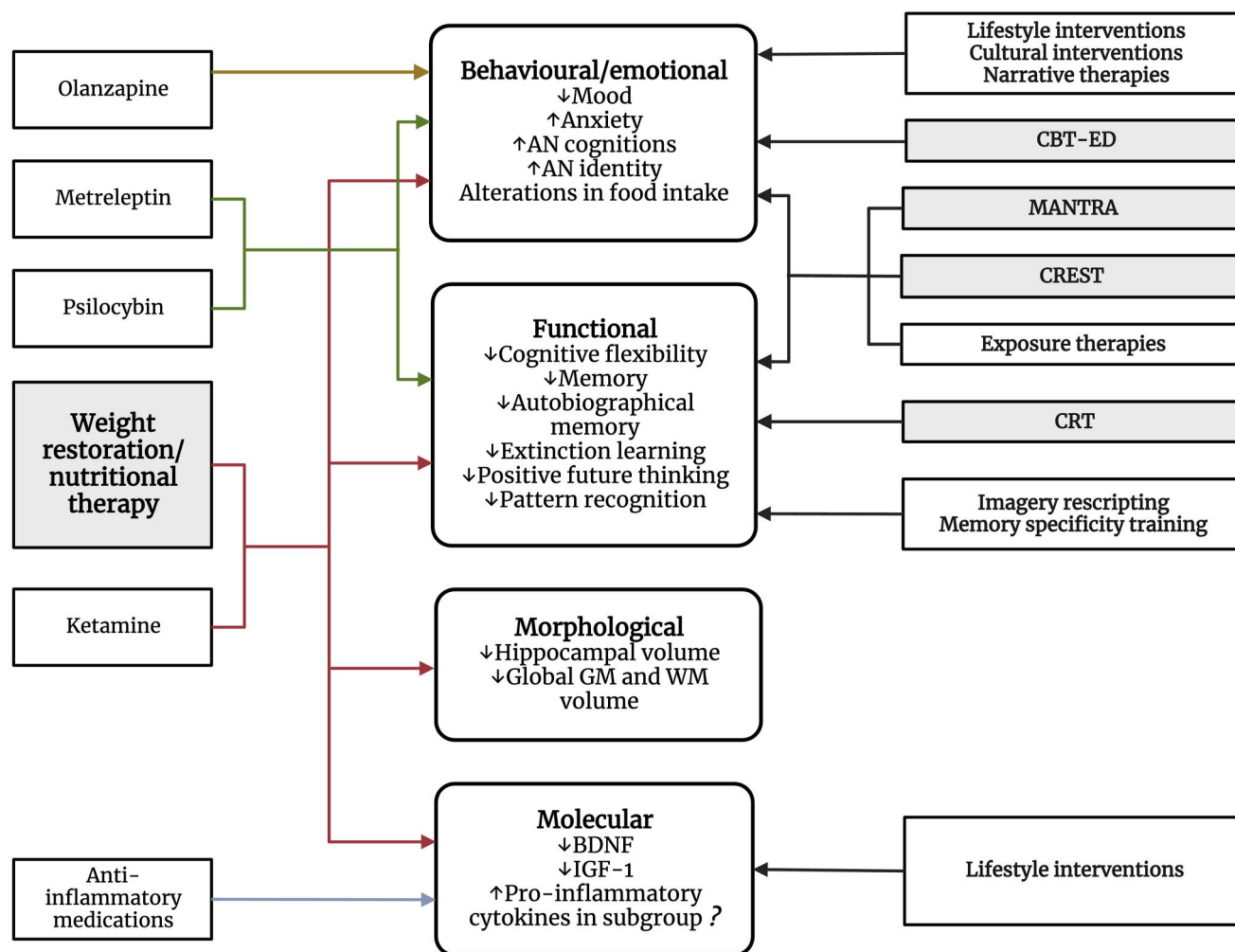


FIGURE 1 Speculative connection between plasticity-related behavioural/emotional, functional, morphological and molecular findings, and potentially suitable biological (left) and psychological (right) interventions. Bidirectional relationships exist between these respective findings. Shaded boxes indicate established treatment approaches and non-shaded boxes indicate novel approaches. BDNF, brain-derived neurotrophic factor; CBT-ED, Eating-Disorder-focused Cognitive Behavioural Therapy; CRT, Cognitive Remediation Therapy; CREST, Cognitive Remediation and Emotional Skills Training; GM, grey matter; IGF-1, insulin growth factor-1; MANTRA, The Maudsley Model of Anorexia Nervosa Treatment for Adults; WM, white matter. Created with [Biorender.com](https://biorender.com). [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/erv.3039)]

growth factors and inflammatory markers, as well as potential targets for psychological intervention, are discussed in the following sections.

7 | PSYCHOPHARMACOLOGICAL APPROACHES

There are several promising novel pharmacological treatments that may target neuroplasticity in AN. Some of these have been investigated extensively for the treatment of depressive disorders, which could be applied to the treatment of AN, including typical (e.g. psilocybin)

and atypical/dissociative (e.g. ketamine) psychedelics. The next section will focus on these novel interventions in relation to AN, as well as the use of human recombinant leptin (metreleptin), anti-inflammatory and neuroprotective medications, and the atypical anti-psychotic olanzapine.

7.1 | Ketamine

Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist and dissociative anaesthetic. Paradoxical increases in glutamate transmission have been observed in

sub-anaesthetic doses (e.g. 0.5 mg/kg intravenously), which produce rapid but transient antidepressant effects in people with major depressive disorders (Newport et al., 2015). In addition, small studies have provided preliminary evidence of its efficacy in people with AN (Calabrese et al., 2022; Dechant et al., 2020; Keeler et al., 2023; Mills et al., 1998; Schwartz et al., 2021; Scolnick et al., 2020). However, its effectiveness in low weight individuals with AN remains unclear and no randomised controlled trials (RCTs) have been conducted thus far (Keeler et al., 2023). Several narrative reviews outlining theoretical rationales for the use of ketamine in the treatment of AN have been published, mostly centred around its potential utility in ameliorating neuroplastic deficiencies (Keeler, Treasure, et al., 2021; Mitchell et al., 2023; Ragnhildstveit et al., 2022). Feasibility studies examining the acceptability, safety and tolerability of ketamine in people with AN are needed.

7.2 | Psilocybin and other typical psychedelics

Psilocybin is a molecule produced by various species of mushrooms, which when consumed leads to psychotropic effects, such as euphoria, changes in consciousness, time distortion, perceptual alterations and spiritual experiences. A meta-analysis has summarised the effectiveness of psilocybin in substantially reducing anxiety and depressive symptoms (Goldberg et al., 2020). Additionally, several narrative reviews have provided theoretical rationales for psychedelics such as psilocybin for the treatment of EDs, including AN (Foldi et al., 2020; Otterman, 2022; Rodan et al., 2021).

Psilocybin is hypothesised to alleviate neurobiological and behavioural features associated with AN, for example, by normalising serotonergic transmission, promoting neuroplasticity via increasing BDNF and glial cell line-derived neurotrophic factor, and improving cognitive flexibility (Rodan et al., 2021). A recent open-label feasibility study in 10 adults with AN found evidence for the safety, tolerability and acceptability of a single 25 mg dose of psilocybin (Peck et al., 2023). Several other trials examining the efficacy of psilocybin as a treatment for AN are underway (NCT04505189; NCT04052568; NCT05481736).

7.3 | Metreleptin

Metreleptin, or human recombinant leptin, is a promising potential biological intervention for AN. Leptin is a

hormone primarily produced by fat cells, and signals satiety. Therefore, the less body fat an individual has, the less leptin produced, and accordingly people with AN have lower levels of leptin (Hebebrand et al., 2007). In rodents, the peripheral administration of leptin prevents hyperactivity upon food restriction within animal models of AN (Exner et al., 2000; Hillebrand et al., 2005). Additionally, 14 days of metreleptin treatment in humans with AN has led to rapid improvements in ED symptomatology in some patients, and depression in all patients, with no impact on weight (Milos et al., 2020). Increased bone mineral density and IGF-1 levels have been reported in lean hypoleptinemic women after 2 years of treatment with metreleptin (Sienkiewicz et al., 2011). It remains to be seen whether metreleptin improves neuroplasticity (e.g. via increases in growth factors such as IGF-1 (Sienkiewicz et al., 2011) or BDNF (Liao et al., 2012)) without adverse effects on appetite or eating behaviour in AN.

7.4 | Anti-inflammatory and neuroprotective medications

To date, the use of anti-inflammatory medications (e.g. cyclooxygenase inhibitors, or TNF- α inhibitors) proposed in some publications (Keeler et al., 2020; Solmi et al., 2015) cannot be recommended for AN, due to the inconclusive evidence regarding a pro-inflammatory profile and the lack of proof of concept trials in AN. This is an rapidly expanding field in psychiatry, with antibiotics such as minocycline (Malys & Mondelli, 2022; Nettis et al., 2021), and dietary supplements such as polyunsaturated fatty acids, probiotics and folic acid (Hastings et al., 2017) being examined as a treatment for people with other psychiatric disorders (e.g. major depressive disorder). There is a potential safety concern of using anti-inflammatory medications in people with AN, who have a higher risk for bacterial (but not viral) infection (Birmingham & Treasure, 2019), as these medications may reduce the activity of the immune system and thus increase the risk of bacterial infection.

BDNF mimetics such as GSB-106 are promising candidates as neuroprotective medications. Both *in vitro* and *in vivo* studies have demonstrated its effectiveness in promoting neuronal survival (Gudasheva et al., 2013), neurogenesis (Gudasheva et al., 2017) and synaptogenesis (Gudasheva et al., 2018), while alleviating depressive symptoms (Seredenin et al., 2013) and easing the impact of stress on depressive symptoms (Gudasheva et al., 2021). However, studies are limited to animal populations.

7.5 | Olanzapine

Olanzapine has been shown to be effective to achieve weight gain during the treatment of AN and has recently received a limited recommendation by the World Federation of Societies of Biological Psychiatry for its use in AN (Himmerich et al., 2023). Some, but not all *in-vitro*, animal and human studies showed anti-inflammatory and neuroprotective effects of olanzapine (for a review see Chen and Nasrallah (2019)). However, clinical RCTs that measure inflammation, neuroplasticity, and the effectiveness of olanzapine in AN are not available. As clinical studies of olanzapine in patients with schizophrenia showed an increase in inflammatory cytokine concentrations in the blood (e.g., (Kluge et al., 2009)), it is from our perspective impossible to draw conclusions about the anti-inflammatory and neuroprotective effects of olanzapine in AN.

8 | PSYCHOTHERAPEUTIC STRATEGIES

Psychological therapies are the mainstay treatment for AN. The following section focuses on potential psychotherapeutic strategies to address the neuroplasticity-related cognitive, emotional and biological sequelae which may contribute to the maintenance of AN.

8.1 | Imagery rescripting and memory specificity training

Imagery rescripting involves modifying the context of aversive memories into more neutral representations, and using positive representations to challenge maladaptive schemas. It has been demonstrated to be effective in reducing the psychological impact of aversive memories (Morina et al., 2017). Imagery rescripting has been trialled in people with mostly subclinical ED symptoms, often focussing on altering body-related memories or representations, with studies producing varied results (Kadriu et al., 2023; Pennesi & Wade, 2018; Zhou & Wade, 2021). People with AN sometimes have difficulties with autobiographical memory retrieval (Bomba et al., 2014; Keeler, Peters-Gill, et al., 2022), and thus, imagery rescripting alone may not be beneficial in this patient group. Another therapeutic approach focused on memory, memory specificity training, consists of cued recall exercises, with the aim of increasing the uniqueness and specificity of a non-specific memory by enriching the contextual and sensory details (Barry et al., 2019). Studies in non-ED populations have demonstrated its

power in increasing autobiographical memory specificity and decreasing psychopathology (Barry et al., 2021; Neshat-Doost et al., 2013).

8.2 | Identity-based interventions

For the treatment of AN, the National Institute for Health and Care Excellence recommend the transdiagnostic individual eating-disorder-focused cognitive behavioural therapy (CBT-ED) and Maudsley Model of AN Treatment for Adults (MANTRA). CBT-ED and MANTRA both address unhelpful thinking styles, while MANTRA also examines identity (Schmidt & Treasure, 2014). Identity-based interventions are warranted in AN given that the development of an identity away from AN has been identified as a core route towards recovery (Keeler, Konyn, et al., 2022). One such intervention, narrative therapy, seeks to distinguish the individual from their problems and exploit their individuality to identify the person's unique skills and strengths. This may be important given that people with AN struggle with retrieving autobiographical memories, which can interrupt the formation of a personal narrative (Fivush & Haden, 2003; Kestenbaum, 2003). Alternative novel treatments that may have benefits for enriching identity include dialogue-based therapies (Chua et al., 2022), and arts- or music-based therapies (Butryn, 2014; Lejonclou & Trondalen, 2009; Shaw, 2020), as well as community-based approaches such as arts and cultural prescribing, which may have the added benefit of promoting self-efficacy and social connectedness.

8.3 | Cognitive remediation therapy

Cognitive remediation therapy (CRT) is designed to target neuropsychological disturbances, an under-addressed area in CBT. CRT focuses on developing thinking processes rather than content, and can be used to address cognitive processes such as central coherence, cognitive flexibility, decision-making and working memory. Most applications of CRT for AN are targeted towards cognitive flexibility and central coherence disturbances, with a meta-analysis finding small improvements in central coherence, a behavioural regulation index and a metacognitive index (Tchanturia et al., 2017). However, CRT could also be expanded to target wider cognitive difficulties such as working memory. For example, one study investigating the use of CRT that incorporates memory tasks, for patients with schizophrenia, found improvements in memory that persisted during a 6-month follow-up (Fiszdon et al., 2004).

Additionally, Cognitive Remediation and Emotional Skills Training is a brief psychological intervention integrating aspects of CRT with emotional regulation skills for AN, which has also shown some promise (Money et al., 2011; Tchanturia et al., 2015).

8.4 | Exposure-based interventions

A key aspect of AN psychopathology is fear around weight, food or body shape, with associated hypervigilance, risk aversion and avoidance (Murray et al., 2018). Exposure and response prevention (ERP) is a well-established therapy for obsessive compulsive disorder (Foa & Kozak, 1996), which could be applied to people with AN. In a pilot RCT in 32 weight-restored individuals with AN, 12-session courses of ERP and CRT were compared, with the study finding a greater caloric intake in the ERP group, which was associated with improvements in eating-related anxiety (Steinglass et al., 2014). Other examples of exposure therapies that have shown preliminary efficacy in AN populations include supported food exposure (Cardi et al., 2019) and mirror/body exposure in weight-restored individuals (Ziser et al., 2018). Studies incorporating new technologies are currently underway, such as food exposure in virtual kitchens delivered via virtual reality headsets, or “avatar therapy”. In “avatar therapy”, people with AN are able to customise a virtual avatar to represent their ED, with the therapy aiming to increase individual agency over, and reduce distress from, the “eating disorder voice” (Cardi et al., 2022). There is emerging evidence to suggest abnormal fear extinction processes in people with AN (Lambert et al., 2021). Augmenting exposure-based interventions with pharmacological agents that promote neuroplasticity and new learning may emerge as a useful approach for AN (Feder et al., 2020; Girenti et al., 2017)).

8.5 | Lifestyle interventions for the mitigation of stress

Lifestyle interventions that aim to reduce stress, such as yoga and meditation, have been found to promote weight gain (Wanden-Berghe et al., 2010) and reduce ED psychopathology (Carei et al., 2010) in people with EDs. A meta-analysis reported an increase in BDNF after exercise- and meditation- mindfulness-based interventions across various clinical populations (Gomutbutra et al., 2020). Similar findings have been reported in people with major depressive disorder, whereby mindfulness-based interventions have led to a reduction in cortisol, concentrations of the pro-inflammatory cytokine IL-6, depressive symptoms and an increase in BDNF (Tolahunase

et al., 2018). Further research focussing on the impact of lifestyle interventions on BDNF, pro-inflammatory cytokines and depressive symptoms in people with AN would be useful.

9 | CONCLUSIONS AND FUTURE DIRECTIONS

Treatment options for AN often have limited efficacy and the identification of novel evidence-based treatments has been somewhat obscured by our limited understanding of the neurobiological sequelae associated with AN. This review paper aimed to collate evidence for potential novel biological and psychological interventions for the treatment of AN, based on emerging evidence of altered neuroplasticity that is present transdiagnostically across psychiatric disorders but, based on volumetric data (Walton et al., 2022), may be the most severe in AN. These potential novel treatments are at varying stages of evidence, which is summarised in Table 1. It is likely that there are a multitude of other treatments that may have beneficial effects on neuroplasticity in AN, that are not covered here. For example, supplementation with probiotics, to normalise the balance of gut microbiota, may have beneficial effects on neuroplasticity via inflammation-reducing mechanisms and/or growth factor-increasing mechanisms (Jena et al., 2022).

The research investigating neuroplasticity and neuroprogression associated with AN is sparse, and how the findings and potential mechanisms discussed in Sections 2, 3 and 4 interact is unclear. Further research may enable future evidence-based precision psychiatry approaches that aim to personalise treatment to the individual's presenting symptoms. This has recently been applied to the treatment of EDs more generally as part of a feasibility study that aimed to identify core networks of symptoms using ecological momentary assessment and network analysis, to provide tailored psychotherapeutic treatment modules for clients based on their own individual core network of symptoms (Levinson et al., 2023). Network theory aims to identify a core network of symptoms, positing that when addressing the core network of symptoms, those associated with that core network should also benefit (Borsboom & Cramer, 2013). For the advancement of precision psychiatry approaches for the treatment of AN, it is necessary for future research to delineate the presence of potential subgroups and endophenotypes of the disorder, as well as advancing stage-based models of AN to identify what types of treatment may be most useful depending on the stage of illness.

TABLE 1 Current stage of evidence for psychopharmacological and psychotherapeutic interventions considered in this review.

Intervention	Stage of evidence			
	Animal studies	Allied psychiatric conditions	Case report/proof of concept in AN	RCT in AN
<i>Psychopharmacological</i>				
Anti-inflammatory medications	✓	✓		
BDNF mimetics (e.g. GSB-106)	✓			
Ketamine	✓	✓	✓	
Metreleptin	✓		✓	
Olanzapine	✓	✓	✓	✓
Psilocybin		✓	✓	
<i>Psychotherapeutic</i>				
CBT		✓	✓	✓
CRT/CREST		✓	✓	✓
Cultural interventions		✓	✓	✓ ^a
Exposure therapies		✓	✓	✓
Imagery rescripting		✓	✓	✓
MANTRA			✓	✓
Memory specificity training		✓		
Narrative therapies		✓	✓	
Yoga/mindfulness interventions		✓	✓	✓

^aPertaining to art therapy.

Abbreviations: BDNF, brain-derived neurotrophic factor; CBT, Cognitive Behavioural Therapy; CRT, Cognitive Remediation Therapy; CREST, Cognitive Remediation and Emotional Skills Training; MANTRA, The Maudsley Model of Anorexia Nervosa Treatment for Adults; RCT, randomised controlled trial.

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CONFLICT OF INTEREST STATEMENT

Hubertus Himmerich has received research funding the NIHR for a feasibility study testing olanzapine in AN and from COMPASS Pathways for a proof-of-concept study on psilocybin in AN.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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