HIGHLIGHTS

- There are changes in the periphery associated with endometriosis-associated pain.
- Central changes also occur in endometriosis-associated pain.
- The use of the characteristics of the pain experienced has lead to useful discoveries.

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Title

Pathophysiology of endometriosis-associated pain: a review of pelvic and central nervous system mechanisms.

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ABSTRACT

Although pain is one of the main symptoms women with endometriosis present with, there is poor correlation between symptom severity and disease burden and the underlying biological mechanisms by which pain arises are still only poorly understood. Here we briefly review the neurobiology of pain before considering mechanisms that may be specifically relevant in the context of endometriosis. The role of pelvic factors, such as new nerve fibre growth, peritoneal fluid and inflammation is explored with a particular focus on studies where these factors have been related to pain symptoms rather than just compared between women with endometriosis and disease free controls. We then consider the role of the central nervous system and associated systems, including the stress axis and psychological factors, in the modulation of pain. The potential for changes in these systems to be both a cause and/or a consequence of the pain and how they might explain some of the known associations between endometriosis and other somatic symptoms is discussed. The chapter concludes by considering the implications of these mechanisms on treatment strategies for these women.

Keywords:

Endometriosis, pain, nervous system, inflammation

INTRODUCTION

Pelvic pain is the commonest presenting symptom of endometriosis. Chronic pelvic pain (i.e. pain perceived to originate in the pelvis lasting for longer than 6 months [1]) and endometriosis are often comorbid but each can exist without the other. For example, it is described that up to 82% of women with chronic pelvic pain have endometriosis [2], but it is also well known that some women with endometriosis experience no pain at all [3]. Furthermore, the relationship between pain and the extent/location/type of endometriosis found at laparoscopy (as measured using rAFS [4]) is much more complex than might be expected [5, 6].

Here we will consider mechanisms in the pelvis (periphery) and the central nervous system (central) that may contribute to the generation and/or maintenance of pain in women with endometriosis. Whilst we focus on evidence from the endometriosis literature, we will also explore parallels with other conditions associated with chronic pain. Finally, we discuss what this means looking forward to the future, both in terms of treatment regimes and research in endometriosis-associated pain.

WHAT IS PAIN?

Before we specifically consider endometriosis-associated pain, it is important to understand pain more generally. Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described

in terms of such damage" [7]. Pain is a very complex, subjective experience and is thus difficult to pin down, however it can be described both in terms of the mechanism(s) by which is arises and by the location/triggers of the pain. For definitions of pain types see Table 1.

Specific receptors (nociceptors) in the periphery detect noxious stimuli and this message then travels to the brain via the spinal cord (nociception) where the conscious experience of pain is generated. As illustrated in Figure 1, throughout this pathway a variety of different factors can exert an influence leading to either amplification or reduction and thus altering the overall pain perceived. The pain experience is therefore produced from a combination of many different factors, including nociception, context, mood and past experiences and thus is not linearly related to the intensity of the peripheral noxious stimulus. This is evident in the brain areas that are active during the perception of pain; areas involved in sensory, discriminatory, affective, emotional, cognitive, motor, decision-making and brainstem modulatory circuits are recruited, but notably in a very flexible manner [8]. There are many mechanisms by which the pain perceived could be amplified or reduced. One pathway that leads to a reduction in the pain perception is endogenous pain inhibition, which arises from cortical and spinal mechanisms.

The combination of brain areas which are involved in the perception of pain have been coined the 'pain neuromatrix' [9]. First thought of as a fixed connection of brain areas which were involved in pain perception in every brain, the idea has since evolved into the 'cerebral signature' [10], a dynamic network of brain regions which

varies between individuals reflecting the complexity and individuality of the pain experience. The role of different brain regions depends on the interaction of many different factors (mood, cognition etc). Some brain areas are very commonly seen to be active in pain perception, whilst other areas appear to be active depending on the circumstances of the pain.

Although ongoing pain can reflect continuing tissue damage, pain can also continue beyond normal tissue healing time (approximately 3 months). This 'chronic' pain is not simply a continuation of an acute pain but has its own mechanisms. Although we are only beginning to understand the factors that make an individual at risk of developing chronic pain after an acute injury [11, 12], the mechanisms maintaining and the changes associated with chronic pain are remarkably consistent no matter where the pain is perceived or what the underlying pathology [13-15]. In fact this has led to the suggestion that chronic pain should be considered as a disease in its own right [14]. Given its association with chronic pain it is probably therefore not surprising that we are beginning to see many parallels between endometriosis-associated pain and other chronic pain conditions, as we will discuss below.

Term	**Definition**	**Endometriosis Setting**
Nociceptive pain	Pain that arises from damage to non-neural tissue. It is due to the activation of nociceptors	Visceral nociceptive C-fibres activated by noxious stimuli from

	(sensory receptor of the peripheral nervous system capable of transducing noxious stimuli). Nociceptive pain can be divided into visceral and somatic depending on the location.	cells in target organs have been implicated as mediators of noxious stimulus intensity.
Inflammatory pain	Pain associated with active inflammation. It falls in the category of nociceptive pain.	Endometriotic implants cause a local inflammatory reaction, which irritates nerves endings [16]. Nerve fibres also play an active role in the mechanism of inflammatory pain by secreting proinflammatory neuromediators [17]. This is called neurogenic inflammation.
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system. Neuropathic pain is a clinical description and not a diagnosis which requires a	Recent work suggests that a small proportion of women with endometriosis-associated pain have definite

	demonstrable lesion or a disease that satisfies established neurological diagnostic criteria.	neuropathic pain, however more than half may have a mixed nociceptive-neuropathic picture [18].
Centralized pain	Pain with central nervous system origins of amplification [19]. This does not imply that peripheral nociceptive input is not contributing to the pain experience.	Evidence is beginning to emerge of these phenomena in women with endometriosis-associated pain [20].
Hyperalgesia	Increased pain from a stimulus that normally provokes pain.	Regional hyperalgesia has been observed most commonly in women with current, biopsy-proven endometriosis compared to those with pain only. It was significantly higher in both groups compared with healthy controls. Increased behavioural responses to noxious stimuli at a distant site

		have been demonstrated in women with chronic pelvic pain and endometriosis likely reflecting plastic changes in the central nervous system [21].
Allodynia	Pain due to a stimulus that does not normally provoke pain.	In women with chronic pelvic pain, allodynia is detected more often than in healthy controls [21].
Dysmenorrhea	Pain during menstruation.	In 78.7% of women with endometriosis dysmenorrhea was a symptom that led to a diagnosis [22].
Dyschezia	Pain during defaecation.	In 29% of women led to diagnosis [22].
Dysuria	Pain during urination.	Led to diagnosis in 9.9% of women [22].
Dyspareunia	Pain during sexual activity. Can be ‘deep’ or ‘superficial’.	44.9% of women reported this led to diagnosis [22].

Table 1: Definitions of pain terminology and its relevance in the endometriosis setting. Definitions from the Kyoto protocol of IASP Basic Terminology [7]. Table adapted and updated from Morotti et al 2017 [23].

PERIPHERAL MECHANISMS

NERVE FIBRES & THE AUTONOMIC NERVOUS SYSTEM

As described above, nerves are responsible for conveying nociceptive signals from the periphery to the brain. Therefore, it is logical to try to determine whether, in patients with pain, there is a change to these nerves that could lead to alterations in the signals the brain is receiving about nociception. Alterations in the structure or function of peripheral nerves has been demonstrated in a variety of conditions associated with chronic pain (e.g. osteoarthritis [24], painful intervertebral discs [25] and interstitial cystitis [26]). When considering this in the context of endometriosis, it is important to realise that endometriotic lesions themselves are innervated, and this has been demonstrated for peritoneal disease [27], ovarian endometriomas [28] and deep infiltrating lesions [29]. Interestingly, however, there is a suggestion that ovarian disease is less well innervated than lesions elsewhere in the pelvis [30].

The autonomic nervous system is made up of the sympathetic and parasympathetic systems, which have different roles generally, and of relevance here, are part of different stages of inflammation. The sympathetic nervous system is involved in the initial phases of inflammation and it gives rise to a proinflammatory environment which can sensitise nerve endings, through adrenoreceptors [31]. In the later stages of inflammation there is an alteration in the balance of proinflammatory and anti-inflammatory nerve fibres. The sympathetic nervous system has been shown to be involved in both the development and severity of chronic inflammatory diseases [32]. Changes in the number of sympathetic neurons have been investigated using a rat arthritis model [33]. Arthritis is a well-studied chronic pain condition and there are similarities between it and endometriosis in this setting. In response to injury the sympathetic nerves of distal regions die back, and more sympathetic nerves sprout in the area of the spleen innervated by nerves from the injury site. This shows that sympathetic innervation can change as a response to injury/inflammation. We will now discuss what changes in the nerve fibres and the autonomic nervous system have been seen in endometriosis specifically in both peritoneal and ovarian endometriosis, and how this can help our understanding of endometriosis.

First, we will discuss studies focussing on peritoneal endometriosis. Endometriosis patients with and without pain have been investigated, along with non-endometriosis controls, for nerve fibre density [34]. There was no difference between the group of endometriosis patients and the endometriosis free group, in terms of the number of nerve fibres in the peritoneum. Also, there was no difference in the nerve fibres between the endometriosis with and without pain groups. This suggests that endometriosis-associated pain is not simply due to an increase in the number of nerve

fibres sending nociceptive signals to the brain. However, another study found contradicting results. When investigating peritoneal endometriotic lesions compared to healthy peritoneum and samples from endosalpingiosis lesions [27] they found significantly more nerve fibres in the peritoneal endometriotic lesions than the 2 control groups. Aδ sensory, C sensory, cholinergic and adrenergic nerves all innervated the endometriotic lesions. The different findings of these two studies could be due to the fact that the latter specifically used endometriotic lesions in the peritoneum, rather than just a peritoneum sample. It is not difficult to believe that changes in nerve fibre density are present at endometriotic lesions but are not the same throughout the peritoneum. Additionally, it is plausible that a subgroup of women with CPP but without macroscopic endometriosis also have altered innervation of their peritoneum. Whether such women will then go on to develop endometriosis that is visible at laparoscopy or if this is a distinct pathology remains unknown. The mechanism by which changes in the innervation of peritoneal lesions occur is starting to be investigated. Mechsner and colleagues have shown that there is an increase in semaphorins and their receptors in peritoneal endometriotic tissue [35]. It has been suggested that semaphorins repel nerves in chronic inflammatory diseases, which could explain the reduced innervation by sympathetic nervous system [35].

Further studies have investigated the types of nerve innervating lesions, and whether this is seen only in endometriosis. Arnold and colleagues compared the relative sympathetic and sensory innervation of peritoneum in different samples [36]. Overall nerve fibre density in unaffected peritoneum of endometriosis patients was significantly reduced, when compared to both endometriotic lesions and to healthy peritoneum. When looking specifically at the sympathetic nerve fibres, healthy

peritoneum had the highest density, then unaffected peritoneum of patients, followed by endometriotic lesions. Pro-inflammatory sensory fibres were significantly higher in areas close to the endometriotic lesion, compared to healthy controls. These results show that there are changes both to the peritoneum which contains the endometriotic lesion, and to the unaffected peritoneum in patients. The mechanisms by which this occurs and how this leads to pain in patients, needs to be further studied.

Studies investigating nerve fibres in ovarian endometriosis have shown that the lining of ovarian endometriomas has many more nerve fibres than both normal ovarian tissue from these patients as well as ovarian tissue from women without endometriosis [28]. These nerve fibres were shown to be a mixture of sensory, sympathetic and parasympathetic. This study did not assess dysmenorrhea however participants were undergoing oophorectomies due to severe dysmenorrhea and other pain symptoms. In contrast to this, McKinnon et al found that lesions in the ovary were not significantly associated with nerve fibres, and that the ovarian endometriosis group had the lowest pain (compared to peritoneal and rectovaginal septum endometriosis) [30]. Further studies should investigate these results compared to patients with endometriosis that have no pain symptoms to determine whether these changes are linked to endometriosis itself or endometriosis-associated pain.

Whilst studies describing alterations in nerve fibres in association with endometriosis are interesting, it is only when they also relate to the pain a patient experiences that they can really help us understand the underlying pain mechanisms and potentially lead to personalised treatments. To date, only a few studies have explored these

relationships but with intriguing results. Mechsner and colleagues demonstrate a relationship between increased nerve growth and pain symptoms [37]. Specifically, they showed that women with higher pain scores for dysmenorrhea and pelvic pain had significantly higher concentrations of neuronal markers (neurofilament (NF) and protein gene product (PGP) 9.5). Similarly, McKinnon and coworkers demonstrate that dysmenorrhoea scores are significantly higher when the lesions are innervated [30], whilst Kajitani and colleagues found nerve growth factor (NGF) in the peritoneal fluid to be more frequently elevated in women with severe endometriosis-associated pain than in those with milder pain [38]. In addition to altered nerve density, differences in peripheral receptors may also be important in generating pain. The transient receptor potential vanilloid 1 (TRPV1) receptor is particularly interesting in this context as it responds to noxious heat and certain chemicals, and has been shown to be of importance in many pain mechanisms including hyperalgesia [39, 40]. Not only is the density of nerve fibres containing TRPV1 higher in ectopic endometrial implants compared to control endometrium from women without endometriosis, but this density also correlated positively with the severity of dysmenorrhea in women with endometriosis [41].

Interestingly, the extent of innervation of the lesions appears to vary with the location of the endometriosis and this relates to the pain experienced [30]. Thus, it has been shown that women with deep endometriosis (rectovaginal septum) experience more pain and more often have nerve fibres close to the lesions, although there was not a direct relationship between the two. Also found was a direct relationship between higher endometriosis-associated nerve fibres in peritoneal lesions and significantly

higher menstrual pain. Endometriosis lesions on the ovary were the least likely to be associated with a nerve fibre and these women reported the lowest pain.

PELVIC ENVIRONMENT

Many studies have explored the difference between the peritoneal fluid of women with and without endometriosis. Although a wide variety of differences have been identified [42-44], as with nerve fibres discussed above, only a very few have actually related these differences to the patient's pain experience. Firstly, we will describe two studies relating pain to growth factors in the peritoneal fluid (PF) whilst inflammatory mediators are discussed later in this section.

Of particular interest given the emerging relationships between nerve fibre density and pain symptoms is a study exploring the influence of PF on nerve fibre growth [45]. Chicken dorsal root ganglia (DRG) cultured in the PF of endometriosis patients showed increased neurite growth compared to controls with other gynaecological conditions. Furthermore, this growth was inhibited by nerve growth factor (NGF) inhibitors, proving that the pathway of nerve growth was NGF dependent. A further study by this group [46] explored the relationship between PF-induced nerve growth and pain symptoms. Interestingly, they found no difference in neurite outgrowth between the women with endometriosis-associated pain and those with endometriosis but no pain. Similarly, there was no difference between those with mild pain and

those with severe pain, suggesting that the altered nerve growth is a correlate of endometriosis, not of endometriosis-associated pain specifically.

Transforming growth factor β1 (TGF-β1) has been shown to be elevated in the PF of women with endometriosis [47] and subsequently also expressed more in the peritoneum of these women [48]. This increased peritoneal expression correlated with the severity of dysmenorrhea assessed using a visual analogue scale [48].

PF protein concentrations have also been compared to generalised hyperexcitability [49]. Generalised hyperexcitability is considered as an alteration in the processing of the nociceptive signal in the central nervous system leading to the amplification of pain, and is therefore thought to be very important in the induction and maintenance of chronic pain [15]. Higher TNF-α correlated with a higher magnitude of central hyperexcitability (lower pain threshold); higher osteoprotegerin (OPG) concentration was correlated with a greater magnitude of central pain sensitivity; glycodelin positively correlated with reflex receptive field area; as well as other interesting results relating to other cytokines. Glycodelin and TNF-α have also been shown to be correlated with the level of menstrual pain endometriosis patients experienced, along with RANTES [50]. These studies highlight that peripheral changes measured in the peritoneal fluid can be associated with central changes that have an effect on the pain a patient experiences.

The nerves that carry the nociceptive signal to the brain (C fibres), could during inflammation, both transduce signals to the central nervous system and release

peptides into the local environment. Once these C fibres are activated, they may display on-going electrical activity, even when the inflammation is resolved. The central nervous system can also become sensitised, which is further discussed below. Several of the molecules which play a part in the start of endometriosis and its maintenance are also involved in the sensitisation and activation of peripheral nerves. One example of this is NGF (discussed previously, has been found to be elevated in endometriosis [38]), which is secreted from inflammatory and endometriotic cells, and triggers the release of other factors. These other factors as well as NGF itself are able to activate the nerve endings in the endometrium, as well as sensitise them, meaning that they will be activated by a lower threshold of stimulus.

CENTRAL CHANGES

BRAIN FUNCTION

There is a very large body of work that shows that there are changes in brain function associated with chronic pain. The most commonly used techniques to investigate brain function in pain are functional MRI (fMRI) and PET imaging. These both give an indirect measurement of activity as they measure metabolic activity (which increases in active areas), as opposed to electrical activity. One problem with neuroimaging studies investigating the response to a noxious stimulus is determining what features are due to central as opposed to peripheral changes. One way to overcome this is to use a distal control site instead of, or as well as, the affected area, enabling the separation of peripheral changes (which will only be seen in the affected area) and central changes (which will be seen in both areas). Although a major focus

of pain research in general over recent decades, there are very few studies that investigate brain function in women with pelvic pain specifically. We envisage this changing in the very near future, however, due to the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) project (http://www.mappnetwork.org/) which is using a variety of approaches, including neuroimaging techniques, to improve understanding of urological pelvic pain.

Dysmenorrhoea is a cardinal symptom of endometriosis but can also occur in isolation. We have shown that women with dysmenorrhea alone (no pain in the pelvis or elsewhere throughout the month, but presence of endometriosis unknown) are significantly more sensitive to a noxious thermal stimulus than dysmenorrhoea-free controls (i.e. they require a significantly lower temperature to produce the same pain intensity) throughout the menstrual cycle [51]. Furthermore, this difference was found in response to stimulation of both their arm (control site) and lower abdomen (referral site). fMRI analysis showed that despite having less peripheral input (a lower temperature), women with dysmenorrhea have increased activation in response to this input. These findings suggest that long-lasting changes have occurred in the central nervous system (central sensitisation). Abnormal cerebral metabolism in women with dysmenorrhoea has also been demonstrated with PET scans [52]. Such findings are concerning given the prevalence of dysmenorrhoea, particularly in young women/adolescents with the majority of adolescents reporting dysmenorrhea [53], with some statistics suggesting 85% suffer [54]. However, an early age of onset may be of particular importance in dysmenorrhoea (whether primary or secondary) as the central nervous system is very plastic in adolescence and thus changes may occur more readily.

Communication between brain regions (connectivity) as well as activity within these regions can also be explored. This allows insights both into the strength of networks involved in pain perception but also how brain connectivity at rest may be altered in patients with chronic pain. Women with endometriosis-associated pain have been shown to have greater resting connectivity of the anterior insula (one of the key pain processing regions) to other brain regions than both healthy controls and women with endometriosis but without pain symptoms [20]. In these women levels of excitatory neurotransmitters in the anterior insula were also measured and found to be higher in the endometriosis-associated pain than in either the healthy controls or endometriosis/no pain group. Moreover, the level of excitatory neurotransmitters measured related to the connectivity between the anterior insula and the medial prefrontal cortex, a key pain modulatory region. Potentially suggesting a mechanism by which hyperalgesia may develop in these women. This was a particularly well-designed study, including a group with endometriosis but no pain, as it allows us to see that these central changes are not due to endometriosis itself, but rather the pain that arises from it. The same group have done many studies in fibromyalgia patients with similar (though subtly different) findings [55], further highlighting the similarities between endometriosis-associated pain and other chronic pain conditions.

Endogenous pain inhibition is a phenomenon which is mediated through a variety of spinal and cortical mechanisms. There are many factors that affect the extent to which these mechanisms are engaged, including genetics, psychological state and cognitive factors. An inability to engage these endogenous mechanisms may predispose an

individual to the development of chronic pain after an acute painful insult [56]. Endogenous pain modulatory mechanisms can be investigated using heterotopic stimulation (two noxious stimuli in different areas given after one another). For example, in a study with female patients with IBS compared to healthy women, it was found that heterotopic stimulation did not have the same effect on the two groups [57]. In controls heterotopic stimulation decreased the pain reported for the second stimulus. This is to be expected as the first noxious stimuli activated the descending pain inhibitory pathway, meaning that the second noxious stimulus is perceived as less painful. In the IBS patients however, the rectal pain intensity was increased if there had been a previous stimulus, suggesting abnormal endogenous pain modulation in this population. Further research in this area is needed, especially in an endometriosis setting, so as to determine if there are such changes in endogenous pain inhibition in patients with endometriosis-associated pain and if such are these changes a result of chronic pain or whether they predispose women to experience chronic pain.

BRAIN STRUCTURE

Alterations in brain structure are well established in chronic neurological conditions such as Alzheimer's disease, Parkinson's disease and Multiple Sclerosis. In these conditions the structural changes likely reflect the underlying pathology. Brain structure in chronic pain has also been widely studied, with alterations in the volume of specific brain regions found [58]. However, the mechanism(s) underlying these findings are not well understood. It is thought that areas whose volume increases reflect an increase in activity of these regions, whilst a reduction in volume may reflect one or more of the following: repeated episodes of pain having a neurotoxic

effect leading to neuronal atrophy; changes in the metabolic activity or neurotransmitter concentration in neurons; neurodegeneration due to pain related inactivity; an effect of co-morbidities or psychological factors; or a neurotoxic effect of the drugs given to relieve pain [13]. It is important to note that once brain cells have died (seen as a volumetric decrease), they are not replaced. Thus, where volumetric decreases reflect cell death they will be irreversible.

As-Sanie and colleagues have investigated brain volume in women with chronic pelvic pain [59]. They employ an elegant design, assessing women with all four combinations of endometriosis/no endometriosis and CPP/no CPP. Compared to healthy controls, women with both endometriosis-associated pelvic pain and pelvic pain without endometriosis had decreased grey matter volume in brain regions involved in pain perception. Again suggesting that it is the presence of pain, not endometriosis *per se* that is related to these structural changes. Perhaps more intriguingly, however, not only were these reductions not seen in the women with endometriosis without pain, in fact this group of women had an increased volume of the periaqueductal grey (PAG), which was positively correlated with the pressure threshold required to induce pain. The PAG is one of the key regions of the descending pain inhibitory system (an endogenous mechanism of analgesia) and thus this finding may explain why some women with endometriosis don't experience pain. Clearly further work needs to be done to determine whether women with endometriosis with and without pain have the same peripheral pain drivers but differ in their ability to engage descending pain inhibitory pathways.

HPA AXIS

Chronic pain can be considered as a repeated stressor and thus it is perhaps not surprising that dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis, a central component of the stress response [60], is seen in a wide variety of chronic pain conditions [61, 62] in line with other chronic somatic conditions. The mechanisms by which the HPA axis is supressed in these conditions are not, however, well understood. Certainly acute stress leads to an activation of the HPA axis and a rise in cortisol levels; however, over time this response will be attenuated; colloquially known as burn out. In fact this may be beneficial for an individual as continued activation of the body's "emergency response" systems could lead to further tissue damage both locally and systemically [63]. However, in the context of pain low levels of cortisol may exacerbate painful symptoms by reducing the endogenous analgesia associated with stress (stress-induced analgesia) that is thought to facilitate the 'fight-flight response' [64].

We previously demonstrated reduced levels of serum cortisol in women with dysmenorrhoea compared to healthy pain-free controls [51]. Interestingly, cortisol levels were negatively correlated with the duration of dysmenorrhea supporting a burnout theory. However, although endometriosis-associated pain has also been associated with low cortisol levels [65, 66], the relationship appears more complex than in dysmenorrhoea alone. In one study considering the multiple symptoms that women with endometriosis may present with, incapacitating pain appeared to be the strongest predictor of cortisol suppression and both frequency of dyspareunia and perceived infertility also influenced salivary cortisol [66].

PAIN PSYCHOLOGY

Historically, chronic pain was frequently assumed to arise from psychological morbidity, thankfully both clinical opinion and scientific evidence have moved forward in this respect! There is a large library of literature highlighting the comorbidity of pain with mood disorders, such as depression, though it is often hard to disentangle the order in which these symptoms arose. Moreover, we now know that mood can alter the pain experience by biological mechanisms, in both healthy individuals and those with chronic pain [67-69].

A variety of studies have either exploited normal variation or used robust experimental paradigms to manipulate psychological or cognitive state in healthy volunteers and explore the impact on the processing of acute pain stimuli. Reviewing these studies, it can be seen that depressed mood [70], anxiety [71], catastrophising [72] and both expectation of [73, 74] and attention to pain [75] are all associated with higher ratings of pain intensity. The central mechanisms underlying these relationships vary however. For example, depressed mood induction disrupts the normal emotion regulatory circuitry [70], anxiety amplifies pain via a hippocampal network [71], whilst high catastrophizers appear less able to engage descending inhibitory pathways [71].

Investigations into depression and chronic pain have found associations in certain brain areas. In rheumatoid arthritis studies it has been suggested that the medial

prefrontal cortex is an important player in the relationship between depressive symptoms and clinical pain severity [76]. In fibromyalgia it has been shown that the symptoms of depression are associated with the size of neuronal activation in areas of the brain involved in affective pain processing [77]; interestingly the extent of depression had no effect on the sensory-discriminative aspects of pain processing (such as the location of the painful stimulus), highlighting that different pain-processing pathways may be influenced by the presence of depression. Evidence for separate processing systems being influenced by depressive scores has also be seen in relation to the correlation between depression and anxiety scores and subject rating of general health, but not with sensitivity to pain, contradicting previous results [78].

Pain catastrophizing scores in chronic pain patients, have been shown to be correlated with activity in many brain areas, including those involved in the anticipation of pain, attention to pain and emotional aspects of pain [79]. Pain catastrophizing may also have a role in the induction of chronic pain and in recovery. For example, it has been shown that in a population with low back pain, high pain catastrophizing predicts pain at follow up as well as chronic low back pain [80], whilst in spinal cord injury pain catastrophizing was consistently strongly associated with outcome measures [81]. It has been shown that pain catastrophizing seems to mediate the outcome of treatment, in active physical treatment, cognitive-behaviour therapy and treatment combining the two [82].

It is highly likely that such interactions between mood and pain experience are of relevance in the context of endometriosis. As with other chronic pain conditions the

daily experience of pain frequently impacts on mood and the additional fertility concerns associated with endometriosis may further exacerbate the situation. Some studies suggest rates of depression and anxiety to be approaching 90% in this population [83, 84]. Although the proportion of these women meeting clinically relevant diagnostic criteria is much lower than this, as described above, subclinical mood alterations can also augment pain perception. To date, however, the role of psychological factors in amplifying the pain experience in women with endometriosis has received only limited interest. Anticipation and expectation of pain may be of particular interest in this context due to the predictability of the functional pain symptoms associated with endometriosis (dysmenorrhoea, dyspareunia, dyschezia), which may differ from other chronic pain conditions where the pain is either less predictable or more constant in nature and severity. Interestingly, women with endometriosis have been shown to have significantly higher pain catastrophizing scores compared to healthy controls [85] and high levels of pain catastrophizing are associated with lower quality of life scores [86] and predict a worse response to treatment [87] for women with endometriosis.

AUTONOMIC NERVOUS SYSTEM

Although the autonomic nervous system has been discussed with relevance to the peripheral nervous system above, it is also of relevance due to its central effects and is thus further discussed here. The parasympathetic nervous system is thought to be antinociceptive whereas the sympathetic nervous system is pronociceptive. The balance between the two has been shown to be altered in both fibromyalgia and functional gastrointestinal disorders [88]. For example, in women with IBS altered

autonomic nervous system function includes increased sympathetic and/or decreased parasympathetic activity during sleep [89] and over 24 hours [90]. Recent work by Aziz and colleagues has highlighted the importance of the autonomic nervous system in pain perception [91]. In a healthy cohort, they were able to identify two clusters that differed in both baseline measures and their response to painful stimuli. Cluster 1 had high sympathetic and low parasympathetic tone at baseline (in addition to high neuroticism, anxiety and cortisol and the SS/LS genotype of the 5-HTTLPR receptor) and demonstrated sympathetic withdrawal and parasympathetic activation in response to pain (associated with less ability to tolerate or habituate to pain and an elevated cortisol response). Whilst cluster 2 had a low baseline sympathetic tone with a high parasympathetic tone (plus high extroversion, low anxiety, low cortisol and the LL genotype of the 5-HTTLPR receptor) and showed sympathetic activation and parasympathetic withdrawal in response to pain (and were able to tolerate more pain and habituate more). These clusters were also shown to be stable across time. This group have subsequently shown that these clusters also exist in a cohort of patients with functional chest pain [92] and that the morphology of the brain varies with autonomic nervous system function [93] furthering our understanding of this emerging area of interest. As with mood-pain interactions discussed above, the autonomic nervous system has not really been explored in the context of endometriosis-associated pain. However, one small study (based on self-report questionnaire responses), does suggest there to be significantly higher incidences of autonomic symptoms in patients with chronic pelvic pain than in the healthy controls [94].

IMPLICATIONS OF OBSERVED CENTRAL CHANGES

We have described a number of mechanisms by which the central nervous system may amplify or even generate pain in association with a peripheral pathology such as endometriosis. Additionally, the changes seen in association with endometriosis-associated pain may be responsible for other features commonly described in the endometriosis literature. For example, it is well known that endometriosis is comorbid with other chronic pain conditions [95-97]. Whilst, this may be due to genetic or environmental factors that increase the risk of both conditions, additionally, the central changes that occur secondary to repeated episodes of pain may subsequently predispose to the development of other chronic pain conditions. For example dysfunction in descending pain modulation or HPA axis activity could both lead to acute or chronic pain from what might previously have been an innocuous insult. Furthermore, endometriosis is associated with a variety of other comorbidities including autoimmune and endocrine disorders [95] and these relationships may in part be explained by altered function of the HPA axis, autonomic nervous system and other as yet undescribed changes. It is hoped that future multi-disciplinary studies focussing on comorbid issues of importance to patients will help to unravel these relationships.

LOOKING FORWARD

The literature reviewed here illustrates that pain associated with all forms of endometriosis (peritoneal, deep and ovarian) can be both generated and modulated at a number of different sites throughout the body. Whilst there are clearly many areas

that need further detailed investigation, both these key findings and a conceptualisation of endometriosis-associated pain as a chronic pain condition rather than purely a peripheral pathology help to explain many of the symptoms and comorbidities that have long been described by patients but dismissed by clinicians as unrelated. We hope that in the future treatments that are commonplace for other chronic pain conditions will be explored in the context of endometriosis-associated pain, including neuropathic adjuncts e.g. amitriptyline, gabapentin, duloxetine and psychological and behavioural therapies. Ideally, women will be able to access treatments from a multi-disciplinary team (including a pain psychologist, gynaecologist and pelvic pain physiotherapist) able to deliver both "traditional" hormonal and surgical therapies in addition to chronic pain management. Such clinics already exist in a handful of centres and describe both clinical success and high levels of patient satisfaction (e.g. [98]).

Novel treatments both targeting the peripheral environment and the central pain mechanisms are on the horizon. For example, therapies targeting the key peripheral pain generators as opposed to inflammation in general; or novel ways of engaging pain inhibitory mechanisms such as non-invasive transcutaneous vagal nerve stimulation. However, to demonstrate their benefit and facilitate translation into clinical practice it is crucial that appropriate strategies are used to both identify an experimental cohort and to choose the correct outcome measures. In this age of personalised medicine we need to move beyond looking for a "one size fits all" treatment and instead aim to identify and then treat an individuals specific combination of pain generating, maintaining and modulating factors.

SUMMARY

In this chapter we have reviewed evidence for mechanisms by which endometriosis-associated pain may arise. The key mechanisms discussed are summarised in Figure 2, which pulls together different factors that influence the perception of endometriosis-associated pain.

We have presented evidence showing changes in the periphery during endometriosis, which includes changes in the nerve growth in the pelvis such as increased sensory nerve fibre growth and decreased sympathetic nerve fibre growth. There is also evidence that there are changes in the pelvic environment including changes in the concentrations of proteins in the peritoneal fluid, including TNF-α and OPG. Examples have been provided of where such studies have related these peripheral changes to the pain experienced by the patients, as these are the most important studies when investigating endometriosis-associated pain.

We have also discussed central changes including changes in the activity of brain areas in patients with endometriosis and how this activity is related to the pain phenotype. Studies investigating changes in the structure of the brain and psychological factors that are involved in the pain perception in endometriosis-associated pain have also been explored.

Finally, it is important to note that assessing pain itself rather than the presence of endometriosis has led to significant advances, as has been discussed in this chapter. In future, both in the clinic and in studies, endometriosis-associated pain should be assessed for all its characteristics, not simply the intensity of the pain. We believe that reconceptualising endometriosis-associated pain as a chronic pain condition albeit with ongoing pelvic pathological processes has the potential to identify novel (likely multidisciplinary) therapeutic strategies to reduce the suffering experienced by the millions of women worldwide with endometriosis-associated pain.

PRACTICE POINTS

- There are changes in the periphery associated with endometriosis-associated pain, including reduced innervation of the sympathetic nervous system, increased sensory innervation and changes in the inflammatory markers in the peritoneal fluid.
- Central changes in endometriosis-associated pain include changes in the activity and connectivity of different brain areas, altered brain area volumes in endometriosis-associated pain compared to pain free endometriosis patients, dysfunction of the HPA axis and altered psychology.
- In future patients should be stratified, both for clinical and scientific purposes, depending on the characteristics of their pain, not simply the presence and intensity of pain.

RESEARCH AGENDA

- The clinical effectiveness, cost effectiveness and tolerability of pharmacological monotherapies, physiotherapy and psychological therapy for treating women with endometriosis-associated pain
- Changes in the structure and function of the brain and how this relates to confounds of the pain perception, such as pain catastrophizing
- How nerve fibre changes in the periphery lead to changes in the overall pain perception of the individual
- Personalised treatment achieved by the stratification of patients based on their pain experience

CONFLICTS OF INTEREST

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FIGURE CAPTIONS

Figure 1: Pain perception can be influenced by a variety of factors. The nociceptive input from the periphery travels to the spinal cord via Aδ or C fibres, this can be amplified by peripheral sensitisation (discussed below). There is both ascending (to brain) and descending (from brain) nociceptive modulation of the pain experience, shown by arrows. This nociceptive modulation can also be altered by peripheral and central sensitisation, often arising from injury. There are many factors that also centrally affect the pain experience: chemical and structure, cognitive set, context and mood. These can be further broken down and can have a variety of effects on the pain experience. Taken from Tracey & Mantyh 2007 [10].

Figure 2: This summary diagram shows some of the many influencers of pain that have been discussed in this chapter. The red box shows processes that occur in the periphery. NGF (nerve growth factor) and other inflammatory mediators are increased in the PF (peritoneal fluid). These have an action on the nerves in the periphery, for example sensitisation. There is also evidence for increase nerve growth in the periphery. The black boxes in the diagram represent an unknown mechanism(s). For example, we do not yet understand how increased growth of neurites in the periphery has an impact on the pain perception, but there is evidence that it does. Similarly, there is an unknown mechanism by which PF influences the pain perception. The surgical knife in the periphery represents the go to method of treatment of endometriosis-associated pain, and also shows how damage to the nerves can occur as a result, which may lead to increased pain. The yellow arrow represents ascending modulation of pain and the blue arrow represents the descending

modulation of pain, which have been shown to be disrupted in chronic pain patients. The external factors are represented, such as mood, as well as other biological factors, i.e. genetics, that are known to influence the pain experience. Both mood and stress impact on the HPA axis, which presents in changes in cortisol levels, which may also affect pain perception.

MCQs

Question 1:

Which of these statements about pain are true?

a) Many different pathologies are associated with chronic pain but the symptoms, brain alterations and treatment are completely different between these groups of patients.
b) With reference to experimental pain: pain experienced is linearly related to the noxious stimulus.
c) Many different factors influence an individual's pain on a daily basis, including mood and context.
d) Neuropathic pain is caused by a lesion or disease of the somatosensory system and can be diagnosed definitively by clinicians.

Answer 1:

A – incorrect; B – incorrect; C – correct; D – incorrect

Different pain conditions have many similarities, sometimes in the peripheral mechanisms and often in the central changes and brain areas which are involved in the processing of pain, it has even been suggested that chronic pain should be a

disease in its own right. The pain experience is not linearly related to the stimulus as it is influenced by many other factors including the situation which the individual is in. Neuropathic pain is a clinical description, not a diagnosis. More information can be found in the section "What is pain?".

Question 2:

Which of the following have been found to be elevated in the pelvis and related to the pain experience of patients?

a) TNF-α
b) Adrenaline
c) NGF
d) OPG

Answer 2:

A – correct; B – incorrect; C – correct; D – correct

Adrenaline has not been found to be elevated in the pelvis. TNF-α has been found to be elevated in the PF of patients with endometriosis and has been shown to be correlated with the level of menstrual pain experienced, as well as the magnitude of central hyperexcitability. NGF has been shown to be more frequently elevated in

patients with severe endometriosis-associated pain. OPG concentration in the PF has been shown to be correlated with the magnitude of central pain sensitivity. More information can be found in the "Peripheral changes" section.

Question 3:

Which of these statements about the study of central changes in endometriosis-associated pain is correct?

a) The neural matrix of pain is a set of pain areas that are active in individuals with chronic pain and the areas involved do not vary between different disorders/individuals.
b) Women who present with pain symptoms are normally hysterical and one cannot trust their description of pain.
c) Mechanisms underlying dysfunction of the HPA axis in women with endometriosis-associated pain have been investigated and are fully understood.
d) Women with endometriosis with and without pain have differences in their brain structures.

Answer 3:

A – incorrect; B – incorrect; C – incorrect; D – correct

Given that the brain areas vary so much between, and even within, individuals, it is now conceptualised as a dynamic cerebral signature rather than a fixed matrix. The experience of pain is subjective, it is therefore what the patient says it is. Psychological factors may have a role in an individual's pain experience but their presence does not take away from the need to treat their pain. More information can be found in the "Central changes" section.

Question 4:

Which of the following should be involved in a patient centred multidisciplinary team for a patient with endometriosis-associated pain?

a) Psychologist
b) Gynaecologist
c) Physiotherapist
d) Psychiatrist

Answer 4:

A – correct; B – correct; C – correct; D – incorrect

A psychologist, gynaecologist and physiotherapist should all be members of a patient centred multidisciplinary team for a chronic pain condition. In the case of frank psychopathology, such as schizophrenia or borderline personality disorder, psychiatric input may be useful. Similarly, informed medical advice (often from a psychiatrist) may be required when a patient already uses multiple centrally acting medications and commencing a neuropathic adjunct, such as gabapentin, is considered appropriate. More information can be found in the “Future Treatment Directions” section.

Figure

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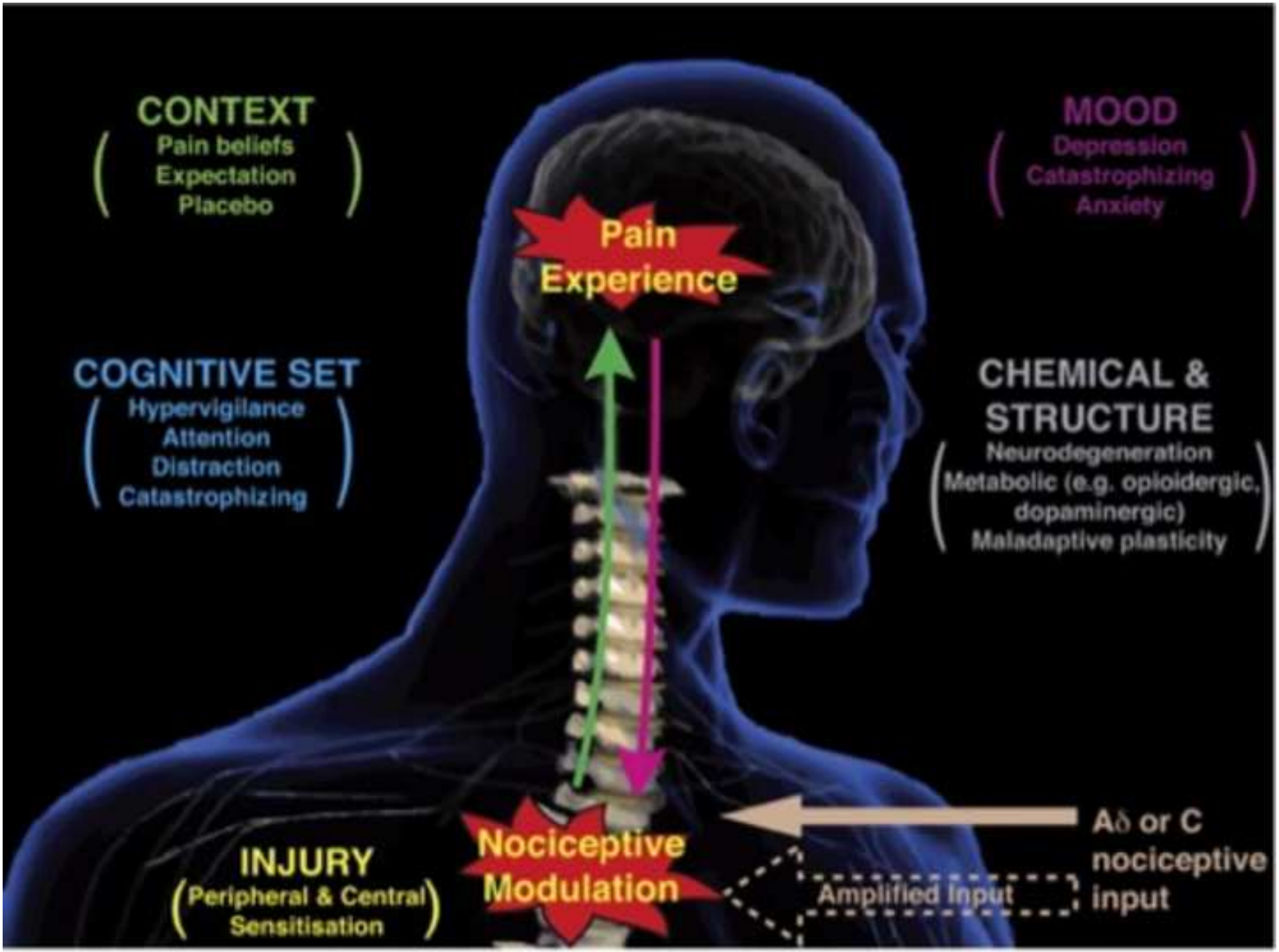

Figure

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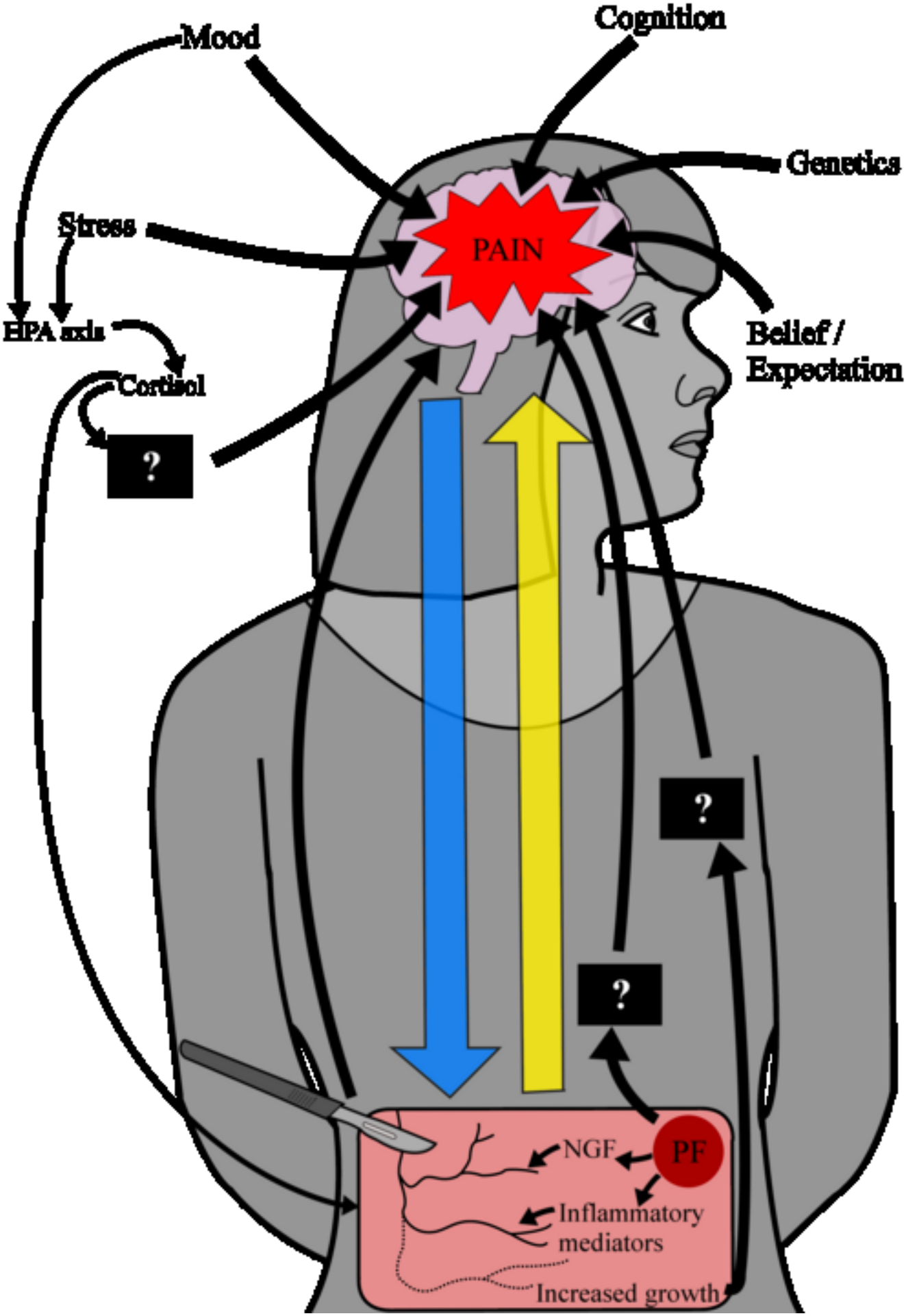

PRACTICE POINTS

- There are changes in the periphery associated with endometriosis-associated pain, including reduced innervation of the sympathetic nervous system, increased sensory innervation and changes in the inflammatory markers in the peritoneal fluid.
- Central changes in endometriosis-associated pain include changes in the activity and connectivity of different brain areas, altered brain area volumes in endometriosis-associated pain compared to pain free endometriosis patients, dysfunction of the HPA axis and altered psychology.
- In future patients should be stratified, both for clinical and scientific purposes, depending on the characteristics of their pain, not simply the presence and intensity of pain.

RESEARCH AGENDA

- The clinical effectiveness, cost effectiveness and tolerability of pharmacological monotherapies, physiotherapy and psychological therapy for treating women with endometriosis-associated pain
- Changes in the structure and function of the brain and how this relates to confounds of the pain perception, such as pain catastrophizing
- How nerve fibre changes in the periphery lead to changes in the overall pain perception of the individual
- Personalised treatment achieved by the stratification of patients based on their pain experience

MCQs

Question 1:

Which of these statements about pain are true?

a) Many different pathologies are associated with chronic pain but the symptoms, brain alterations and treatment are completely different between these groups of patients.
b) With reference to experimental pain: pain experienced is linearly related to the noxious stimulus.
c) Many different factors influence an individual's pain on a daily basis, including mood and context.
d) Neuropathic pain is caused by a lesion or disease of the somatosensory system and can be diagnosed definitively by clinicians.

Answer 1:

A – incorrect; B – incorrect; C – correct; D – incorrect

Different pain conditions have many similarities, sometimes in the peripheral mechanisms and often in the central changes and brain areas which are involved in the processing of pain, it has even been suggested that chronic pain should be a

disease in its own right. The pain experience is not linearly related to the stimulus as it is influenced by many other factors including the situation which the individual is in. Neuropathic pain is a clinical description, not a diagnosis. More information can be found in the section “What is pain?”.

Question 2:

Which of the following have been found to be elevated in the pelvis and related to the pain experience of patients?

a) TNF-α
b) Adrenaline
c) NGF
d) OPG

Answer 2:

A – correct; B – incorrect; C – correct; D – correct

Adrenaline has not been found to be elevated in the pelvis. TNF-α has been found to be elevated in the PF of patients with endometriosis and has been shown to be correlated with the level of menstrual pain experienced, as well as the magnitude of central hyperexcitability. NGF has been shown to be more frequently elevated in

patients with severe endometriosis-associated pain. OPG concentration in the PF has been shown to be correlated with the magnitude of central pain sensitivity. More information can be found in the “Peripheral changes” section.

Question 3:

Which of these statements about the study of central changes in endometriosis-associated pain is correct?

a) The neural matrix of pain is a set of pain areas that are active in individuals with chronic pain and the areas involved do not vary between different disorders/individuals.
b) Women who present with pain symptoms are normally hysterical and one cannot trust their description of pain.
c) Mechanisms underlying dysfunction of the HPA axis in women with endometriosis-associated pain have been investigated and are fully understood.
d) Women with endometriosis with and without pain have differences in their brain structures.

Answer 3:

A – incorrect; B – incorrect; C – incorrect; D – correct

Given that the brain areas vary so much between, and even within, individuals, it is now conceptualised as a dynamic cerebral signature rather than a fixed matrix. The experience of pain is subjective, it is therefore what the patient says it is. Psychological factors may have a role in an individual's pain experience but their presence does not take away from the need to treat their pain. More information can be found in the "Central changes" section.

Question 4:

Which of the following should be involved in a patient centred multidisciplinary team for a patient with endometriosis-associated pain?

a) Psychologist
b) Gynaecologist
c) Physiotherapist
d) Psychiatrist

Answer 4:

A – correct; B – correct; C – correct; D – incorrect

A psychologist, gynaecologist and physiotherapist should all be members of a patient centred multidisciplinary team for a chronic pain condition. In the case of frank psychopathology, such as schizophrenia or borderline personality disorder, psychiatric input may be useful. Similarly, informed medical advice (often from a psychiatrist) may be required when a patient already uses multiple centrally acting medications and commencing a neuropathic adjunct, such as gabapentin, is considered appropriate. More information can be found in the “Future Treatment Directions” section.