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Unconscious amygdalar fear conditioning in a subset of chronic fatigue syndrome patients

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Summary Here, a novel hypothesis for chronic fatigue syndrome (CFS) is proposed. CFS may be a neurophysiological disorder focussing on the amygdala. During a 'traumatic' neurological event often involving acute psychological stress combined with a viral infection or other chemical or physiological stressor, a conditioned network or 'cell assembly' may be created in the amygdala. The unconscious amygdala may become conditioned to be chronically sensitised to negative symptoms arising from the body. Negative signals from the viscera or physiological, chemical and dietary stressors, become conditioned stimuli and the conditioned response is a chronic sympathetic outpouring from the amygdala via various brain pathways including the hypothalamus.

This cell assembly then produces the CFS vicious circle, where an unconscious negative reaction to symptoms causes immune reactivation/dysfunction, chronic sympathetic stimulation, leading to sympathetic dysfunction, mental and physical exhaustion, and a host of other distressing symptoms and secondary complications. And these are exactly the symptoms that the amygdala and associated limbic structures are trained to monitor and respond to, perpetuating a vicious circle. Recovery from CFS may involve projections from the medial prefrontal cortex to the amygdala, to control the amygdala's expressions.

I shall firstly discuss predisposing, precipitating, and perpetuating factors involved in the possible etiology of chronic fatigue syndrome (CFS), followed by the patient's experience of the illness. Finally, I shall look at a suggested explanation for the symptoms of CFS.

PREDISPOSING FACTORS

Much of the literature identifies personality characteristics pertinent to CFS. I would argue that whilst anyone can develop CFS, there is a tendency for patients to be more prone to stress and anxiety. Certain personality types can be prone to overworking and may spend little time relaxing. Over long periods of time, higher plasma levels of catecholamines are present.

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There may also be some genetic factors to consider and panic disorder has been identified as the having the highest rate of familial comorbidity in CFS (1). The combination of personality, long term elevated stress levels, and genetics are risk factors for CFS, but the development of CFS may tend to require a combination of precipitating factors.

PRECIPITATING FACTORS

Many CFS patients generally recall a period of acute psychological stress (or 'life event') which seemed to accompany the onset of the illness, combined with a viral infection. Etiological studies on viral illnesses have shown that they have widespread neurological and physiological effects on the body and can act as an added

bodily stressor. The effectiveness of the immune system is generally lowered during stress and therefore the viral illness is likely to be more severe and prolonged.

About a quarter of patients develop CFS without recalling a specific viral trigger. In fact, for some the onset is related to inoculations, exposure to pesticides, toxins, etc. However, CFS may not necessarily require a virus to trigger the illness. Any physical or chemical stressor on the body which occurs while the mind is experiencing acute psychological stress, may potentially trigger CFS.

Recent research into the neuroscience of emotion by Professor Ledoux (2) has implicated the amygdala in fear responses, stress and anxiety disorders. The amygdala operates at an unconscious level and has two roles. First, it determines whether immediately present stimuli pose a threat to well-being. Second, if the stimuli are negative, the amygdala must 'orchestrate behavioural responses and associated autonomic and endocrine reactions that increase the likelihood of surviving that danger' (3). During the period of stress before the onset of the illness therefore, I hypothesise that the amygdala is highly aroused (in association with many other limbic brain structures) and the amygdala mediates this emotional response, stimulating the 'freeze, fight or flight' response via the hypothalamus and other brain pathways.

Whilst the psychological stress is being experienced, there are physical symptoms which are being endured simultaneously. The physical symptoms may derive from the following sources:

1. The symptoms of an overactive sympathetic nervous system in response to psychological stress.
2. The effects of a viral infection acting on a weakened immune system.
3. The effects of an active immune system (which itself produces symptoms of general weakness).
4. Potentially also a prolonged period of post-viral fatigue.

(Patients who do not recall a specific viral or other environmental/pharmacological trigger may experience 1 as the main source of negative bodily symptoms.)

From this point onwards, there may be other etiologies in heterogeneous subgroups of CFS patients which proceed. However, I believe that there is a significant subset of CFS patients for which the following etiology unfolds.

The amygdala plays an important role in assigning affective significance to any cognitive or sensory input and this includes negative somatic signals from the viscera. For instance, Ketterer et al. (4) found increased blood flow in the amygdala in response to pharmacological elicitors of negative effect and this underlines that the amygdala operates at an unconscious level. The amygdala can detect any psychological, pharmacological, or visceral stimulus of negative effect which may pose even minor danger to a person. Recent work has implicated the basal ganglia (of which the amygdala is a sub-structure) in the processing of noxious (and non-noxious) somatosensory processing, including nociception and pain (5).

According to Ledoux, subcortical thalamo-amygdala pathways are often used to decide what is of affective significance and these pathways are 'quick and dirty', i.e., they are not accurate in describing what is actually the source of danger. Therefore, fear and anxiety can generalise unconsciously. This explains how being 'stressed' about one particular stimulus can make us generally more stressed about other things. As Ledoux comments (6),

> '...a neutral stimulus...that occurs in the presence of a 'trauma' will acquire the capacity to elicit fear reactions, and that phobias are nothing more than fear (anxiety) that has been conditioned to some otherwise meaningless event'

When the amygdala is at a heightened state of arousal during a period of anxiety, it may be prone to 'learning' new sensitivities. The limbic structures gradually attribute the source of the danger to the physical symptoms the body is experiencing, as well as the external source of the psychological stress, and this is reinforced through conscious thought processes described below. The amygdala is becoming conditioned to implicitly be highly sensitised to any negative physical symptoms arising from the body. The immune system is less effective in dealing with the virus during stress and hence the episode of 'Pavlovian fear conditioning' occurs over a prolonged period of time. The amygdala has been strongly implicated in unconscious fear conditioning which can occur in phobias and other anxiety disorders (7).

The above effects tend to occur mainly at an unconscious level. The following process operating consciously may also contribute to fear conditioning. Acute psychological stress brings on feelings of anxiety and vulnerability, and this makes the person feel increasingly vulnerable to negative bodily symptoms, which seem more noxious and troublesome given the intense emotional arousal. Certain personality characteristics may contribute to this bodily introspection. The person may begin to monitor the body for the symptoms of stress and the virus in anticipatory concern, especially given the prolonged nature of the illness, and the person's urgency to return to full health in order to deal with the source of the psychological stress. Areas of the prefrontal cortex, orbital cortex, and the anterior cingulate are involved in attention to dangerous or negative stimuli (8). There may be associated anxieties about the prolonged length of the period of post-viral fatigue and anticipatory concern about long-term illness. These concerns contribute to fear conditioning in the amygdala. It is important to bear in mind that fear conditioning

can occur whilst the person still has the viral illness (or other physical stressor) and/or even once the viral illness has passed during a period of post-viral fatigue.

The release of noradrenaline and adrenaline via the stress response affects the formation of memories in various parts of the brain, including the amygdala and the hippocampus. Adrenaline indirectly 'stamps' and strengthens memories in the amygdale via the viscera, meaning that if the same stimuli present themselves again, the amygdala can recognise them and react to them – an 'emotional memory' (*9*). It is thought that learning through association of co-occurring events may be due to 'long-term potentiation' (LTP), where synaptic strength between co-firing neurones increases after brief but repetitive stimulation. Activation of NMDA receptors is thought to be involved in the mechanism of this process of forming associations between stimuli.

During neurological learning, conditioning increases the functional interaction between neurones so that the likelihood that two cells will fire at the same time in the future dramatically increases. This can create 'cell assemblies' or conditioned networks in the lateral nucleus of the amygdala, which means that a given input will produce a larger output (10–12). (As Ledoux notes, the concept of 'cell assemblies' is still hypothetical, although it fits very closely to laboratory observations and is a likely process.) As above, the amygdala has become conditioned to believe that negative symptoms from the viscera are 'dangerous'. In the future, a detection of negative bodily symptoms by the amygdala via the thalamus will elicit a stress response which is out of keeping with the danger the symptoms actually present. Fig. 1 shows the formation of a cell assembly.

This cell assembly represents the neurological activities, which were occurring during the 'traumatic' learning period, and it is the intense emotional arousal which facilitates such strong plasticity encouraging neurological learning. In the future, any inputs as described in Fig. 1 which occurred during conditioning trigger the cell assembly, which produces a conditioned output or response that was also associated with the learning period. After even a few stimulations, the output will be much stronger for a given input. This cell assembly is particularly resistant to 'extinction', which is the process involved in reprogramming the amygdala. This means that once conditioning occurs, the 'hard-wiring' may stay with a person for life, and for some patients, the amygdala's expressions can only be regulated rather than fully extinguished (13). Complete extinction resistant plasticity may represent extreme long-term morbidity.

On the right in Fig. 1, I have labelled a potential output as the 'stress signature'. Given that during the fear conditioning period, the immune response may have been activated (with or without conscious awareness of an external pathogen), the neurones involved in immune activation may be re-triggered in the future as part of the conditioned response, causing a unique immuno-response in each patient – the 'stress signature'. This effect may occur to differing intensities in each patient dependent on a number of other factors to be identified. The amygdala has strong interconnections with the hypothalamus, which itself is implicated in activation of the immune system in association with the pituitary gland.

Pavlovian immune system conditioning in association with stress pathways is not a new concept (Ader) (14). Psychologists Robert Ader and Nicholas Cohen were the first to demonstrate this effect in rats in 1974.

PERPETUATING FACTORS

Once sensitisation or 'fear conditioning' has occurred, a vicious circle is produced. Negative bodily symptoms in the future act as conditioned stimuli for the unconditioned stimulus of being in the throes of a debilitating illness. The thalamo-amygdala pathway takes on the role of monitoring the body for these negative stimuli and there is consistent evidence of increased blood flow in the thalamus (15). The amygdala drives arousal systems which keep brain cortical networks that are processing

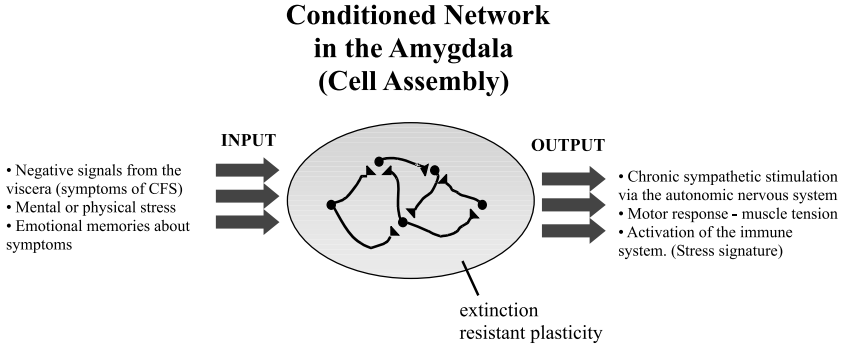


Fig. 1 Formation of cell assemblies in the Amygdala.

the stimuli in a state of hypersensitivity. Dopamine has a role to play in riveting attention to the source of the danger. This explains the hyper-vigilance or 'symptom monitoring' observed in some patients. Furthermore, the more the amygdala becomes stimulated into action, the more its initiated stress response stimulates and arouses itself, prolonging the entire response. This process is facilitated by glutamate-containing excitatory neurones in the amygdala, but may be moderated by GABA inhibitory neurones in the amygdala. Fig. 2 illustrates the CFS vicious circle.

Once any symptoms of CFS are detected by the thalamus as on the right, information is passed directly to the amygdala, as well as the cortex. The amygdala implicitly remembers that the symptoms are of affective significance and explicit emotionally charged memories are retrieved from the hippocampus and other memory centres to justify this conclusion. Information about symptoms is also transferred to the cortex. The cortex is 'arrested' or 'emotionally hijacked' by the amygdala, which can regulate the inputs which the cortex receives. Areas of the prefrontal cortex and anterior cingulate may be involved in continuous attentional processing of these stimuli, which makes it difficult for a patient to shift their attention to other stimuli. The patient simply has to consciously believe that the symptoms are negative or of concern, and this message is enough of a confirmation response for the amygdala. Given the debilitating nature of the illness, it is no surprise that patients are concerned or anxious about the symptoms. The amygdala then orchestrates a chronic stress response via the conditioned network which is out of keeping with the very minor danger which the symptoms might pose to the patient. The amygdala has strong projections to the hypothalamus to stimulate sympathetic (and parasympathetic) stimulation, as well as other brain structures normally involved in sensitisation responses. The observed over-activity of the sympathetic nervous system leading to sympathetic dysfunction is a key marker of this process. The chronic long-term stress response becomes pathological to the body, and contributes to the myriad of different symptoms and secondary illnesses observed in patients, of which fatigue is but one.

Whilst a stress response in itself could not cause such severe symptoms, a continuous unremitting sympathetic

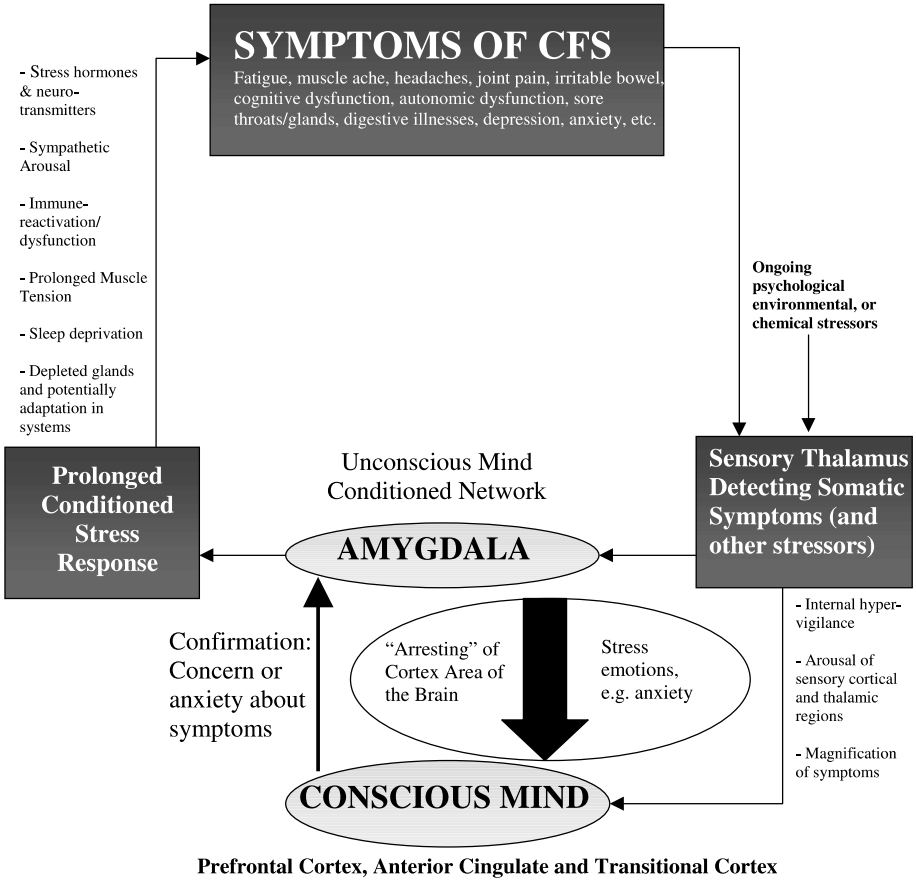


Fig. 2 CFS vicious circle.

stimulation will eventually lead to mental and physical exhaustion with glandular depletion, as well as secondary abnormalities in bodily systems. And it is exactly these symptoms to which the patient has become sensitised to, increasing the distress associated with the entire morbid experience. A patient's heightened perception of the symptoms, and increased symptoms in response to effort, can further contribute to avoidance behaviour and symptom distress. On an anecdotal level, continued stimulation of an exhausted mind and body to an 'always-present danger' is likely to lead to various complications and chronic suffering.

Any external stressor, based on an individual's individual sensitivities, has the ability to trigger or reinforce the CFS vicious circle, making it more difficult to recover. On-going psychological, pharmacological, dietary or environmental stressors may now have the ability to increase chronic stress to levels out of proportion to the danger these stimuli actually present, given the excitatory state of the amygdala, reinforcing the vicious circle. In fact, it may be exactly these triggers which a patient attributes the illness to. Furthermore, every time the vicious circle is initiated, it further ingrains the unconscious sensitisation to symptoms into the amygdala and associated emotional memory centres such as the hippocampus, making it far more difficult to moderate the amygdala's expressions in the future.

There may be an added idiosyncrasy to the conditioned responses initiated. Individual patients' conditioned response may mimic the response initiated during the 'traumatic' period of learning in response to the conditioned stimuli, which may involve a reactivation of certain aspects of the immune system, or stress signature as mentioned earlier. Alternatively, there may be a host of other reasons for the observed immune abnormalities, as there is a whole literature in psychoneuroimmunology emphasising the close links between stress and immune function. Stress hormones and neurotransmitters are well known to have complex and wide-ranging effects on the immune system (16). The levels of these chemicals may in themselves be unique to each patient, depending on the level of glandular depletion and/or adaptation in stress systems to chronic stimulation.

THE PATIENTS EXPERIENCE OF THE ILLNESS

Patients are far more sophisticated in their mental approach to their illness than this hypothesis may convey and the role of conditioned and unconditioned stimuli may seem over-simplistic. There are a wide variety of coping strategies and belief mechanisms which operate. Patients are also heterogeneous in terms of the amount of overlapping psychiatric morbidity, with some patients suffering severe depression or anxiety, and some exhibiting few signs of this at all. However, I believe that the patient is 'in the grip of' a predominantly unconscious process over which they have little control and which they are not necessarily aware of. Differing cognitive approaches to dealing with the illness may have only modest effects, unless the approach is specifically involved in the reprogramming of the amygdala's conditioned responses.

Whilst patients may question the direct causal link between concern about their symptoms and symptom perpetuation, the whole process eventually occurs automatically, and a patient is not consciously aware of it until he or she feels concern or worry about the symptoms. Fig. 3 shows how any level of concern about symptoms can lead to symptoms perpetuation.

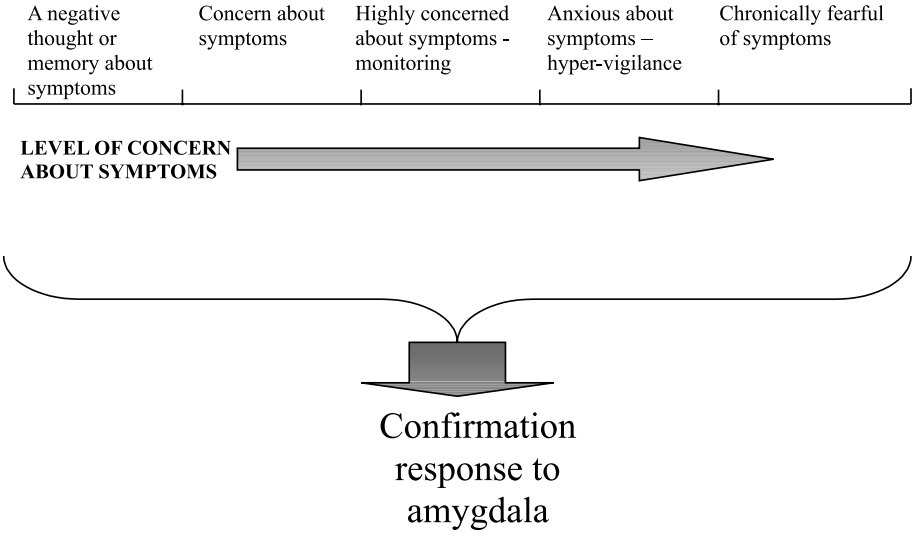


Fig. 3 Range of conscious cognitions concerning symptoms.

Moreover, concern about symptoms is governed by previous memories of the illness. The amygdala retrieves memories mainly from the hippocampus and the cortex also retrieves memories from other memory centres such as the temporal lobe. Cortical memory systems are reshuffled so that knowledge and memories most relevant to CFS will be recalled, taking precedence over other less relevant strands of thought. Therefore, the response from the cortex to the amygdala becomes automatic, with little conscious control once powerful unconscious emotional memory centres have been stimulated. Fig. 4, based on Ledoux's work, shows how immediate conscious experience within areas of the prefrontal cortex are affected.

Conscious experience during symptoms involves detection of symptoms from the sensory cortex, as well as arousal by the amygdala and the hippocampus (17). The amygdala arrests the cortex because of the negative salience of the symptoms. The hippocampus brings back explicit emotionally charged memories of the last time the symptoms were encountered, and how the person felt, and what emotional response was initiated. This diagram shows that it is little wonder that a patient's concern about symptoms can occasionally turn into full-blown anxiety about symptoms, given the arousal from unconscious brain structures. However, once again I wish to underline that any negative thoughts or memories about symptoms are enough to trigger the amygdala's chronic outpourings (18), and the more anxious a patient is about the symptoms, the stronger the response will be. Interestingly, there is evidence in studies showing that patients may acknowledge persistent stress as a possible cause of ongoing fatigue (19).

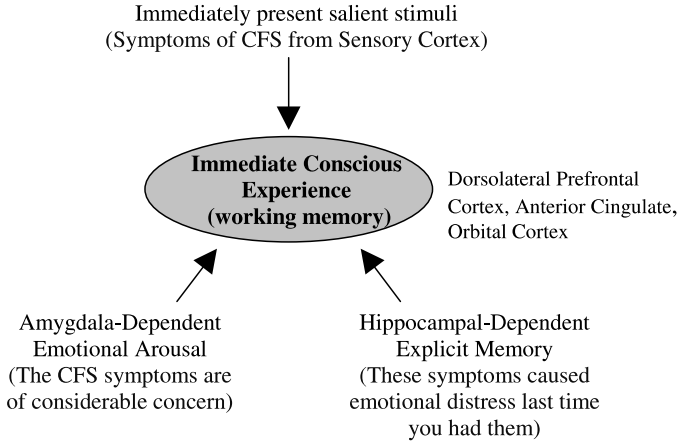
WHAT IS NEW ABOUT THIS HYPOTHESIS?

Previously conditioned fear responses have mainly been thought of in terms of external stimuli, with a notable exceptions being panic disorder (20,21) and tinnitus. However, the amygdala, which mediates fear mechanisms in the brain, receives direct projections from the sensory thalamus, which monitors the entire viscera, as well as receiving information about the outside world from the senses. Therefore, it is not inconceivable that sensitised responses to bodily events can be 'learned' by the amygdala.

The conditioned fear mechanism described is *not* to be confused with

- Hypochondriasis, which is a fear that one might be suffering from a serious disease. Patients are already aware that they probably suffer from CFS.
- Somatisation disorder – 'the expression of personal and social distress in an idiom of bodily complaints with medical help seeking'. Although the etiology described above may have some minor links to somatisation, they are very different illnesses, and CFS in the context of fear conditioning deserves a whole new classification.
- Unhelpful beliefs about the illness – fear conditioning represents a deep-seated unconscious fear of symptoms and unhelpful beliefs are an output rather than an input to the illness.

A fear conditioning model for tinnitus is now acknowledged in the literature as a likely etiology (22,23). Although tinnitus is a very different physiological illness to CFS, the evidence points to the ease with which conditioned sensitisation can occur in response to bodily signals.



(Based on a diagram reproduced by the kind permission of Weidenfeld and Nicolson from Ledoux, J (1998) The Emotional Brain p204)

Fig. 4 Factors affecting conscious experience.

EXPLANATION OF THE SYMPTOMATOLOGY OF CFS

Several commentators have argued that a chronic stress response could act as a final common pathway for CFS. Prolonged stress is known to have pathogenic effects on the body and the stress response affects every organ and system in the body. This leads to a wide-ranging number of chronic symptoms, which can differ, from patient to patient depending on individual sensitivities, leading to the observation that CFS may form a heterogeneous group. The neurophysiology described may then cause secondary abnormalities in other systems such as the immune system and the digestive system, which further exacerbate symptoms, and lead practitioners to observe these various abnormalities in patients. Furthermore, the continual stress response may eventually lead to glandular depletion and eventually adaptation, where the body adapts to over-stimulation. This may make it difficult to pinpoint sympathetic activity. Continual mental and physical tension with intrusive negative thoughts about a patient's state of health causes interrupted sleep patterns, which may contribute to the general exhaustion experienced, with patients not experiencing refreshing sleep. In fact, there is evidence of disturbed circardian sleep/temperature rhythms (24).

Whilst the symptomatology may exhibit some similarities to that observed in major affective disorder, physiological morbidity may be far worse, given that CFS patients cannot engage in avoidance to the same extent that anxiety patients can. The stress response is continuous and unremitting, and such a chronic response may cause the secondary abnormalities which may or may not be observed in patients suffering from psychiatric disorders. This may characterise CFS as a unique illness in terms of patient experiences, e.g., secondary allergies and sensitivities, with immune system abnormalities.

The literature on CFS and immunity is complex and there are numerous observations of abnormalities found in patients, some of them contradictory. I hypothesise that there may be two contrasting processes occurring that may account for some of these observations, which may differ from patient to patient. First, the conditioned response may re-trigger certain aspects of the immune system due to the 'stress signature' hypothesis expressed earlier. For instance, there may be certain aspects of an over-active immune response which may contribute to symptoms such as fever, and sore throats and glands (e.g., effects of cytokines). Second, it has been known for many decades that chronic stress decreases the effectiveness of the immune system, as research within disciplines such as psychoneuroimmunology exemplifies. For instance, there is evidence of significant suppression of natural killer cell activity in CFS patients, but this has also been linked to a person's reaction to emotional stress (25). These co-occurring processes unique to each patient may help to explain the immune abnormalities observed.

The observed downgrading of the hypothalamic–pituitary–adrenal (HPA) axis in response to stress (lower response to CRF and lower circulating levels of cortisol) may be due to adaptation in systems to chronic stimulation. It may be due to enhanced sensitivity of the HPA feedback mechanism with increased hippocampal inhibition, and is also seen in some patients suffering from post-traumatic stress disorder, which is another chronic stress disorder (26). This means that when a patient tries to engage in activity, the body feels too exhausted to cope with the rigours of life. HPA abnormalities themselves may also have a function in stimulating aspects of the immune system.

Intolerance to alcohol has often been cited as a characteristic marker of CFS. Much medical research demonstrates that alcohol actually induces the stress response by stimulating hormone release via the hypothalamus (27,28). This is exactly the response which the amygdala is conditioned to respond to, causing further symptoms. Furthermore, in CFS this reaction may malfunction due to a downgraded HPA axis and other hormonal abnormalities as a result of the stress response, causing increased sensitivity to alcohol.

Identifying the exact nature of muscle aches and fatigue can be problematic. However, a hypothesis can be made. Actual muscular fatigue may be caused by continuous tension leading to fatigue. Prolonged tension is initiated and maintained by the freeze, fight, or flight response, as the muscles are primed for reaction to dangerous stimuli. Adrenaline is particularly potent in maintaining muscle contraction (29), and the amygdala also projects to the reticulopontis caudalis, the fibres of the central gray, and corpus striatum, which all play a role in tightening muscle groups in response to fearful stimuli (the 'freeze' response). Continuous muscle tension may cause the chemicals of fatigue such as lactic acid to temporarily accumulate and disperse, but lead researchers to find few physical abnormalities in the muscles. Continuous tension may cause secondary abnormalities in muscles, which require further definition The muscle de-conditioning which some researchers have identified may be an added factor rather than the central cause of fatigue.

A stress response causes vasoconstriction except in those vessels supplying the heart and the limbs, where vessels actually dilate. Over a prolonged period of time, this effect may cause gravitational venous pooling in the legs, which can contribute to the observed orthostatic intolerance and general weakness experienced (30).

Generalised anxiety and depression may be overlapping psychiatric conditions which occur in CFS, but are a result of the actual underlying fear conditioning which causes an increase in the excitatory level of the amygdala, rather than the original cause of the illness. They may further contribute to symptoms themselves, given that fatigue is also characteristic of these illnesses. General avoidance behaviour may increase the perceived effort of tasks in the future, further ingraining fear of activity into the amygdala's and hippocampus' circuitry. Therefore, a routine task in the future may have the ability to elicit an ultimately exhausting sympathetic response which is out of keeping with the actual effort involved.

There may be various reasons for cognitive impairment seen in patients. The hippocampus can become damaged during a chronic stress response and no longer is able to fulfil its role in short-term memory retrieval. Studies have shown that a brief period of stress can disrupt spatial memory in rats and interfere with long-term potentiation in the hippocampus (31).Therefore, the formation of new memories in the hippocampus may be inhibited (32). General concentration and attentional deficits may be due to mental exhaustion after short periods of continual stimulation. Concentrating on external stimuli for long periods of time may be difficult as cortical memory systems are reshuffled so that knowledge and memories most relevant to CFS will be recalled, taking precedence over other less relevant strands of thought.

CONSEQUENCES FOR PATIENT RECOVERY

Recovery is likely to involve two distinct processes. First, symptoms resulting from secondary illnesses such as digestive problems need to be addressed initially. Once symptoms have moderated, further recovery may involve the amygdala's expression of danger becoming regulated by the cortex, or more specifically the medial prefrontal cortex, in a process called 'extinction'. It may be particularly difficult to regulate ingrained fear of stimuli which are continually present (i.e., the symptoms of CFS) and patients cannot simply be told to try and not think about or worry about symptoms at a cognitive level, because the cortex is continually arrested and fear processing mainly occurs unconsciously. New therapies may be required which may be distinct to received wisdom in this area and further research is required to test the validity of new therapies resulting from this hypothesis.

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