Review

Fibromyalgia and the concept of resilience

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ABSTRACT

The concept of resilience varies according to the context in which it is used. Resilience is broadly defined as a protective factor that makes people less vulnerable to future adverse life events, in this implying the previous occurrence of an adverse event that has to be confronted before individual equilibrium can be restored. This definition can be applied to fibromyalgia and other chronic pain situations. Resilience is profoundly related to reaction to acute or chronic stress, and is therefore involved in the stress response system. Corticotropin-releasing factor can be considered a fundamental biological element of resilience, which also involves neural mechanisms such as the hypothalamic-pituitary-adrenal (HPA) axis, the locus coeruleus/norepinephrine system, the mesolimbic reward circuit and the fear circuit. Resilience also has a genetic basis: certain genetic characteristics, affect the degree of vulnerability to chronic stress. The number of psychiatric symptoms in healthy adults with high resilience scores do not change when they are exposed to stressing life events, whereas less resilient people develop additional symptoms. This is a typical clinical feature of fibromyalgia. Although resilience could be a therapeutic target for any chronic pain condition, it is an under-developed area of research, particularly in the light of the emerging interactions of positive emotions, physical health, and changes in pro-inflammatory cytokine levels. Given the lack of any pharmacological treatment capable of controlling more than 30-50% of the cases of chronic pain, there is a need to discover new therapeutic targets and strategies capable of changing a non-resilient phenotype into a more resilient phenotype, especially in the case of chronic pain conditions that cannot be explained by a lesion or a disease affecting the somatosensory system. This holds true of fibromyalgia, which is characterised by a complex combination of positive signs and symptoms that vary enormously from person to person depending on a wide range of pathophysiological changes in which genotype and, more importantly, environmental factors may play a major role in developing a more or less resilient personality.

Introduction

Fibromyalgia (FM), which has a worldwide general population prevalence of 2–4%, is characterised by chronic widespread pain, fatigue, unrefreshing sleep, and cognitive difficulties (1). Chronic widespread pain remains the defining feature of FM, but individual patients may also attribute variable weight to other symptoms. The transition to chronicity after acute pain and the composite symptoms of FM patients raises the question of whether the symptoms are merely the consequence of chronic pain or a uniquely critical component of the disorder.

The pathogenesis of FM involves psychological, behavioural and social factors that also complicate its treatment. FM patients are more likely have psychiatric disorders (including depression, anxiety, obsessive-compulsive disorder, and post-traumatic stress disorder [PTSD]) that may be due to triggers shared with FM, such as early-life stress or trauma (2). In particular, FM patients may show significantly reduced resilience that can lead to the development of PTSD, depression and other psychiatric disorders, whereas most people do not develop such conditions after experiencing stressful life events and are therefore thought to be resilient.

The concept of resilience: definitions and development

The concept of resilience dates back to the early 1900s, when the Shackleton model (derived from a long and successful naval expedition during which the explorer and his men had to face extreme and life-threatening conditions) was first applied to resilience (3). Later, other historical narratives involving resilient men highlighted the need to develop research into how to define resilience theoretically (4).

Developmental psychology was the first discipline to approach the subject, when authors such as Bonanno, Garmezy and Werner introduced the term "resilience" to indicate children's capacity to face prolonged adversity and adapt to difficult situations (5), a concept that was subsequently developed by other disciplines as various as psychiatry, education, ecology, microbiology, medicine, engineering, economics and epidemiology (3, 4). The clinical application of the concept of "resilience" therefore has to be carefully defined and contextualised.

Researchers in the field of human sciences first tried to identify the salient aspects of so-called "resilient personalities" (5) on the basis of the hypothesis that people may have or not hove certain resilient personality traits, and came up with the personal internal characteristics of balance, perseverance, self-reliance and the attribution of meaning and purpose to life (3, 6). However, it was not long before this started a scientific debate as to whether resilience was a personality trait or a dynamic process (5), and this led to it being considered an ability that develops during life on the basis of existential circumstances. Subsequent studies elaborated models of resilience that focused on the biological basis of the construct (3), and new research studies are currently using neuroimaging to explore the "resilient brain".

Nevertheless, the dichotomy of traits and processes is still salient, especially in adult mental health research, in which the central areas of investigation are the acquisition of resilient capacities, the development of resilience, the recovery of a previous equilibrium, immunity, and growth after a stressful event. According to Ayed *et al*. (4), the concept of immunity suggests that resilience is a protective factor that makes people less vulnerable to future adverse life events, whereas recovery (or "bouncing back") refers to the post-stressor restoration of health and normal functioning, and "post-traumatic growth" involves improving coping strategies, attributing new meanings to events, and modifying priorities, relationships and life perspectives.

In terms of individual characteristics, the most salient personal resources are a high degree of expectancy (reflected by an internal or external sense of purpose and achievement in life), self-determination (an ability to overcome life's obstacles), flexibility (being adaptable to change, cooperative, amiable and tolerant, and having good self-esteem/self-efficacy), optimism (prevalently expecting the occurrence of positive outcomes), cognitive reappraisal (an ability to monitor and change one's cognitive and emotional points of view on life), and active coping (an ability to act directly in stressful situation in order to change it or one's reactions to it) (5-8).

The level of individual resilience can be increased by having access to social resources, being a member of a community, cultivating social relationships, having a supportive family, and maintaining affective bonds (4, 7), and is also influenced by attachment, social learning, socio-economic status, religion and culture (9). Finally, as pointed out by Rutter (10), it is a contextual ability insofar as individuals may be resilient in certain environmental circumstances, but not in others.

All of the subjective and psychosocial factors above can have a significant impact on individual resilience (11): *i.e.,* the same stressor can have very different effects on people with different cognitive and emotional capacities and social resources. However, in order to really understand what resilience means, it is important to remember that it necessarily implies the previous occurrence of an adverse event that has to be confronted before individual equilibrium can be restored. This can be done by acquiring new resilient characteristics and/or strengthening those that already exist in such a way as to give rise to a sense of mastery and allow positive adaptation (5).

From an evolutionary point of view, the concept of resilience is strictly connected to that of survival. During the course of their lives, everyone faces external or internal stressors that threaten their allostatic equilibrium in a way that mirrors the evolution of the human species. In this sense, evolution favours resilient people who can functionally adapt to the demands of environmental changes (12). It is no accident that we have been living on this planet for about two million years: something like 60–80% of us can rely on our resilience (13).

As resilience always manifests itself as a reaction to acute or chronic stress, it is also involved in the stress response system (13). Bonanno (14) distinguished "emergent" resilience, which is developed by people facing chronic adversity, and "minimal-impact" resilience, which applies to cases of little or no dysregulation and is due to a single potentially traumatic event. These different types of resilience guarantee a certain degree of mental health and good physiological functioning and, as they limit vulnerability to future stressors (7, 12, 13), are clearly biologically valuable. Maladaptive coping with a certain stressor and/or the consequent dysregulation can evolve into the state of chronic stress that is acknowledged to be associated with an immediate or delayed risk of developing various somatic and affective disorders (13, 15). Furthermore, the self-perception of a poor state of health can act as a warning of an inadequate level of resilience to future events. Resilience is synonymous with an ability to adapt well to stressful events (12) and, in this regard, it is useful to distinguish the eustress that promotes resilience and adaptation from the distress that emerges when an individual fails to adapt functionally to a stressor.

Resilience in FM patients can be defined as their ability to adapt to and recover from stressful events (8, 9, 11). It can also be intended as "a stable trajectory of healthy functioning after a highly adverse event, and the conscious ef-

fort to move forward in an insightful, integrated positive manner as a result of lessons learned from an adverse experience" (6). In this sense, it is an "active stress-coping mechanism" (6): *i.e.*, a pro-active attitude by means of which an individual personally strives to recover and grow after receiving a stressful stimulus. In other words, resilience to FM can be seen as the "capacity to adapt successfully to disturbances that threaten [a patient's] viability, function or development" (16).

Neurobiology of resilience

The word "system" has a quite broad meaning: it can be used to describe molecular architecture, biological functioning, a person, society or many other things, and the characteristics of a system that allow it to react functionally to a given perturbation are flexibility, openness, and structural internal connectivity (17). The neurobiological substrate of resilience involves the various central and peripheral systems and processes that are involved in the stress response and the extent of individual vulnerability or resilience (18).

The hypothalamic-pituitary-adrenal (HPA) axis that implements the stress response is a neuro-endocrine system that plays a crucial role in adapting an organism to stressful events (11). During an acute stress, resilience is favoured by glucocorticoids (the steroid hormones produced by the adrenal gland) that contribute to the onset of the fight-or-flight mechanism and protect against possible dendritic alterations in the hippocampus and amygdala. However, under conditions of chronic stress, excessive and prolonged concentrations of cortisol and glucocorticoids are harmful because they lead to severe structural and functional changes in the central nervous system, such as increased glutamate tone, hippocampus atrophy and inflammation (12), which have direct consequences on physical health, behaviour, cognitive capacities and the emotions, increase vulnerability, and can lead to the development of a number of immune, metabolic, neuropsychiatric and endocrine diseases (13).

The concept of "habituation" has acquired clinical relevance because too little HPA axis habituation and a high level of sympathetic nervous system (SNS) sensitisation have a negative impact on resilience. Furthermore, repeated experiences of the same stressor can down-regulate the HPA axis and thus reduce biological activation even if some of the components of the SNS remain unaltered (13), and an ability to face stressors and control stress responses can preserve physical and mental health. Habituation is related to an individual's socio-demographic and psychological characteristics: for example, greater IL-6 sensitisation can be observed in people of low social status and those with a reduced sense of purpose in life or psychological characteristics that do not favour adaptive coping (13).

Corticotropin-releasing factor (CRF), an important mediator of the acute response to stress, can be considered a fundamental biological element of resilience. Acute stress responses lead to high concentrations of mineralcorticoid receptors (MRs) in rat hippocampus, and higher levels of CRF raise MR levels and therefore acting as an inhibitory control of the HPA axis (11).

In addition to HPA axis, other neural mechanisms involved in resilience include the locus coeruleus/norepinephrine system, the mesolimbic reward circuit and the fear circuit. The first contributes to activating the fight-or-flight mechanism and the second is related to positive emotions and mutual cooperation, and favours the confrontation of stress. Finally, a series of psychic fear-related phenomena (fear learning, memory, responses, modulation and extinction) are modulated by various brain areas, including the amygdala, hippocampus, medial prefrontal cortex (PFC), nucleus accumbens (NAc), ventromedial hypothalamus and brain stem nuclei, and the good functioning of this circuit allows control of fear processes under stressful conditions (6, 8).

Resilient and non-resilient people show significant differences in neurotransmitter and neuromodulatory systems, particularly those involving neuropeptide Y (NPY), brain-derived neurotrophic factor (BDNF), and serotonin (5-HT) (13), which can modify MR levels (11). Mouse experiments have revealed a sub-group of serotoninergic neurons located in the dorsal raphe nucleus and the medial PFC that are responsive to immune signals (15). The serotonin transporter gene (*5-HTT*) may determine the extent of individual sensitivity to stressful events (9). Furthermore, low 5-HT levels increase vulnerability to stress (7) and dysregulated 5-HT functioning leads to maladaptive coping strategies and major depression (15). It therefore seems that the 5-HT system facilitates coping responses to stress and moderates the impact of distress.

The dopaminergic and cholinergic systems are also in determining resilience (7). Dopamine release depends on the nature of the stressor: dopaminergic tone decreases in the NAc in the case of chronic unavoidable stress, but not when stress can be avoided (19).

Resilience also has a genetic basis: certain genetic characteristics, such as single-nucleotide polymorphisms (SNPs) in the glucocorticoid receptor (GR, Nr3c1), affect the degree of vulnerability to chronic stress (11). It has been demonstrated that gene expression is characterised by more plasticity in resilient mice than in susceptible mice, and that many more genes are regulated in the NAc and ventral tegmental area (6). Furthermore, resilient phenotypes are determined by specific genes and polymorphisms that regulate the functioning of the HPA axis, neuropeptide Y, and the noradrenergic, dopaminergic and serotoninergic systems (8) which, together with the autonomic nervous system, increase individual susceptibility to early-life events and an inflammatory stress response, as well as vulnerability to depression and other psychiatric disorders (8, 18).

Resilience itself has a considerable neurological impact as it can modify the body's neuro-anatomy and neurophysiology. For example, early-life traumatic experiences weaken the medial PFC/amygdala connection, increase emotional susceptibility, and reducing the size of the hippocampus due to potentiated glutamatergic activity (13), but cognitive appraisal of the stressor, emotional regulation, and coping strategies

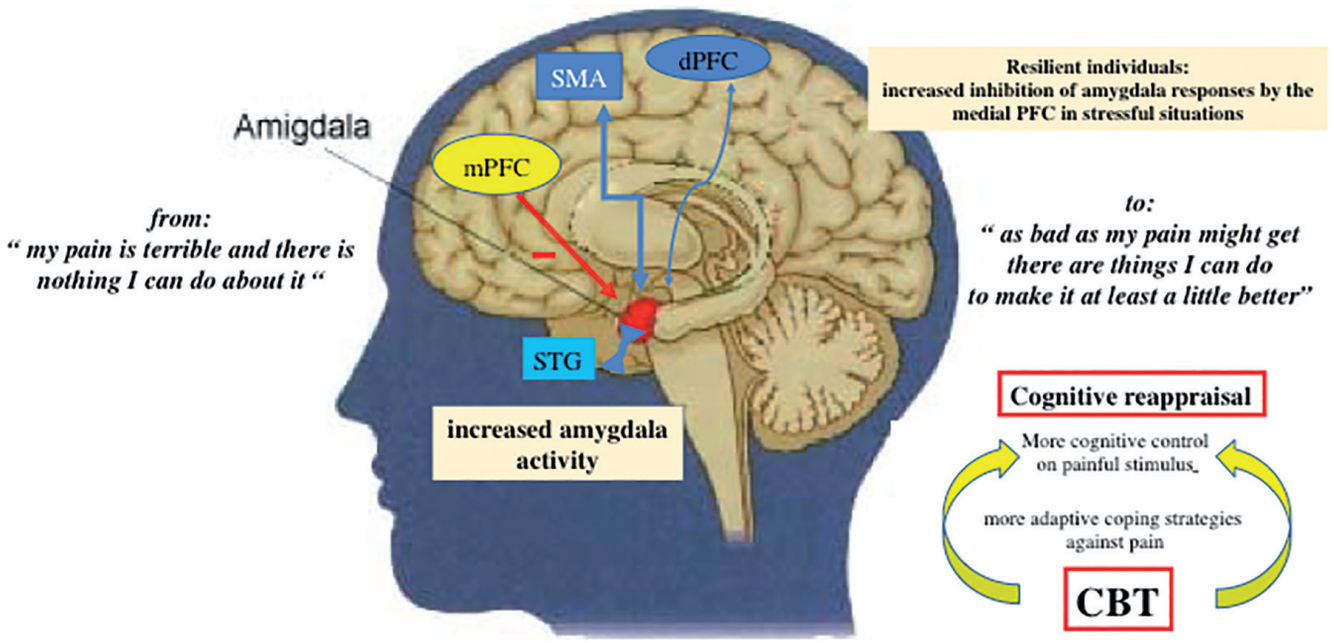


Fig. 1. Resilient paradigma and therapeutic perspectives. The inhibition of the amygdala by the mPFC could represent a protective factor for PTSD, such as altered interaction between amygdala and different brain area, *i.e.* amygdala-SMA and amygdala-STG may reflect compensatory mechanisms of brain function. These data may inform future therapeutic perspectives
A: amygdala; SMA: supplementary motor area; STG: superior temporal gyrus; dIPFC: dorsolateral prefrontal cortex; mPFC: medial prefrontal cortex.

can act on this stress-related cascade of neurobiological events. In this regard, it is important to note that the amygdala contributes to hyper-activating the HPA axis, whereas the medial PFC and hippocampus inhibit it (20). Structural neuroimaging studies have shown that a reduction in the grey matter of the ventral medial PFC and anterior cingulate cortex leads to emotive dysregulation and greater vulnerability to stress (21). Resilience is therefore not only an individual's psychological and behavioural adaptation to a stressful event, but also the functional neurobiological reaction of the body to the event itself. It is associated with many neural processes and plays a crucial role in psychological and physical health, thus demonstrating that this philosophical and psychological concept is a profoundly embodied construct.

All of the above has crucial clinical implications in terms of stress interventions.

Resilience in relation to depression and anxiety

Indeed the aim of psychotherapy, particularly cognitive-behavioural therapy (CBT), is to reinforce the repressive influence of the cortex on stress responses by constructing new and more functional thoughts and meanings to the occurrence of life events. At the same time, it treats a patient's emotional sphere to in order promote greater awareness and the regulation of emotional reactions, and has the effect of reducing amygdala activation (Fig. 1). Personal skills training and mindfulness/meditation protocols are other techniques that are effective in mitigating stress and potentiating individual resilience (13).

Optimism, cognitive reappraisal, active coping, humour, perceived social support, pro-social behaviour and mindfulness are all associated with greater vagal control of heart rate variability (HRV), a well-known autonomic stress response (21). Psychological resilience is also related to spontaneous fluctuations in the left orbitofrontal cortex, an area of the brain that belongs to the neural circuits governing life satisfaction, hedonism/pleasure, reward and the regulation of emotions. By mediating the activity of this area, psychological resilience can have a significant impact on such feelings of well-being (22).

Thus the risk of developing depression is related to a complex combination of genetic and biological characteristics, early-life stressors, ongoing stress and protective factors. A prolonged stressful event is a known risk factor for major depressive disorder (MDD). Most stress-exposed individuals appear resilient by maintaining their usual psychological functioning, but some develop psychiatric disorders. It has been shown that the number of psychiatric symptoms in healthy adults with high resilience scores do not change when they are exposed to stressing life events, whereas less resilient people develop additional symptoms (23). Similarly, higher resilience scores in adolescents (due to their personal dispositions, sound social support, and perceived family cohesion) predict fewer depressive symptoms after controlling for age, gender, and the number of stressful life events (24).

The biological mechanism of resilience to depression and anxiety

Over the last 20 to 30 years, increasing efforts have been made to investigate the biological basis of susceptibility and resilience to depressive and anxiety disorders with the aim of developing new therapeutic strategies based on the mechanisms promoting natural resilience.

A number of the neurotransmitters, hormones and neuropeptides involved

in the pathogenesis of depression and anxiety are also involved in resilience to stress. It has been shown that chronic psychosocial stress decreases 5-HT1A receptor density in limbic brain structures, and that a stress-induced increase in corticotropin-releasing hormone (CRH) and cortisol down-regulates 5-HT1A receptors in patients with MDD and anxiety disorders. It is thought that people who are at risk of developing depression and/or anxiety due to genetic, developmental and neurobiological factors may experience greater alterations in the serotonin receptor system under conditions of extreme or chronic stress than those who are stress resilient (25).

Mimicking in a quite striking way the systems and processes involved in resilience (6, 8, 11, 12), stress leads to the release of noradrenaline from the locus coeruleus, which stimulates areas of the brain involved in emotional behaviour, including the amygdala, the NAc, the PFC, and the hippocampus. These regions consistently show anatomical and functional abnormalities in patients with depressive and anxiety disorders (26). Resilience to stress has been related to a greater ability to regulate emotions, as is suggested by the findings of studies showing that differential amygdala reactivity to negative stimuli in healthy subjects is associated with vulnerability to anxiety and depressive disorders (27).

There is increasing evidence that reward circuits play an important role in mediating stress susceptibility, depression and the response to antidepressants. The most well-established reward circuit consists of the dopaminergic (DA) neurons in the ventral tegmental area (VTA) and their innervation of the NAc and other limbic regions (the VTA-NAc pathways). Some recent studies have shown that the K^+ channel in VTA dopamine neurons differentially mediates neuronal activity in resilient, normal and susceptible mice. This suggests that resilience is not the passive absence of stress-induced depression, but an active process in which resilient mice use more K^+ channels than susceptible mice in order to counteract the pathological hyperactivity of VTA dopaminergic neurons. KCNQ-type K^+ channel openers such as retigabine (an FDA- approved anticonvulsant used to treat partial epilepsies) have antidepressant effects in mice, a finding that indicates KCNQ as a target for conceptually new antidepressants that act by potentiating active resilience mechanisms (28).

Psychosocial factors of resilience to stress-induced mood and anxiety disorders

As stated in the previous chapters, positive emotions, particularly optimism and humour, are important psychosocial factors of resilience (4, 7, 9). The generalised expectation that good things will happen is 25% heritable, but can be increased by means of specific psychological interventions (29). It has been shown that there is an association between optimism and lower rates of depressive symptoms and pain intensity in patients with early/intermediate rheumatoid arthritis (30). Humour is one of the most mature defence mechanisms and may lessen depressive symptoms by reframing a situation in such a way as to make it less threatening and attracting social support.

Cognitive flexibility plays a central role in the ability to prevent stress-induced depressive and anxiety disorders. One component of cognitive flexibility is the positive explanatory style that characterises resilient people, who do not automatically blame themselves or others for a difficulty, but see it as a temporary problem that only affects limited areas of their life. Cognitive flexibility often includes cognitive reappraisal: *i.e.* the ability to reframe experiences in a more positive light (25). Acceptance (not to be confused with resignation) acknowledges the uncontrollable nature of certain stressors and focuses on the aspects that can be controlled, including viewing psychological reactions to external events as understandable and transient rather than unbearable conditions that must be avoided. Studies have shown that experiential avoidance, avoidant coping, and thought suppression are all associated with greater PTSD symptoms, depression, and general distress following a traumatic event, and that psychological interventions that emphasise the acquisition of acceptance and the reduction of experiential avoidance improve the symptoms of PTSD and depression (31).

Another characteristic of resilient people is their moral compass, particularly their adherence to religious/spiritual beliefs and altruism (25). Greater religiousness has been associated with lower levels of depression in bereaved adults, and healthy and medically ill elderly people (32). An altruistic outlook provides a framework on which to construct meaning in the face of adversity, and is a powerful contributor to resilience. Research has shown that during World War II the citizens who cared for others after bombing attacks suffered from fewer trauma-related mood and anxiety symptoms than might be expected, and experienced a significant decrease in pre-attack psychological distress (33).

Social support is another powerful contributor to resilience. A review of 36 studies (34) showed that the vast majority (89%) reported a significant association between social support (especially spousal support) and protection from depression among adults. Furthermore, emotional support provides more substantial protection than instrumental support, such as having someone to help with chores.

Recent studies have suggested that psychological treatment can also improve resilience. It has been shown that brief cognitive psychotherapy courses can improve the pre-therapy resilience scores of MDD patients immediately after the intervention and maintain the improvement for up to six months; furthermore, the patients with higher baseline resilience scores showed less severe depressive and anxious symptoms at the same time points (35).

Resilience and chronic pain

As described above, psychological resilience has been studied as a general process associated with the development and maintenance of healthy adaptation to events (36), or as a cluster of psychological abilities, characteristics and resources (37). It is particularly interesting in the case of patients affected

by chronic pain because it is becoming increasingly seen as an important element in the experience of pain and its self-management (38, 39), and a growing number of studies have investigated the construct of psychologically resilient functioning (40), a psychological factor that can promotes adaptive responses to pain and pain-related negative changes in the patients' quality of life.

Resilience may also play an important (although not clearly defined) role in the development of chronic pain (41). It has been shown that resilience is a personality trait (42), and that being resilient can have a positive impact on recovery and the acceptance of healing processes (39-43), and lead to favourable outcomes after experiencing adversity (44). However, as psychological resilience questionnaires have been used to try to explain acute and chronic stressful life casualties and very different populations (children, families and communities) and settings (see Box 1), there are a number of indication that, when taken in isolation and applied as a single construct as in the case of pain, the word may lose its conceptual meaning and scientific precision (40).

Haase *et al*. (45) has suggested that there is a link between resilience and interoception, thus supporting the idea that people who are less aware of the possibility of internal bodily changes are more susceptible to stress and less capable of coping with stressful events such as pain. Furthermore, another line of research has indicated that chronic pain patients have a poor representation of their affected part as a possible distortion of their body matrix (46), thus suggesting even closer relationships between interoception, a low resilience level and chronic pain (45).

However, this intriguing approach raises some critical points. First of all, it is necessary to establish a clear definition of resilience that that is compatible with IASP definition of pain (Box 2). Secondly, it is necessary to determine how it can be measured in such a way as to distinguish resilient and non-resilient traits, and identify the clinically useful correlations between such measurements and the presence and intensity of chronic pain. Finally, it is necessary to define what resilience means in relation to pain in general, and under particular conditions ranging from the dramatic bodily changes associated with amputation to situations in which there are no evident signs of nervous lesions or disease as in the case of FM.

BOX 1

- Academic Resilience Scale (ARS-30) (Simon Cassidy, 2016) assess resilience in this particular context.
- The Scale of Protective Factors (SPF) (Ponce-Garcia *et al*. 2015) is a comprehensive measurement of resilience.
- Predictive 6-Factor Resilience Scale (Roussouw & Roussouw, 2016) theorised relationship with health hygiene factors.
- Ego Resilience Scale (Block & Kremen, 1996).
- The Resilience Scale, (Wagnild & Young, 1993).
- The Brief Resilience Scale (BRS) (Smith *et al*., 2008) self-rating questionnaire measuring an individuals' ability to "bounce back from stress".
- Connor-Davidson resilience scale (2003) self-report scale within the Post Traumatic Stress Disorder.

Resilience Scale for Adults (RSA) (Windle, Bennett, & Noyes, 2011) (Friborg *et al*. 2003) self-report scale targeting.

BOX 2

In the IASP definition pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Of great importance is the note that follows this definition, where some pivotal clues are stressed: the definition purposely avoids tying pain to the stimulus, the subjectivity of the pain experience, its unquestionable sensory aspect in a part or parts of the body, its unpleasantness and emotional experience. Experiences which resemble pain but are not unpleasant, should not be defined as pain.

The IASP definition of pain states that it is an emotional experience that always carries an aspect of unpleasantness associated with a variety of negative effects on the quality of life. In this context, resilience can be broadly considered as a cluster of psychological abilities, characteristics and resources (37) that can be pitted against pain as a powerful stressor, and further studies can give insights into its psychosocial aspects.

However, to the best of our knowledge, there is no single questionnaire that can be used to investigate resilience in chronic pain patients because, as resilience dynamically changes over time (see Bonanno's graph), it is difficult to use a single measurement to define certain levels of resilience and predict their evolution in such a way as to be able to make decisions concerning therapeutic strategies. Furthermore, other factors influence the level of resilience, such as background (military amputees have a much higher level of resilience than their civilian counterparts) (48, 50) and gender (49, 50).

The loss of a limb is certainly an event that leads to a high level of stress levels, challenges individual coping strategies, and is associated with obvious psychological changes that have emotional, familial and social repercussions on lifestyle and the quality of life. Ocampo *et al*. (47) have suggested that there five stages in post-amputation recovery (mourning for the loss of a limb, shock and denial, anger, depression and, finally, acceptance), and this quite nicely reflects the development of gradually fading phantom limb pain; however, it does not give any information as to why some patients experience pain and phantom pain for the rest of their lives.

Although promising, the clinical applicability of resilience to an objectively stressful event such as an amputation is still shrouded by uncertainty, and is even foggier when comes to phenotyping FM patients. In a very recent paper,

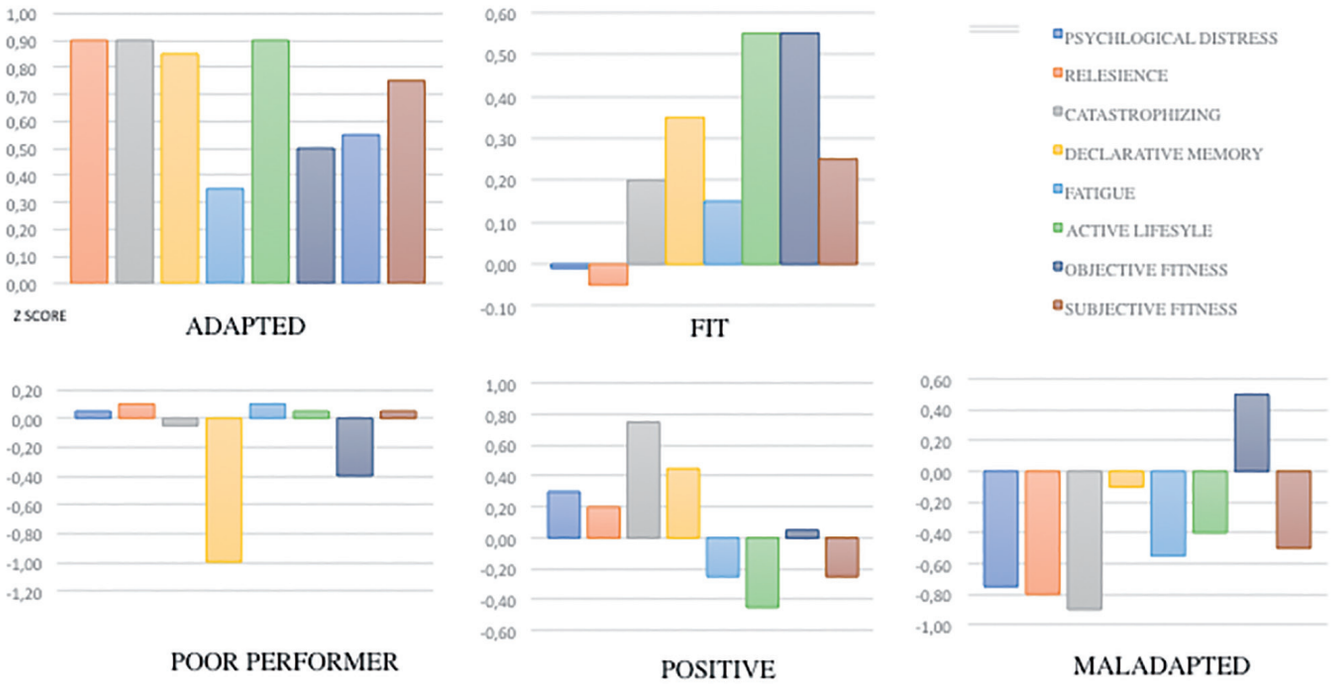
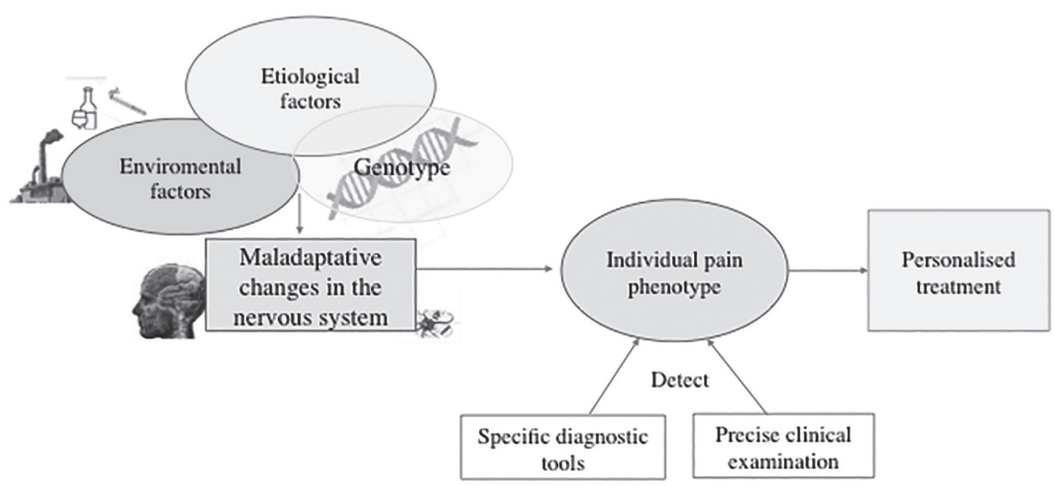


Fig. 2. The five FM profiles. The Adapted profile showed markedly favourable psychological distress, resilience, catastrophising, fatigue and subjective physical fitness, and favourable declarative memory, active lifestyle and objective physical fitness. The Fit profile was characterised by favourable declarative memory, active lifestyle and objective physical fitness. The Poor performer profile showed average scores on all factors, except for declarative memory and objective fitness, which were markedly unfavourable. The Positive profile showed favourable scores on psychological factors and average scores on physical factors. The Maladapted profile was characterised by unfavourable scores on most of the factors, with markedly unfavourable scores for resilience and catastrophising, and average scores for declarative memory.

Fig. 3. Individual pain phenotype requires personalised treatment Neuropathic and central pain are very heterogeneous and are the results of interaction between environmental factors, genotype and initiating disease. Accurate recognition of different pain phenotype will lead to personalised treatment.



Estevez-Lopez *et al*. (51) identify five possible subgroups in terms of adaptation to FM that are highly heterogeneous in terms of modifiable resilience and vulnerability factors (adaptation profiles) and cover a broad range of severity from adaptation to maladaptation (the most unfavourable profile) (Fig. 2). However, as the authors did not use any specific questionnaires to assess resilience, the suggestion that adaptation profiles may help to tailor FM treatments should be taken cautiously (see Box 1). Furthermore, a large number of studies have indicated that FM patients are often characterised by a clinical history of episodes of abuse and difficult social environments (52), situations in which resilience can be of the utmost importance (53) in determining the development of person-

alities susceptible to the development of chronic pain.

A Resilience Scale for patients suffering from chronic musculoskeletal pain (RS-18) has recently been proposed (54), and its validation provided empirical support for the hypothesis that resilience is a protective variable in patients with chronic pain, and could be considered when deciding on possible treatment strategies (44). However, although resilience may be a therapeutic target for chronic pain conditions, it is still an under-developed area of research, particularly in the light of the emerging interactions of positive emotions, physical health, and changes in pro-inflammatory cytokine levels (54). Given the lack of any pharmacological treatment capable of controlling more than 30-50% of the cases of chronic pain, there is a need to discover new therapeutic targets and strategies capable of changing a non-resilient phenotype into a more resilient phenotype (55, 56), especially in the case of chronic pain conditions that cannot be explained by a nerve injury or somatosensory disease inducing maladaptive changes (Fig. 3). This is particularly true of fibromyalgia, which is characterised by a complex combination of positive signs and symptoms that vary enormously from person to person depending on a wide range of pathophysiological changes in which genotype and, more importantly, environmental factors may play a major role. Nevertheless, assessing resilience in maladaptive chronic pain patients can lead to a better understanding of the underlying pathophysiological mechanisms (57) and guide the development of tailored pain medicine (58, 59).

Finally, it is worth mentioning that stressors in general may have bi-directional effects on pain responses, and generate both stress-induced analgesia and hyperalgic reactions. It is not known whether stress directs human neural, endocrine and behavioural responses to chronicity or whether this can be broadly attributed to a more or less resilient personality. One of the major difficulties is to define resilience as it encompasses genotypes, phenotypes and environmental factors. One classic example is the study of Beecher concerning why wounded soldiers request less analgesic treatment than wounded civilians: the motivation-decision model proposed by Howard Fields suggests that this may be due to the soldiers' perceived avoidance of death. In other words, chronic pain can be interpreted as missing a possible reward (hopelessness) or as the worst situation imaginable (catastrophising).

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