Understanding depression and anxiety
Introduction

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Introduction

You will notice that stress forms the backbone of this course. This is no accident, as the role of stress has attracted much attention in the last few decades, and it is now recognised as a powerful factor in the cause of emotional disorders. We start by considering what is meant by the term ‘stress’, how it is perceived, and the evidence that it is a risk factor for the development of emotional disorders. We then move on to look at the biology of stress, in particular how it affects the brain.

The theme of effects on the brain is continued with a consideration of what has been learnt about the brain mechanisms underlying depression from the workings of antidepressants.

Finally, we consider the interaction between genes and the environment, and how this might influence the development of emotional disorders.

The related OpenLearn course Emotions and emotional disorders introduces you to the study of emotions and emotional disorders in the context of our evolutionary heritage, and goes on to consider how we might recognise emotional disorders, together with some of the problems associated with diagnosis and classification.

This OpenLearn course is an adapted extract from the Open University course SDK228 The science of the mind: investigating mental health.
Learning Outcomes

After studying this course, you should be able to:

- describe how stressful life events may be linked to emotional disorders such as depression and anxiety
- describe the main features of the physiological stress response
- evaluate the role of genetic and environmental factors in emotional disorders
- describe the different kinds of biological abnormalities that have been linked to emotional disorders.
1 Understanding the role of stress

It is often the case that those developing depression or anxiety have experienced significant stress in childhood or in adult life or both. A case of work-related stress that precipitated serious depression is described in Vignette 1.

Vignette 1 An experience of stress

The following extract is taken from an interview with a 43-year-old woman, who was diagnosed with depression at 40.

Background: Is a divorced part time carer. Before her depression and suicide attempt she was a workaholic in a job that was becoming more demanding. Her depression required hospitalisation.

‘Work had always been really important to me and I’m more like a perfectionist. So everything has to be a 100%, you know, and all that. And I got made promotion several times with my job, and then suddenly, I think like many companies, people started making people redundant, and requesting people to take on more and more and more. In the end I was doing the job 5 people used to do. I was enjoying it. I enjoyed it to the point where it was just getting, physically it was just getting an impossibility. But I’d always loved my job, but it was then becoming that I was away 5, 6 days a week, getting home and I couldn’t get away from work basically, because I would get back here and there would be faxes and messages and goodness knows what and … A lot of my job was travelling a lot I was covering a huge area, not just the UK. And one day I just sort of came home after I had been away for a week, parked my car outside, sat on the pavement and just broke down, basically.’

(Health Experience Research Group, 2010)

1.1 What do we mean by stress?

We tend to think of ‘stress’ as a state of demand that is likely to stretch us to breaking point, and hence as a bad thing, to be avoided. An image of stress this brings to mind is pulling on a chain with increasing force: sooner or later the chain will break at the weakest link, leading to collapse. However Hans Selye, the distinguished Austro-Hungarian endocrinologist who developed the concept of stress in the 1930s, felt this was a very one-sided view – he regarded stress as ubiquitous and vitally important, calling it ‘the salt of life’ (Selye, 1978 [1956]).

Selye distinguished two kinds of stress:

Within the general concept of stress … we must differentiate between distress (from the Latin dis = bad, as in dissonance, disagreement), and eustress (from the Greek eu = good, as in euphonia, euphoria). During both eustress and distress the body undergoes virtually the same nonspecific responses to the various positive or negative stimuli acting upon it. However, the fact that
The distinction between eustress and distress is not current, but Selye and others found it helpful to understand how stress could be ‘good’ as well as ‘bad’. The critical point that Selye was making is that an understanding of biology by itself may not be enough to understand the effects of stress because the same physiological mechanism underlies both positive and negative stress. Selye’s point about ‘how you take it’ is relevant to the concept of ‘appraisal’ which we cover later in Section 1.4. Selye saw a stressor as anything eliciting the physiological stress or ‘emergency’ response. The stress response is elicited not just in a classic ‘fight or flight’ situation, but also when the body is fighting an infection, and in situations that are stimulating and enjoyable, such as ‘playing a game of tennis, or engaging in a passionate kiss’ (Selye, 1978 [1956]; Figure 1). Emotions such as joy, anger and fear are potent elicitors of the stress response. Expectations play a part in generating stress too. Stress is present, for instance, if people believe – correctly or incorrectly – that something threatening or unpleasant is just round the corner.
Figure 1 Both pleasant (a, b) and unpleasant events or situations (c, d) have the potential to activate the biological stress response.

Despite Selye’s broad definition of stress, when used in the context of emotional disorders, the term is generally taken to mean negative stress (or distress). Unfortunately it is virtually impossible to live a life free from this form of stress and whilst it has been suggested that the experience of mild to moderate levels of stress in early life may ‘inoculate’ animals and people against more serious stress later on (e.g. Maddi, 2006), severe or chronic stress can have very damaging effects, as you will see next.

1.2 Recent life events and stress

Many episodes of depression and anxiety are apparently associated with a severe or chronic stressor. Loss of a loved one, unemployment, divorce, poverty, racism and discrimination, illness, a car accident, being mugged, are just some examples. Research supports this notion. For instance, Kenneth Kendler and his team (e.g. Kendler and Prescott, 2006) found that the onset of episodes of major depression (MD) and generalised anxiety disorder (GAD) was strongly linked to stressful life events in the last month in their study population of women (Figure 2).
Figure 2 Odds ratios for major depression and generalised anxiety disorder among women associated with the occurrence of a life event in the same month. ‘Network’ is a woman’s social network, such as family and friends. An asterisk indicates that the odds ratio for MD or GAD associated with the given life event is statistically significant.

Activity 1 Linking MD or GAD to a stressful life event
Allow 5 minutes

Using the information in Figure 2, which disorder, MD or GAD, do women who have experienced assault tend to develop? Try to explain your answer.

Answer

Odds ratios in Figure 2 indicate the increase in the chances of women experiencing MD or GAD following different life events. After assault, the odds ratio for developing MD is 18, while the odds ratio for developing GAD is 10. Thus after an assault women appear more likely to develop MD than GAD.

The chances of experiencing depression and anxiety are increased if a number of stressful life events follow in quick succession, if events are experienced as severe, and if they involve significant loss or personal humiliation (Kendler et al., 2003).

The chances of experiencing such disorders are also increased if other risk factors are present (Turner and Lloyd, 1995). For instance, in January 2010, the Office for National Statistics (ONS) reported that the number of suicides in the UK had risen sharply since the recession began, reversing the downward trend of the previous decade. Suicides rose by 6% from 5377 deaths in 2007 to 5706 deaths in 2008 among people over 15.

Commenting on these results, Professor Rory O’Connor of Stirling University’s Suicidal Behaviour Research Group said: ‘Sadly this increase in suicide is not unexpected given we know there’s a relationship between past recessions and an increase in suicides … as well as the financial implications, there’s added stress on families and relationships, as well as the loss of social networks to support people’ (Bowcott, 2010).

However, the situation is even more complex because some personality traits can kindle stressful situations. Some stressful life events are independent of our own actions, but in others our actions may have helped create the stressful circumstances.
Activity 2 Stressful life events and our actions
Allow 5 minutes

Can you think of an example of a stressful life event that is independent of, and one that may be dependent on, our own actions?

Answer
Natural disasters such as earthquakes and hurricanes would fall into the first category. Many relationship crises may fall into the second. You may have thought of other examples.

The chances of experiencing the second kind of stressful life event are higher in those with a ‘difficult’ or ‘neurotic’ temperament compared to those with a more ‘easygoing’ temperament (Section 1.5).

1.3 Early life events and stress

One of the most potent factors associated with mental disorders such as depression and anxiety later in life is mistreatment and abuse in childhood (Browne and Finkelhor, 1986; Turner and Lloyd, 1995). This includes sexual abuse as well as physical, mental and emotional neglect or mistreatment.

Child sexual abuse affects at least twice as many females as males and appears to be a particularly powerful risk factor for adult-onset depression (Weiss et al., 1999). It is also a strong predictor of post-traumatic stress disorder (Browne and Finkelhor, 1986). It may therefore be a factor that contributes to the well-established epidemiological finding that women are much more likely to be diagnosed with depression and other emotional disorders than men, not only in England – see Figure 3 – but around the world (Weissman et al., 1996).
Childhood abuse may have psychosocial consequences that increase the risk of depression, as it can lead to shame, humiliation, isolation and an inability to trust others. Another possibility is that, especially if severe and repeated, childhood abuse biologically sensitises the stress response systems of children so that stress is triggered much more easily later on, and for longer periods (Perry et al, 1995).

An important study by Christine Heim and her associates (Heim et al., 2000) showed that the stress response of women who had suffered childhood abuse (sexual or physical) did indeed show evidence of having been 'sensitised'. The women in Heim's study fell into four groups:

1. ELS/MD: those who experienced early life stress (ELS) – that is, were sexually or physically abused as children, and were also diagnosed with major depression in adulthood
2. ELS/no MD: those who were abused in childhood but did not get depression
3. No ELS/MD: those who did not suffer child abuse but had major depression
4. Controls: those with no history of childhood abuse or depression, who acted as a control group.

All the women underwent the Trier social stress test, which involves public speaking and solving arithmetical problems in front of a critical audience. The levels of the stress hormones ACTH (adrenocorticotrophic hormone) and cortisol in the women's blood were measured before, during and after the test, as were their heart rates (Figure 4). When individuals feel threatened the SNS (sympathetic nervous system) is activated and this leads to the release of adrenalin, which elevates heart rate. Stressors also trigger a parallel stress response involving the hypothalamus, which triggers release of ACTH (adrenocorticotrophic hormone) from the pituitary gland, which in turn triggers the release of cortisol from the adrenal cortex.
Figure 4 Mean levels (± SEMs) of (a) adrenocorticotrophic hormone, ACTH, and (b) cortisol, in the blood; (c) heart rate in women who underwent a Trier social stress test. The shaded area shows the duration of the Trier test. Statistically significant differences between groups are indicated on the figure as follows: * between controls and ELS/no MD; § between controls and ELS/MD; ‡ between ELS/no MD and no ELS/MD; † between ELS/MD and no ELS/MD; ¶ between ELS/no MD and ELS/MD.

Figure 4 shows that before the Trier test, the four groups of women did not differ significantly on any of the three measures of stress, but some clear differences emerged during the test.

- Was there a clear difference in any of the stress response measures between women who had and had not experienced childhood abuse?
- Yes, Figure 4a shows that ACTH levels were markedly higher in women who had been abused as children (ELS/MD and ELS/no-MD) than in women who had not been abused (no-ELS/MD and the controls, no-ELS/no-MD).

Women whose stress systems were most reactive in the test were those who had been abused in childhood and were also currently depressed (ELS/MD). They showed the most extreme responses in all three measures – a rise in levels of ACTH and cortisol and an increased heart rate. Thus there is evidence for a marked sensitisation of the stress response system, and a link with depression, in at least some women who experience childhood abuse.

However, note that not all women who experience childhood abuse develop depression (ELS/no-MD group), and not all women who are depressed as adults have experienced childhood abuse (the no-ELS-MD group). This suggests that other risk factors must be operating for depression to develop. There are many possibilities. For those who were abused, the level and kind of abuse may matter. Social and psychological support...
networks available during childhood and adulthood, or genes that make some women more vulnerable to stress or affect other personality factors, could also play a part. Having considered the role of stressful life experiences we next look at how cognitive factors can also play a part in emotional disorders.

1.4 Cognition, appraisal and stress

Psychologists suggest that there are cognitive styles, or ways of thinking, that predispose people to stress and therefore the development of anxiety and depression. Selye’s concept of stress and the idea that ‘it is how you take it’ that is important, informed the work of the eminent American psychologist Richard Lazarus. Lazarus suggested that how an individual interprets or evaluates an event or situation – a cognitive process he called appraisal – plays a critical part in feeling stressed (Lazarus and Folkman, 1984). Imagine that you are travelling in a desert and find your water bottle has been leaking. Half the water is gone: a classic ‘Is the bottle half full or half empty?’ scenario. The amount of water in the bottle is a constant, but one kind of evaluation could well lead to more stress and panic than the other. Lazarus and his colleagues also suggested that people are more likely to suffer from stress when they believe that they lack the resources to deal with difficult events than if they feel confident that they have the resources to cope.

- How is the concept of appraisal relevant to understanding and treating emotional disorders?
- First, it highlights the fact that unhelpful or unrealistic appraisals, rather than particular events or situations in themselves, can cause stress. Second, it holds out hope, as appraisals and styles of appraisal may be amenable to change.

Challenging and re-framing appraisals is a crucial part of some of the strategies used by psychotherapists to help people with emotional disorders, such as in the therapy ‘cognitive behavioural therapy’.

An important element affecting how stressed individuals feel is how much control they think they have: people feel more anxious and frustrated if they feel they cannot predict or control a situation or get the outcomes they want.

This kind of helplessness or hopelessness resembles that of subordinate, defeated non-human animals in status hierarchies (see the related OpenLearn course Emotions and emotional disorders). In humans, it is easy to see how it might arise in an abused child, or in a woman experiencing domestic violence. Circumstances of entrapment and humiliation seem particularly potent in their capacity to trigger severe depression.

Activity 3 How you think and how you feel
Allow 5 minutes

Is there any truth in the assertion that ‘How you think affects how stressed you feel’?

Answer
Yes, ‘appraisal’ – how you perceive events or situations, and how much control you feel you have over them, makes a difference to whether you feel stressed or not.
1.5 Temperament, personality and heritability

Some people seem to have easy-going temperaments and to remain unruffled by the kinds of events or situations that leave others tense and fraught, or upset and tearful. Responses to life events, and differences in cognitive interpretation of negative events, have therefore been linked to personality factors (Hirschfeld and Shea, 1992). Here, personality is understood to mean a person’s attitudes and beliefs as well as aspects of temperament which can be very stable. The topic of ‘trait anxiety’ is discussed in the related OpenLearn course Emotions and emotional disorders.

There is evidence that personality traits are associated with affective and anxiety disorders. For instance neuroticism, the tendency to be emotionally unstable, predisposes to anxiety and depression, while having an easy-going temperament seems to protect against depression (Clark et al., 1994). Also, there is evidence that those who are very dependent on the approval of others, need to maintain tight control of everything, are impulsive or easily angered, cope less effectively with stressors.

All these personality characteristics may result in situations that make life even worse – think of the young man who is quick to anger and assaults a traffic warden who is giving him a parking ticket. He may end up in court, his own actions having landed him in a yet more stressful situation. Thus personality factors have the potential to mediate the relationship between stress and the development of emotional disorders.

1.6 Inheritance of temperament

Why do people have such different temperaments? Our early experiences may well make a significant contribution; however, genetic inheritance undoubtedly contributes to temperamental characteristics.

This is most clearly shown by experiments on animals. A fascinating experiment started in 1959 by the Russian geneticist Dmitri Belayev to tame captive-bred red foxes provides a good illustration of the fact that genetic inheritance affects temperament. In foxes, as in humans, there is variation in temperamental traits, with different individuals behaving differently. Most captive red foxes were either ferociously aggressive towards humans or afraid of them, but a small proportion showed neither of these traits – they showed the desirable trait of lack of fear and aggression towards humans.

In the experimental population, only those foxes that showed this desirable trait were selected for breeding. After repeating the process for 10 generations, 18% of the foxes in the experimental population were tame and happy to be with humans (Figure 5). They approached and licked people, wagged their tails, whined and begged for food. After 20 generations (40 years and 45 000 foxes later!), 35% were tame. The increasing proportion that exhibited the selected trait provided clear evidence that temperamental traits are heritable (Trut, 1999). The proportion showing the trait in the ‘control’ population remained low throughout the study.

Intriguingly, the genes mediating tameness also mediated a dramatic change in the appearance of the foxes. As Figure 5c shows, their coat colours and markings became very similar to those of domestic dogs such as border collies (Figure 5d). Genes affecting one character are often linked to genes affecting other characters, and can be passed on together – that is, genetic inheritance is complex in its effects.
You may feel surprised that, although Belayev and his colleagues bred only from foxes showing the ‘tameness’ trait, after 40 years only around one-third of the experimental population were ‘tame’. In fact, this is not really surprising as a trait of this kind is complex. It is linked to the activity not just of one gene but a whole constellation of genes. It is highly likely that many different genes contribute to the trait of ‘lack of fear and aggression towards humans’, and need to be inherited from its parents for an individual to manifest the trait. By analogy, getting one winning number on a lottery ticket is very common, but to win a substantial prize you need to get many or all numbers correct at the same time, and that is a much rarer occurrence.

### 1.7 Familial inheritance and heritability in humans

Temperamental characteristics and mental disorders frequently run in families. Thus the close blood relatives (children, siblings and parents) of patients with major depression or bipolar disorder are much more likely to suffer from these conditions than people from the general population.

How can it be ascertained what contribution genetic factors make to such disorders? One way is to look at what combinations of genetic factors make it more likely that a person will be vulnerable to environmental factors such as stressful events, and hence to developing disorders such as depression. This approach is discussed later, in Section 3.1.
Another way is to look in detail at precisely how genetic factors act on the brain and body to make a disorder more likely. Here we restrict ourselves to considering, briefly, the issue of heritability (Box 1), which attempts to give a numeric value to the contribution genetic factors make to the development of particular traits or mental health conditions.

### Box 1 Heritability

Heritability is a measure of how much of the variation between individuals in a given character is due to differences in their genes, rather than differences in their environments, in a particular population. It is expressed as a number between 0 (definitely not due to differences in genes) and 1 (wholly due to differences in genes). It can also be expressed as a percentage, from 0% to 100%. Note that a heritability of 0.4 for a disorder such as depression does not mean that 40% of cases of depression are caused by genes, or even that a specific individual’s depression is 40% due to genes. Every case is caused by genes and the environment in combination. The heritability figure of 0.4 means that, within the study population, 40% of the variation in whether people get depression or not is due to differences in their genes.

Trying to put a figure on genetic contributions to characteristics that run in families is, of course, complicated by the fact that inheritance in families can arise from social learning or culture. For instance, the children of Christians tend to be Christians, while those of Muslims tend to be Muslims, but the inheritance of religious affiliation is clearly sociocultural rather than genetic, so in this case heritability is 0 (or 0%) (Box 1).

In many other situations the relative contribution of genes and environment is much less obvious. Epidemiologists who are interested in the genetic basis of disorders have a number of strategies to overcome this difficulty. One important approach is to look at the incidence of a disorder amongst sets of identical twins. Identical twins inherit the same genes from their parents, so any differences between them are likely to be due to environmental effects. Adoption studies involving identical twins have proved invaluable in disentangling genetic and environmental influences.

### Activity 4 Characters of identical twins

Allow 5 minutes

Imagine that a study of identical twins adopted into very different family environments at birth showed that as adults: (i) they were very similar in character X; (ii) they were very different in character Y. Explain, with reasons, what this suggests about the heritability of characters X and Y.

**Answer**

The environment in which the identical twins were raised was very different but their genetic inheritance was the same, so (i) suggests that genes had most impact on the development of character X (i.e. X has high heritability); (ii) suggests that the environment had most impact on the development of character Y (i.e. Y has low heritability).

Using approaches such as these, genetic epidemiologists have estimated that the heritability of major depression is 31%–42% (Sullivan et al., 2000). The heritabilities of
anxiety disorders such as GAD, OCD, specific phobias and panic disorder have a similar range, from 30% to 40% (Smoller et al., 2008). For comparison, the heritabilities of schizophrenia and bipolar disorder are estimated to be 50%–70%.

Their heritability values suggest that both major depression and anxiety disorders are multicausal, since both genetic and environmental factors make substantial contributions. Genetic influences, and the interaction of genetic and environmental factors, will be considered further in more detail later in this course.

But first we will look in more detail at the biological stress response.

## 2 Stress and the brain

Following on from the consideration of stressful life events, and in the knowledge that such events are often linked to the development of depression and anxiety, in this section we look more closely at the biological stress response and its effects on the brain.

The stress response evolved as a coordinated survival reaction to stimuli perceived to be threatening. There are two strands to the stress response. One elicits extremely rapid responses to cope with an emergency. This operates via the SNS and triggers the release of hormones such as adrenalin, which increases alertness. It also increases heart rate so that blood, and the oxygen and nutrients it carries, get to muscles used in running or fighting quickly.

The response is triggered in the first instance by the amygdala, which is of central importance in emotional perception and behaviour, and this can result in the detection of the potential threat and danger before we are consciously aware of it. Of course, in some cases, conscious consideration may convince us that there was no real threat! The amygdala releases CRF (corticotrophin-releasing factor) to stimulate the response from the SNS.

CRF release from the amygdala also triggers the second strand of the stress response – here the CRF signal from the amygdala goes to a brain region called the hypothalamus. The hypothalamus then itself releases CRF as a signal to the pituitary gland, which in turn releases a hormone ACTH (adrenocorticotrophic hormone) into the blood circulation. The main function of ACTH is to signal to the adrenal glands to begin releasing corticosteroids into the blood. This system is called the HPA (hypothalamic–pituitary–adrenal) axis (Figure 6).

If the response is effective (that is, the stressor disappears, or after conscious reflection is judged not to be a danger after all) then body and mind calm down: both the SNS response and the HPA axis become less active, allowing adrenalin levels, heart rate and cortisol levels to return to normal. However, if an external stressor remains, or if an individual continues to feel threatened, the stress response is prolonged and stress becomes chronic. Cortisol and corticosterone are examples of corticosteroids. These are also called glucocorticoids as they affect glucose metabolism.

The effects of prolonged activation of the HPA axis by stressors are of particular interest for understanding depression and anxiety, hence this strand of the stress response will be considered further.

The glucocorticoids produced as a result of HPA axis activity perform a vital function. They mobilise the body’s fat and other energy reserves for release into the bloodstream, where they are then available to sustain the high-energy needs of an individual should there be a prolonged struggle or flight. However, glucocorticoids are damaging to neurons and other
cells if present for long periods and in high concentrations. Thus it is important that levels of glucocorticoids are brought back to normal or ‘baseline’ levels as soon as possible.

A mechanism exists to control the level of glucocorticoids and to switch off further production if it is too high. This mechanism involves the hypothalamus, the hippocampus and the prefrontal cortex (all of which are discussed in the related OpenLearn course Emotions and emotional disorders). Neurons in these brain areas carry special receptors called glucocorticoid receptors (GRs), to which glucocorticoids such as cortisol and corticosterone attach when they are released into the bloodstream. In Activity 6 you will see how glucocorticoid receptors play a crucial part in controlling the HPA axis and hence the stress response, and you will also see what happens when this control fails under conditions of chronic stress.

Figure 6 shows the HPA axis, its links to brain areas such as amygdala, the hippocampus and the prefrontal cortex, and the locations of the GRs.