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Understanding depression and anxiety

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Contents

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 eustress causes much less damage than distress graphically demonstrates that it is 'how you take it' that determines, ultimately, whether you can adapt successfully to change.
>
> (Selye, 1978 [1956]), p. 29)

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).

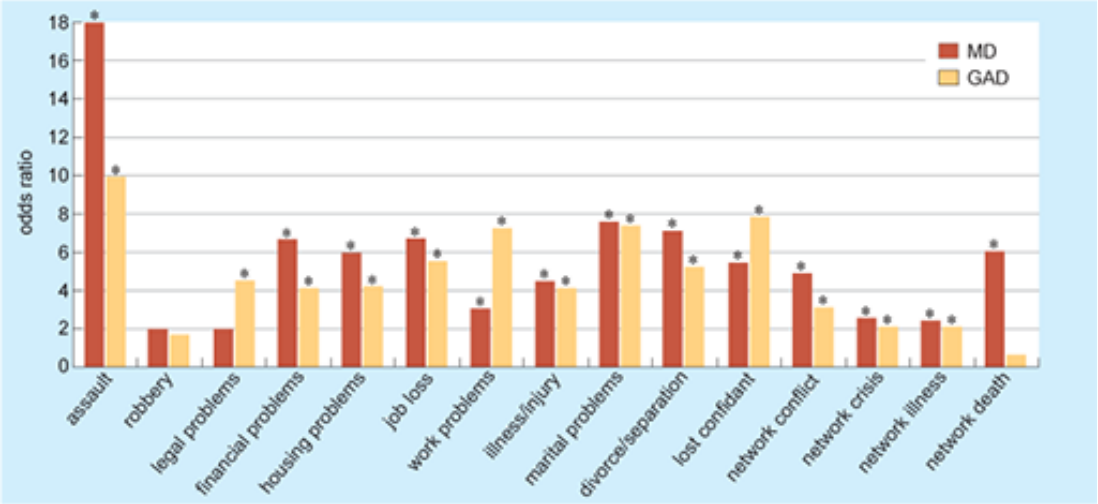

Figure 2 Odds ratios for major depression and generalised anxiety disorder among women associated with the occurrence of a life event in the same month. 'Network' is a woman's social network, such as family and friends. An asterisk indicates that the odds ratio for MD or GAD associated with the given 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).

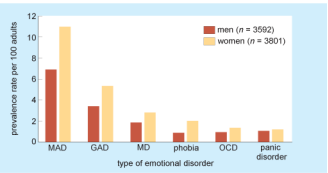

Figure 3 Prevalence rates in England in 2007 of a range of emotional disorders (also known as common mental disorders) by gender. MAD: mixed anxiety and depression; GAD: generalised anxiety disorder; MD: major depression; OCD: obsessive compulsive disorder.

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 (adrenocorticotropic 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.

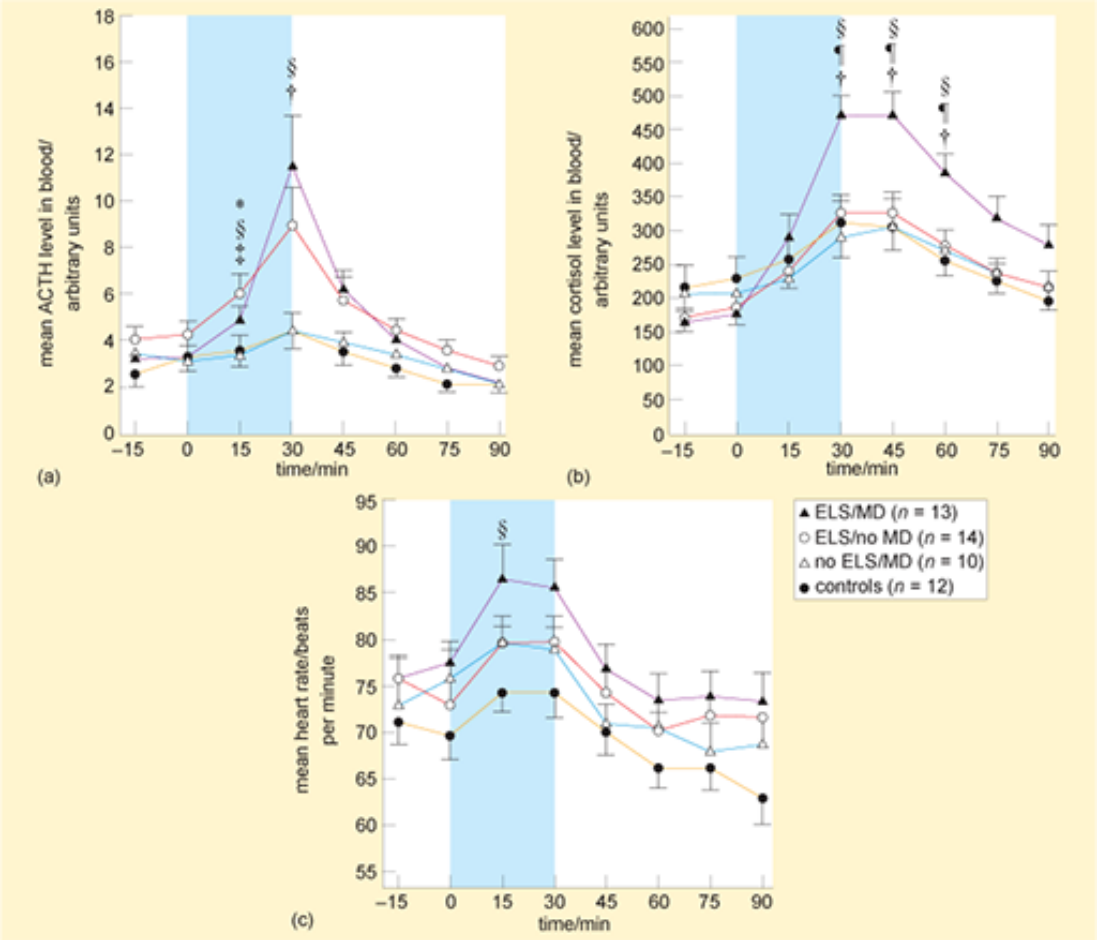

Figure 4 Mean levels (± SEMs)of (a) adrenocorticotrophic hormone, ACTH, and (b) cortisol, in the blood; (c) heart rate in women who underwent a Trier social stress test. The shaded area shows the duration of the Trier test. Statistically significant differences between groups are indicated on the figure 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.

Figure 5 Photos of (a) a wild fox, (b) and (c) foxes bred to be tame and (d) a border collie, illustrating the change in markings on the tame foxes to resemble border collies.

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 to 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.

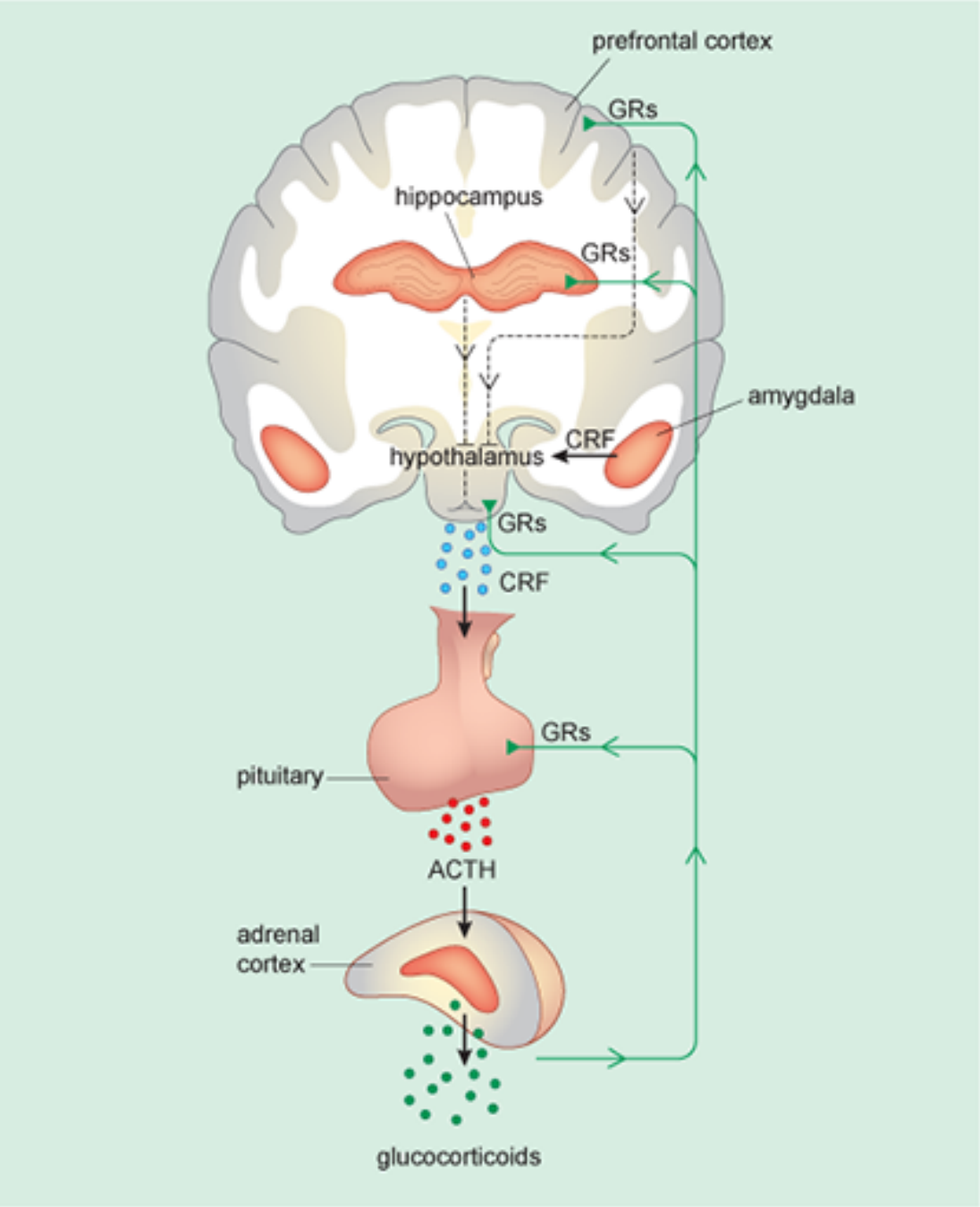

Figure 6 The hypothalamic-pituitary-adrenal (HPA) axis. The end product of a cascade of events is the release of glucocorticoids (such as cortisol) which travel via the bloodstream and attach to glucorcorticoid receptors (GRs, shown as green triangles).The dashed lines show neural connections via which the prefrontal cortex and the hippocampus can influence the activity of the hypothalamus. CRF: corticotrophin releasing factor; ACTH: adrenocorticotrophic hormone.

Activity 5 Cortisol and its inhibitory effect

Allow 5 minutes

Where is cortisol produced, and on which part(s) of the HPA (hypothalamic–pituitary–adrenal) axis does it have an inhibitory effect?

Answer

Cortisol is produced by the adrenal cortex. It has an inhibitory effect on the pituitary gland and the hypothalamus. (*Note*: it also has an inhibitory effect on the hippocampus and the prefrontal cortex but these are not part of the HPA.)

2.1 The operation and control of the HPA axis

The following activity includes an interactive animation that will help you to appreciate the nature of stress and the role played by stress and the hypothalamic–pituitary–adrenal (HPA) axis when we come to consider the aetiology of emotional disorders such as depression and anxiety.

The animation is designed to help you understand the operation of the HPA axis – how it is controlled under normal conditions and how the controls are disrupted under conditions of chronic stress.

Activity 6 The operation and control of the hypothalamic–pituitary–adrenal (HPA) axis

Allow 1 hour

The stress response has evolved to mobilise the body and mind for action when a threat is perceived. The response has two main strands which act in parallel. The first is the sympathetic response, which triggers the release of adrenalin from the medulla of the adrenal gland. The second strand involves the hypothalamic–pituitary–adrenal, or HPA, axis, and triggers the release of cortisol from the cortex of the adrenal gland.

In this activity you will look at the operation and control of the HPA axis in three different conditions – first, under normal relaxed or baseline conditions; second, under normal conditions when there is an episode of stress which is resolved; and third, under conditions of continual or chronic stress when regulation of the HPA axis breaks down.

Overview of the HPA axis flow diagram

Video content is not available in this format.

Baseline, acute and chronic stages

Video content is not available in this format.

Re-run of HPA animation stages

Baseline

Video content is not available in this format.

Acute

Video content is not available in this format.

Chronic

Video content is not available in this format.

HPA axis components: more information

Interactive content is not available in this format.

Identify two factors from the list below that would help to bring cortisol levels back to baseline levels after experiencing a stressful event.

- ☐ (a) The positive feedback loop.
- ☐ (b) Stimulation by the amygdala.
- ☐ (c) Enzymes in the blood that break down cortisol.
- ☐ (d) The negative feedback loop.
- ☐ (e) The secretion of ACTH.

Identify the correct statements about cortisol from the following:

- ☐ (a) Cortisol is released upon stimulation of the adrenal cortex by ACTH.
- ☐ (b) Cortisol is released upon stimulation of the adrenal cortex by CRF.

  Go through the sequences showing the acute and chronic stress conditions again.
- ☐ (c) Cortisol attaches to glucocorticoid receptors on the adrenal cortex.

  Go through the sequences showing the acute and chronic stress conditions again.
- ☐ (d) Cortisol has an inhibitory effect on secretion of ACTH by the pituitary.
- ☐ (e) Cortisol attaches to glucocorticoid receptors.

Cortisol acts via glucocorticoid receptors to inhibit the activity of the HPA axis, so less cortisol is secreted. Why does cortisol become less effective in inhibiting the HPA axis during chronic stress? Select the best explanation from the list below.

- ○ (a) Because the high levels of cortisol present during chronic stress damage the glucocorticoid receptors via which cortisol exerts an inhibitory effect on the HPA axis.
- ○ (b) Because there is less cortisol present during chronic stress to exert an inhibitory effect on the HPA axis, including on the hypothalamus and the pituitary.
- ○ (c) Because there is more activity in the HPA axis during chronic stress, as the axis is constantly being stimulated by stressors to release CRF, ACTH and cortisol.

Answer

Statement (a) provides the best explanation for why cortisol becomes less effective in inhibiting the HPA axis during chronic stress. Statement (b) is incorrect because there is more, not less, cortisol present during chronic stress. Statement (c) is correct in that there is more activity in the HPA axis during chronic stress, but it does not explain why cortisol fails to control the activity of the HPA axis.

Select, from the following, the statement(s) that explain why the high activity of the HPA axis during chronic stress can affect how we feel and act.

- ☐ (a) The adrenalin secreted makes us more alert and makes our hearts beat faster.
- ☐ (b) High levels of cortisol secreted during chronic stress can damage neurons in the hippocampus, which can affect conscious memories, including recall of events and facts.
- ☐ (c) High levels of cortisol secreted during chronic stress can damage neurons in the prefrontal cortex, which can affect our ability to evaluate and plan, and to make judgements.
- ☐ (d) The amygdala is less active when the HPA axis is more active, so we are less likely to react to stressors.

2.2 Relating stress and depression biologically

Evidence from studies on humans suggests that dysregulation (the breakdown of regulation) of the HPA axis due to chronic activation of the axis is linked to depression.

For instance, high levels of cortisol are found in the urine, blood and cerebrospinal fluid (CSF) (the fluid that bathes the brain and spinal cord) of many untreated depressed patients compared to controls who are not depressed.

- What do high levels of cortisol suggest?
- They suggest *hyperactivity* in the HPA axis of those who are depressed, as cortisol levels are high and uncontrolled.

- Do these results tell us if high levels of cortisol cause depression?
- No – they tell us there is a correlation. The depression might have led to high cortisol levels, rather than vice versa.

However some evidence that high levels of glucocorticoids such as cortisol can actually *cause* low mood in people is provided by Cushing's disease. This disease is sometimes caused by a tumour in the pituitary gland, which consequently secretes extra ACTH, which then stimulates the adrenal cortex to secrete more cortisol. If the level of cortisol is reduced (for instance by using drug treatment), the depression lifts.

- Why does this suggest a causal role for high levels of cortisol in depression?

- In Cushing's disease the direction of causation is fairly certain: high levels of cortisol lead to depression. The fact that reducing cortisol levels lifts depression strengthens the case that cortisol plays a causal role.

As well as high cortisol levels, CRF concentrations in the cerebrospinal fluid of depressed patients are also high, compared to those who do not have depression.

- Where is CRF produced?

- CRF is produced by neurons in the hypothalamus, and also in the amygdala; both are involved in the activating the stress response in the HPA axis.

This fits in with the finding from post-mortem studies that the brains of people with depression have more CRF-producing neurons in the hypothalamus compared to controls. Moreover, if CRF is injected into the brains of rats, these animals show some behaviours characteristic of depression such as insomnia, decreased appetite, decreased interest in sex, and increased anxiety (Arborelius et al., 1999). All these findings lend weight to the idea that hyperactivity in the HPA axis plays a causal role in depression and anxiety.

2.3 Effects on the hippocampus and prefrontal cortex

As you will have seen from Activity 6, the constant barrage of glucocorticoids during chronic stress is deleterious for glucocorticoid receptors, which play a critical role in controlling the stress response. Uncontrolled, high levels of glucocorticoids are also thought to weaken neurons in the hippocampus and the prefrontal cortex, making them more susceptible to damage or death.

- Based on what you learned about these brain structures in Activity 6, what would be the psychological effect of:

  a. hippocampal damage?

  b. prefrontal cortex damage, of the kind caused by HPA hyperactivity?

- a. It might affect our ability to retrieve conscious memories of facts or events or the ability to form new ones.

  b. It would become more difficult to make judgements and decisions; to concentrate on a task in hand, and to exert conscious control over behaviour, thoughts or impulses.

There is evidence from brain imaging data that the volume of the hippocampus, and of areas in the prefrontal cortex, is lower in people with depression (Campbell et al., 2004; Drevets et al., 1997). There is also evidence that activity in the prefrontal cortex is reduced in areas that are thought to be implicated in the control of emotions (Drevets, 1998). Via its effects on the hippocampus and the prefrontal cortex, stress may thus cause some of the symptoms of depression, such as difficulties in learning, remembering and concentrating, and the inability to control negative thoughts and

emotions (see Lewis Wolpert's account (Vignette 1) and diagnostic criterion 8 in DSM-IV-TR, described in the related OpenLearn course *Emotions and emotional disorders*).

Depression and anxiety often comorbid, so it is not surprising that anxiety too has links to stress – as considered in the next section.

2.4 Relating stress and anxiety biologically

Anxiety is linked to fear, and the amygdala plays a central role in attaching emotional significance to what we perceive and 'deciding' if fear, and hence 'fight or flight', is an appropriate reaction. It is important for animals to remember threatening situations and to avoid them, hence the amygdala also plays a crucial role in consolidating and storing memories of emotionally arousing, stressful experiences, including unconscious fear memories. As you saw above, it is the amygdala that initiates the stress response. But how is it itself affected by the consequences of that stress, and how might this be linked to anxiety?

A part of the amygdala, the basolateral amygdala (BLA), is well-supplied with glucocorticoid receptors, raising the possibility that the amygdala could be directly affected by a rise in glucocorticoid levels following stress. It is tempting to speculate that the kind of effect described is relevant to disorders such as post-traumatic stress disorder (PTSD), which can result from a single, traumatic event. Chronic stress is also known to 'boost' dendrite formation in the amygdala in a similar way to that shown for acute stress (Mitra and Sapolsky, 2008). Dendrites are the part of neurons (brain cells) that receive incoming signals or information from other brain cells. Therefore the more dendrites a neuron has, the more signals (or synaptic inputs) from other neurons it can receive. Clearly the amygdala is profoundly structurally changed by stress, and as you will see below, this leads to it exerting a more powerful influence on other parts of the brain.

The amygdala is also rich in receptors for the inhibitory neurotransmitter GABA. A neurotransmitter is a substance or chemical that neurons also use to talk to one another since these chemicals can cross the gaps that exist between neurons in the brain. Stress is known to lower levels of the neurotransmitter GABA and hence GABA inhibition on the amygdala (Roozendaal et al., 2009). GABA is the main inhibitory neurotransmitter in the brain meaning that when neurons receive a GABA signal from other neurons this signal depresses or inhibits their activity. Overall therefore you can see that reducing the amount of this inhibitory neurotransmitter will have a net effect of increasing activity in the amygdala. Some drugs (such as benzodiazepines) prescribed to reduce anxiety bind to GABA receptors and reinforce the effects of GABA.

A hyperactive amygdala may contribute to the well-established vividness of emotionally significant memories, as the amygdala sends powerful inputs to the hippocampus to give emotional flavour to conscious memories. A more active amygdala, via its triggering effects on the HPA axis, might also intensify the stress response further. It might also underlie the emotional symptoms seen in affective and anxiety disorders.

Next, the amygdala's activity in humans with generalised anxiety disorder (GAD) is considered.

2.5 The amygdala and generalised anxiety disorder

There is some evidence that the amygdalas of people with generalised anxiety disorder (GAD) may be abnormally active, so that they feel anxious and fearful without apparent reason. For instance, Nitschke et al. (2009) recorded activity in the amygdalas of patients with GAD and controls without GAD as they looked at images of unpleasant objects such as mutilated bodies, or neutral objects such as fire hydrants.

A few seconds before seeing the images, all participants received a cue to let them know whether to expect an unpleasant or neutral photograph. Nitschke et al. found that the amygdala activation of those with GAD did *not* differ significantly from that of controls (without GAD) when they were *viewing* unpleasant or neutral images (Figure 7).

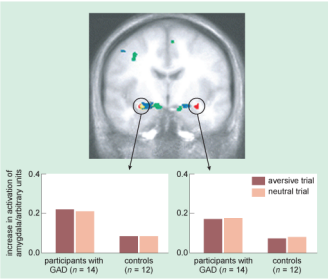

Figure 7 Anticipatory amygdala activation differentiating participants with generalised anxiety disorder (GAD) and healthy comparison subjects. Participants with GAD had significantly greater activation in the amygdala on both sides of the brain compared to healthy controls without GAD. This was the case both in aversive trials (in which a cue predicting an aversive image was presented) and in neutral trials (in which a cue predicting a neutral image was presented. (The amygdalas are circled.)

However, the amygdalas of GAD patients became much more active than those of controls when they were shown cues signalling that a negative or neutral image would be appearing.

- What does this suggest?
- It suggests that anticipation stirs up a high level of activity in the amygdala of those with GAD. They become abnormally anxious even when what is being anticipated is not in the least unpleasant.

Currently it is not known why the amygdalas of patients with GAD are over-active. As GAD has a heritability of 30%–40%, genetic factors clearly play some part. However, stress and its 'boosting' effect on the amygdala, discussed above, may also be important.

3 The life cycle model of stress

As you have seen, the overall picture emerging from studies of how stress affects the brain is that chronic or repeated exposure to stress can affect the structure of several areas of the brain via the action of glucocorticoids released during activation of the HPA axis.

Recently, researchers have begun to ask whether this is too simplistic and whether the effects of stressful or traumatic experiences depend on the *age* at which they occur.

Developmental biologists have long known that environmental (including social) factors can have particularly long-lasting effects if experienced early in life or at other 'vulnerability periods'. Early effects, which can set an individual on a particular developmental path for life, have been described as 'programming effects'.

The life-cycle model of stress proposes that stressful experiences will have a high impact on brain structures that are growing most rapidly at the time of the stress exposure (in young individuals), or that are undergoing age-related decline (in adult and old individuals).

As Figure 8 shows, in humans, different brain structures develop or reach maturity at different ages. This is certainly true of the three brain regions we have already identified as having an important role in the control of the HPA axis, and which are therefore of particular interest – the hippocampus, the prefrontal cortex and the amygdala.

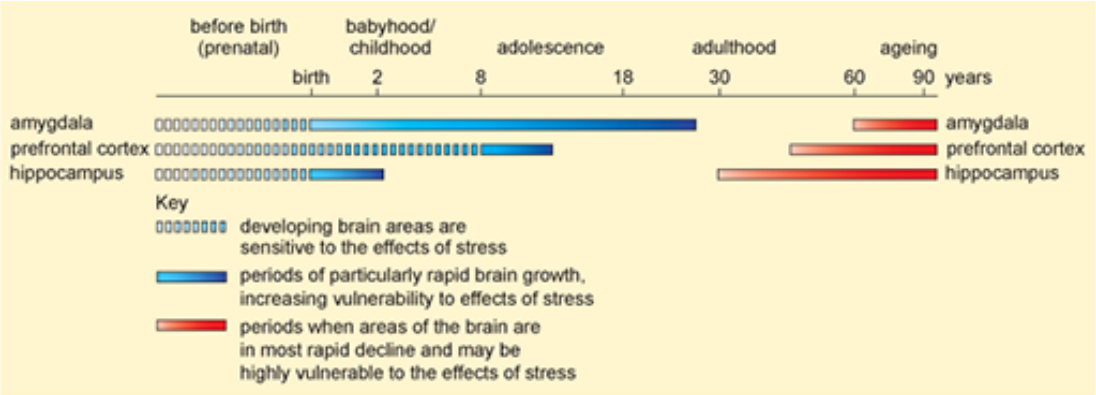

Figure 8 The effects of stress on the brain may in part depend on the stage of growth and development of particular brain areas during the human lifespan.

- Which areas of the human brain are developing or growing rapidly in the period:

  a. prenatally
  b. from birth to 2 years
  c. between 11 and 12 years?

- a. The hippocampus, prefrontal cortex and amygdala.
  b. The hippocampus and amygdala.
  c. The prefrontal cortex and the amygdala.

Effects on the hippocampus, which in humans is actively growing prenatally and after birth, have been of particular interest because of its importance in the control of the HPA axis.

Studies have shown that if stress occurs when participants or subjects are young, damage to the hippocampus and the subsequent effects on behaviour are indeed long-lasting and difficult to reverse. But if stress occurs in adulthood, the effects, even of chronic stress, are reversed after only a few weeks of non-stress.

Age-related effects were found by McCauley et al. (1997) in a study of more than 1900 women: they found that in childhood, but not adulthood, sexual or physical abuse was a strong predictor of increases in depression and anxiety.

How might the link between child abuse and depression arise? In Activity 6 you saw that the undamaged hippocampus has an important role in controlling the HPA axis and calming the stress response. Early damage to the hippocampus, as a result of severe or prolonged stressful experiences such as childhood abuse, has potentially long-lasting effects on control of the stress response.

- What is a human example from earlier in this section where adverse early experience was linked to an over-active stress response?
- Women who had been abused as children had a stress response that was over-active during the Trier social stress test, compared to women who had not been abused in childhood.

A poorly functioning hippocampus may thus be a ‘vulnerability factor’ or ‘diathesis’, for depression when further stress is experienced. Such stress would trigger a badly controlled stress response which could further damage the hippocampus and other brain structures and could predispose to depression. Repeated episodes could lead to significant changes in the volume of the hippocampus and other brain areas.

- Can you be sure that early life stress is the only factor contributing to small hippocampus size and dysfunction?
- No, it is crucial to recognise that you cannot. It is possible that other influences such as genetic factors also influence hippocampus size and dysfunction.

The life-cycle approach thus promises to add a valuable perspective to research on the aetiology of affective and anxiety disorders, as a very brief consideration of another example, to conclude this section, will confirm.

Hall (1998) suggested that if different parts of the brain are vulnerable to stressful, adverse circumstances at different ages, different mental disorders might be associated with stressful experiences at different ages. Thus stress at the time of rapid hippocampal development might lead to different emotional disorders than stress at times of rapid prefrontal cortex development.

Some recent human data seem to offer support for this hypothesis: women who experienced trauma before the age of 12 years had increased risk for major depression, whereas women who experienced trauma between 12 and 18 years of age more frequently developed PTSD (Maercker et al, 2004).

More longitudinal studies of individuals are clearly needed to fully explore the potential of the life-cycle approach.

3.1 Adaptive value of developmental programming of stress

It has been tacitly assumed in the preceding section that the effects of stress on the brain are disadvantageous. However, there is another view, which makes sense if we consider brains as 'survival machines' that evolved to be moulded by experience. Our ancestors must have experienced stress and difficulty in their early lives, so it seems plausible that the developing brain evolved to cope with maltreatment.

From this view, early stress might trigger *adaptive* changes in the brain – changes that allow an individual to survive and reproduce in a dangerous world. Thus, an intense 'fight or flight' response, and constant alertness, might be exactly what is needed in some circumstances. This programme or strategy might give an individual an advantage in a dangerous, unpredictable environment.

Unfortunately, there is a dark side to this postulated adaptation as high levels of vigilance and stress-responsiveness do physiological and psychological damage – in humans they are associated with hypertension, obesity, increased risk of suicide, accelerated aging and degeneration of brain structures, including the hippocampus. However, if survival and reproduction were enhanced by this strategy more than by the 'laid-back' alternative, the strategy would have to have been favoured in some situations.

From what has been described so far about stress, it is clear that an understanding of the effects of stress on the brain sheds a valuable light on the aetiology of depression and anxiety. But this is not the only knowledge of brain function that is important in this regard, as we shall now see.

4 Insights from antidepressants

Antidepressant drugs (also known as antidepressant medications or ADMs) were discovered completely by accident in the 1950s, starting a revolution in the treatment of affective disorders. The fact that they were effective in helping many people who were depressed led to a major research effort to find out how they worked. As often happens in science, research into *how* the drugs work happened after the discovery that they *did* work.

This research has led to a number of influential hypotheses that attempt to explain the brain bases of such disorders. We shall consider three of these hypotheses here: the monoamine hypothesis, the neurotrophic hypothesis and the network hypothesis. Reserpine was isolated in 1952 from the dried root of Rauwolfia serpentina, a species of flowering plant also known as sarpaganda or 'snakeroot' in India. It was an ancient remedy for insanity, fever and snakebite. Apparently Gandhi used it as a tranquilliser.

4.1 The monoamine hypothesis of mood disorders

In the 1950s it was noticed that around 20% of those patients prescribed the drug reserpine, used at the time to control high blood pressure, developed severe depression as a side effect.

It was subsequently discovered that reserpine depletes a group of neurotransmitters called monoamines, which include serotonin, noradrenalin and dopamine. Recall from earlier in this course that neurotransmitters are chemicals that neurons use to communicate with one another. Once neurotransmitter is released into a gap between neurons it must effectively bind to (join on to) an adjacent neuron in order to pass on its message. The point where it binds is known as a 'receptor'. Every neuron therefore has a multitude of receptors for receiving neurotransmitter molecules. These receptors are like the glucocorticoid receptors that you saw in Activity 6.

Reserpine actually works *inside* neurons by preventing monoamines from being taken up into vesicles, leaving them vulnerable to being broken down inside neurons. Vesicles are small 'bubbles' inside neurons in which neurotransmitters are stored after they are made by the neuron and before they are released into synaptic gaps, the gaps between neurons – see Figure 9.)

- What are the consequences if reserpine stops monoamine neurotransmitter from entering its vesicles?
- There will be less of it available for release into the synaptic gap. So communication between neurons using this neurotransmitter will be hampered – cells are not able to signal to one another using this particular signal as effectively.

Around the same time it was noticed that tuberculosis patients, prescribed a different drug, isoniazid, sometimes experienced a *lifting* of pre-existing depression. Isoniazid inhibits (slows down or prevents the activity of) the substance monoamine oxidase (MAO). MAO is important because it breaks down monoamine neurotransmitters. As MAO destroys monoamines, inhibiting MAO would have the net effect of *increasing* the levels of monoamines available for neuron to neuron communication.

Such monoamine oxidase inhibitors (or MAOIs) became the first generation of antidepressants.

Subsequently it emerged that there was yet another way that available monoamine levels might increase: imipramine, another antidepressant, inhibited the *reuptake* of serotonin and noradrenalin that had been released into the synaptic gap (Figure 9). Reuptake is a clever process by which neurons try to reuse the neurotransmitter they have released. They simply take it back into themselves via special reuptake channels and try to package it neatly back into the vesicles (or storage bubbles) ready to be released the next time the neuron needs to signal to another neuron.

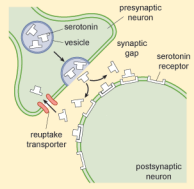

Figure 9 The serotonin synapse. Serotonin secreted by a presynaptic neuron into the synaptic gap binds to receptors on the postsynaptic neuron to affect the activity of the postsynaptic neuron. The postsynaptic neuron's response depends on the amount of serotonin in the synaptic gap. Serotonin levels in the synaptic gap fall partly because reuptake transporters take back the neurotransmitter into the presynaptic neuron.

- What effect would inhibition of reuptake have on neurotransmission involving monoamines such as serotonin and noradrenalin?
- It would increase the amount of monoamines in the synaptic gap, so it would enhance neurotransmission as more would be available to bind to receptors enabling the process of neuron to neuron communication.

These findings about monoamines caused much excitement and led to the monoamine hypothesis of mood disorders. This postulated that monoamine levels have a *primary* role in causing depression, as lowering the levels of monoamines causes depression, while raising them lifts depression (see Hirschfeld (2000) for an overview). The mechanism postulated for this is shown in Figure 10.

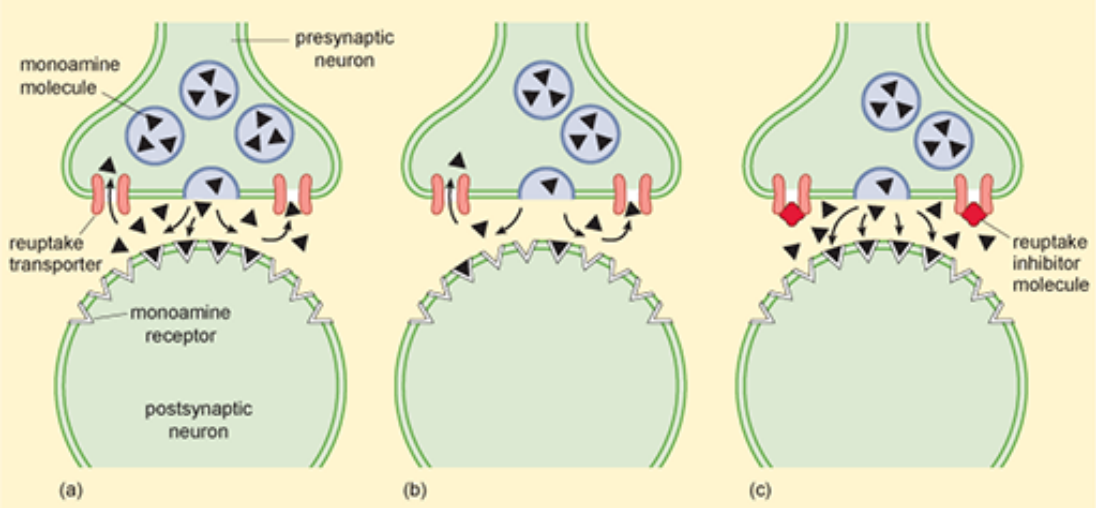

Figure 10 The monoamine hypothesis of mood disorders. (a) In normal brain, monoamine molecules are released and bind to receptors on the neighbouring neuron; (b) In

depression, fewer monoamine molecules are available for binding to receptors, leading to a mood disorder; (c) Treatment with a reuptake inhibitor (the red shape blocking the reuptake transporter channel; here the SSRI Prozac®) increases the number of monoamine molecules in the synaptic gap, so more are available to bind to receptors on the neighbouring neuron. This corrects the mood disorder.

ADMs that inhibit the reuptake of specific monoamines such as serotonin (SSRIs, selective serotonin reuptake inhibitors), noradrenalin (noradrenergic reuptake inhibitors, NRIs), or combinations of monoamines such as serotonin and noradrenalin (serotonin noradrenergic reuptake inhibitors, SNRIs) are nowadays amongst the most prescribed drugs in Western societies, showing that the biomedical approach, and the monoamine hypothesis, still have a powerful influence on the treatment of depression. This is, in part at least, because many people see drugs as a 'quick fix' for depression and there is pressure to prescribe them.

Activity 7 Neurotransmitters and mood disorders

Allow 5 minutes

Name the main neurotransmitters implicated in the monoamine hypothesis of mood disorders. Are the levels of these neurotransmitters higher or lower in people who are depressed?

Answer

Serotonin and noradrenalin. Their levels are lower in those who are depressed.

4.2 Evidence for the monoamine hypothesis

Serotonin is eventually broken down by the body and new serotonin is made by neurons. The breakdown products can be detected in the cerebrospinal fluid (CSF), which bathes the brain and spinal cord. Levels of serotonin breakdown products appear to be low in the CSF of people suffering from serious depression.

- What do low levels of serotonin breakdown products suggest about levels of serotonin in the brain?
- That levels of serotonin in the brain are low – the less there is, the less there is to break down.

Other evidence supporting the monoamine hypothesis comes from post-mortem studies of the brains of depressed people who unfortunately committed suicide. Some studies have found abnormally high numbers of serotonin receptors in the prefrontal cortex in suicide cases (Stanley and Mann, 1983; Yates et al., 1990). The significance of increased numbers of serotonin receptors in the brain is that it may enhance neuron to neuron communication when serotonin levels are low, by facilitating the capture of as much of the available serotonin as possible.

However, such effects are not always found in those who are depressed or have committed suicide. It has also become clear that not all those with depression respond to antidepressants such as SSRIs. One possibility is that the category of 'major depression' lumps together different kinds of depression (for instance early onset, late-onset and chronic or recurrent), which may differ in their biological bases. However, any such

differences are not currently well-understood, in part because they have not been well-explored.

4.3 Tryptophan depletion experiments

While the monoamine hypothesis still underlies the treatment of depression, researchers now consider that, in its original form at least, it is too simplistic to explain the complex aetiology of depression.

The hypothesis postulates that low levels of monoamines cause depression, and as we have seen in Section 4.2, there appears to be some evidence for this. However investigations into the link between monoamine levels and depression were typically carried out on people who were depressed at the time.

- Why might this be a problem when studying, for instance, serotonin levels in depressed people?
- Because cause cannot be distinguished from effect. Low serotonin levels in depressed people could be a *cause* of depression, but they could also be a *result* of depression. Or some unknown, third factor could underlie both depression and low serotonin levels.

Researchers have since tried to clarify the relationship between low monoamine levels and depression experimentally, by depleting the levels of monoamines in the brains of participants.

Serotonin is manufactured in the body from a chemical commonly found in the diet; the amino acid tryptophan. Tryptophan is found in protein-rich foods, including meat, eggs, cheese and soybeans.

By feeding participants a special, otherwise well-balanced, diet free of tryptophan it is possible to reduce serotonin levels in their brains. The levels of the other monoamines, noradrenalin and dopamine, can also be depleted using similar techniques. Amino acids are the building blocks of proteins. Proteins are molecules that contribute to the structure and functioning of all our cells, including our neurons.

The findings of a meta-analysis by Ruhé et al. (2007) on the results of studies of monoamine depletion are summarised in Table 1. (A meta-analysis is discussed in the related OpenLearn course *Emotions and emotional disorders*.) The groups listed in Table 1 are:

> Group 1 – healthy participants who do not, and have never had, major depression (MD), and have no family history of MD
>
> Group 2 – Healthy participants who do not, and have never had, MD, but do have a family history of MD
>
> Group 3 – Patients in remission from MD who are not currently taking antidepressants
>
> Group 4 – Patients in remission from MD who are currently taking antidepressants.

Table 1 Reaction to monoamine depletion.

	Participants			
	Group 1	**Group 2**	**Group 3**	**Group 4**
Depletion of tryptophan/ serotonin	No lowering of mood	Slightly lowered mood	Moderate decrease in mood	Induced relapse in those taking antidepressants that affect the serotonin system (such as SSRIs and SNRIs)
Depletion of noradrenalin/ dopamine levels	No lowering of mood	Slightly lowered mood	No lowering of mood	(no studies were available in this category)

Activity 8 Serotonin levels and mood

Allow 5 minutes

Do any of these results (Table 1) suggest that lowering serotonin levels causes a lowering of mood or results in depression?

Answer

Patients in remission from MD who were taking antidepressants such as SSRIs and SNRIs that affect the serotonin system (Group 4) were likely to have a relapse if tryptophan/serotonin was depleted. Patients in remission from MD, but who were not currently taking antidepressants (Group 3) were also likely to experience low mood if serotonin was depleted. Participants (Group 2) who had a family history of depression showed slightly lowered mood. Thus lowering serotonin levels can have an effect on mood, albeit to different extents.

However, healthy participants without a personal or family history of major depression (Group 1) showed no mood changes, so serotonin depletion did not lower mood in everyone.

Overall, therefore, the results in Table 1 do not suggest a direct or consistent link between monoamine levels and major depression.

Activity 9 Analysing tryptophan depletion

Allow 10 minutes

Booij et al. (2002), also analysed studies on tryptophan depletion, showed that (a) having had previous depressive episodes, (b) being female, (c) having had treatment with an SSRI, and (d) having a history of suicidal thoughts or attempts, were all strong predictors of whether tryptophan depletion (and hence serotonin depletion) would depress mood.

Consider Booij et al.'s suggestions above. Do any of them chime with any of the findings shown in Table 1?

Answer

Yes, (a) is consistent with the lowering of mood of patients in Group 3 and Group 4; (c) is consistent with the relapse of patients in Group 4.

One possibility is that a depressive episode changes the serotonin system in some way, making a person more vulnerable to the effects of future changes in serotonin

levels. A related possibility is that a subgroup of those with depression have a vulnerability or diathesis, due to their genetic make-up, that affects the workings of the serotonin system, making them particularly susceptible to depression when serotonin levels are depleted.

Is there any information in Table 1 which might fit in with this?

Answer

Yes – the finding that people in Group 2, who have not experienced major depression themselves but have a family history of depression, experience some lowering of mood following serotonin depletion.

To conclude, tryptophan-depletion experiments suggest that serotonin depletion has some effects on mood, but that there is no simple relationship between levels of monoamines and depression.

The next section considers an even more significant problem with the monoamine hypothesis, one that has fuelled much research and has led to a more sophisticated chemical and molecular hypothesis for the aetiology of depression.

4.4 The neurotrophic hypothesis of mood disorders

The most significant problem with the monoamine hypothesis in its original form is that, even though ADMs such as SSRIs raise the levels of serotonin in the brain almost immediately, it is many weeks before depressive symptoms are eased (Duman et al., 1997). Clearly, such a long delay is incompatible with the idea that monoamine levels *per se* are linked to mood.

What might be the reason for the delay? One influential idea is that processes such as the birth of neurons (or neurogenesis), or the growth or remodelling of connections between neurons, or changes to the number of receptors, which take time, are involved.

A class of brain chemicals called brain growth factors may play an important part in this. Such chemicals ‘nurture’ existing neurons and promote neurogenesis. Brain-derived neurotrophic factor (BDNF), one of these brain growth factors, is known to operate in many areas of the brain, and significantly for our purposes, this includes the hippocampus and prefrontal cortex, which we already know are implicated in affective disorders. (Neurotrophic means, literally, ‘brain-feeding ‘ or ‘brain- nurturing’.)

4.5 Depression and levels of BDNF

As with monoamine levels, researchers have tried to establish whether there is a relationship between levels of BDNF and depression. BDNF levels in the blood of patients with major depression are abnormally low (Sen et al., 2008), and post-mortem studies show low levels of BDNF in the hippocampus and prefrontal cortex of depressed patients (Martinowich et al., 2007).

Such findings suggest that BDNF levels are correlated (associated) with mood, and have led to the neurotrophic hypothesis of mood disorders. In essence, the hypothesis states that ‘reduced brain BDNF levels predispose to depression, whereas increases in brain BDNF levels produce an antidepressant action’ (Duman and Monteggia, 2006). This may sound like a remarkably similar approach to that of the monoamine hypothesis, in that the

level of a neurochemical, or neurotransmitter, in this case BDNF, again seems the focus of a hypothesis to explain depression. Indeed the hypothesis has been criticised for this limited viewpoint on aetiology.

However, a major difference between the simple monoamine hypothesis and the neurotrophic hypothesis is that levels of BDNF have been linked to a complex series of processes involving the birth and death of neurons in some parts of the brain, and the experience of stress has been linked to such effects. Hence there is a strong potential for psychosocial factors to link into the neurotrophic model, as you will see now.

4.6 Stress, depression and neurogenesis in the hippocampus

Duman et al. (1997, 1999) suggested that the development of depression was likely to involve processes that affected plasticity in the brain. Plasticity essentially means remodeling. Several brain areas including the prefrontal cortex and hippocampus are likely to be affected, but Duman and his colleagues focused their research on the hippocampus for a number of reasons. First, it had been discovered in the 1990s that, unusually for a structure in the adult human brain, the hippocampus continues to exhibit neurogenesis, making it a good candidate for the study of any changes in neurogenesis associated with depression or antidepressant treatment.

Second, there is evidence to suggest that neurogenesis in the hippocampus is highly susceptible to the effects of stress: especially when severe or prolonged, stress can inhibit neurogenesis and accelerate cell loss in the hippocampus. This effect appears to be due in large part to the effects of hormones such as cortisol (a glucocorticoid) that are overproduced by the adrenal gland during situations of chronic stress (Activity 6).

Third, as we also considered there is evidence that stress and stressful events are important in triggering clinical depression (Kendler et al., 1999), and that depression in humans is associated with hyperactivity of the stress system.

Putting these pieces of the jigsaw together, current thinking is that stress, via the effects of glucocorticoid hormones, leads to a decline in hippocampal function (through some combination of decline in hippocampal neurogenesis and increase in hippocampal atrophy), and that hippocampal dysfunction is linked to some of the symptoms of depression.

- Given what you know about the hippocampus, what kinds of symptoms of depression might be associated with hippocampal atrophy?
- Impairments of some kinds of conscious memory, such as recollection of facts: the hippocampus plays a central part in memory processes supporting such memories.

4.7 Antidepressants, BDNF levels and neurogenesis in the hippocampus

If stress leads to a decline in neurogenesis, antidepressants seem to have exactly the opposite effect. There is now good evidence, from experimental work on rats, that ADMs

such as Prozac®, an SSRI which increases levels of serotonin in the brain, stimulate the production of new neurons in the hippocampus (Malberg et al., 2000).

Importantly, Malberg et al. (2000) found that ADMs such as SSRIs only stimulate neurogenesis in the hippocampus if given every day for several weeks.

- Why is this an important finding?
- Because it fits well with, and has the potential to explain, the observation above that ADMs such as SSRIs show clinical efficacy only after several weeks of being given daily.

How does serotonin, levels of which are increased by SSRIs, have an effect on neurogenesis? It appears that serotonin stimulates the production of BDNF.

Why are BDNF levels low in the first place? Experimental evidence suggests that stress (which, as you saw, releases powerful hormones such as glucocorticoids into the blood), reduces the levels of BDNF produced in the hippocampus, by damaging neurons in the hippocampus. This reduction in BDNF levels appears to be prevented or reversed by ADM treatment (Warner-Schmidt and Duman, 2006).

Indeed current evidence suggests that many antidepressant treatments, including SSRIs, electroconvulsive therapy (ECT), and exercise exert their effects by stimulating the production of BDNF in brain areas such as the hippocampus.

Clearly, the neurotrophic hypothesis offers a much more complex and integrated view of the possible causes of depression, as shown in Figure 11. (The schema shown in Figure 11 also allows for the possibility that unknown genetic vulnerabilities could affect neurons and their capacity to produce BDNF.)

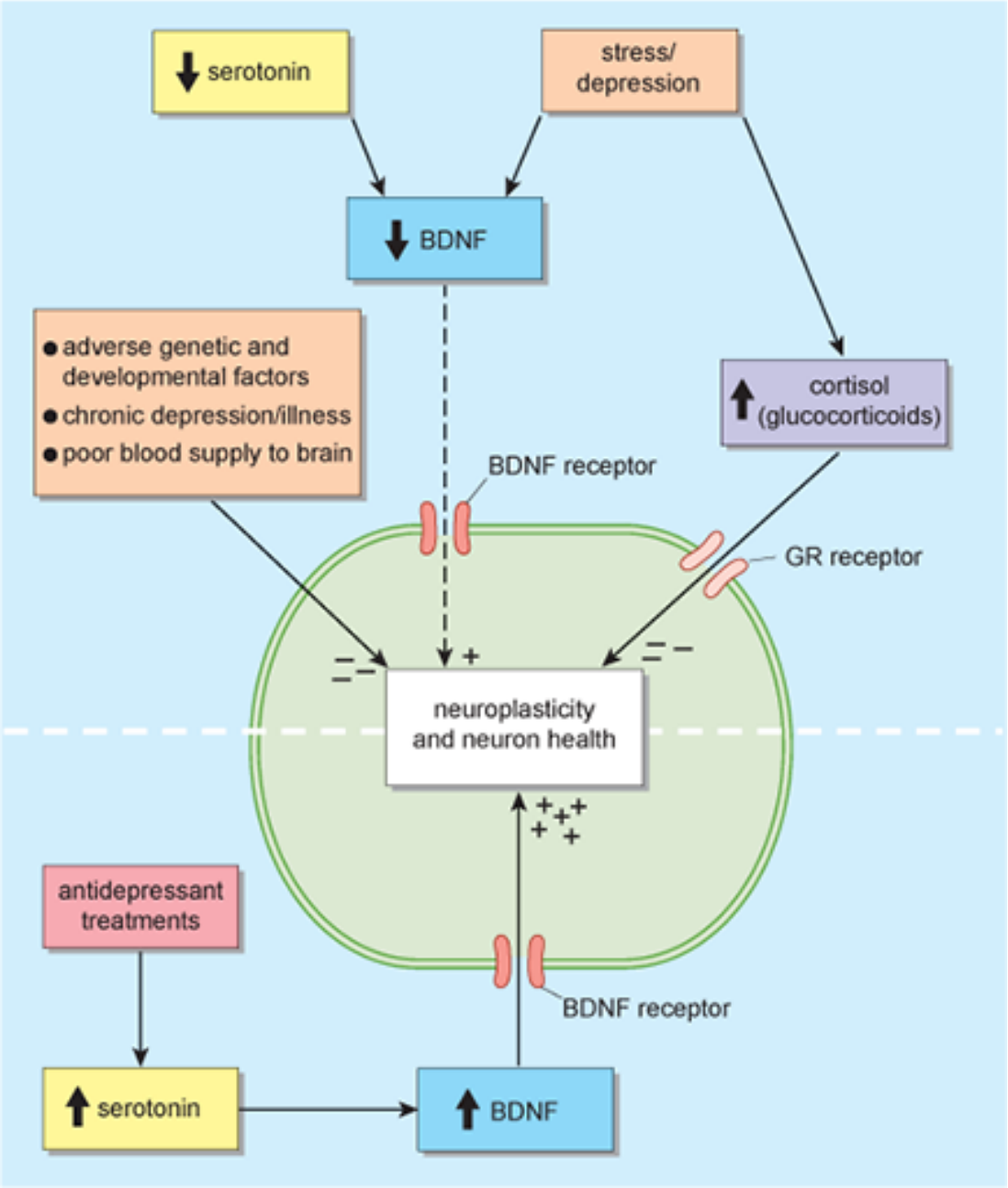

Figure 11 The neurotrophic hypothesis of mood disorders. The green area represents a neuronal cell. Within the cell is a box representing neuroplasticity and neuron health. Minus signs (-) indicate factors that damage neuroplasticity and neuron health, while plus signs (+) indicate factors that promote it. Some factors deleterious to neuroplasticity and neuron health are represented in the top half of the figure. For instance, low serotonin levels, and stress and depression, reduce the level of BDNF, weakening (as indicated by the broken line) its positive impact on neuroplasticity and neuron health; stress and depression also raise the level of cortisol, enhancing its negative impact on neuroplasticity and neuron health. The bottom half of the figure shows that antidepressant treatments, by raising levels of serotonin, and hence of BDNF, promote neuroplasticity and neuron health. BDNF: brain derived neurotrophic factor; GR: glucocorticoid receptor. Up-arrows ↑ indicate an increase; down-arrows ↓ indicate a decrease.

To recap, the implication is that neurogenesis, promoted by ADMs via the release of BDNF, underlies the efficacy of ADMs. Thus a final question is whether there is any

evidence for this. That is, are changes in behaviour consequent on taking ADMs linked to hippocampal neurogenesis? So far, this issue has been addressed in a study using animals, but it appears that there is indeed a link. Santarelli et al. (2003) found that if neurogenesis in the hippocampus was suppressed, ADMs failed to affect behaviour. The results do not prove that a lack of neurogenesis causes depression, or that increased neurogenesis cures it, but it does suggest that neurogenesis is an important factor.

5 The network hypothesis of mood disorders

While the neurotrophic hypothesis of mood disorders recognises the importance of BDNF and neurogenesis in explaining how antidepressants work, according to Eero Castre´n of the University of Helsinki, it does not go far enough in recognising the impact and significance of neurogenesis. He suggests that we need a conceptual framework to understand why neurogenesis might be important.

Castre´n (2005) quotes from the Nobel lecture given by Arvid Carlsson, the Swedish scientist who received the prize in 2000 in recognition of his work on the neurotransmitter dopamine: '…the brain is not a chemical factory but an extremely complicated survival machine'.

What does this mean? Castre´n argues that to understand how antidepressants work, and what their operation tells us about the brain bases of mood disorders, we need to look beyond the 'tools' – molecules such as BDNF – and try to understand what the tools are doing, which, he suggests, is repairing essential functional networks in the brain (Figure 12). A related point he makes is that there may be many different 'routes', including psychotherapy and ECT, that set in motion the plasticity processes needed to repair damaged networks (Figure 12c).

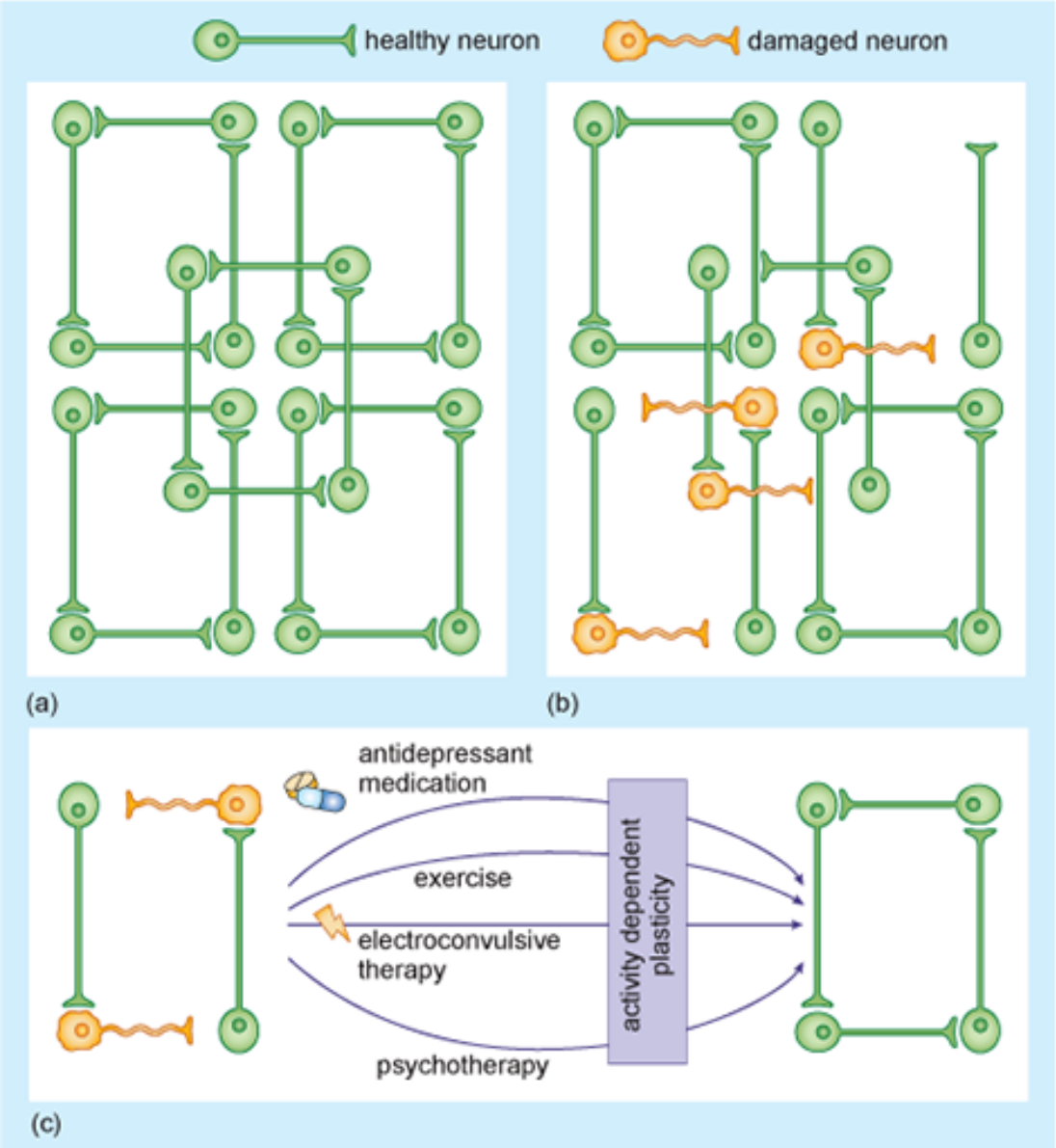

Figure 12 The network hypothesis of depression and antidepressant action (a) Networks of neurons process information in a healthy brain; (b) In depression, information processing networks do not function properly, as some neurons are damaged or have died; (c) Antidepressant treatment enhances connectivity in neuron networks: antidepressant medication, electroconvulsive therapy, exercise and psychotherapy can all enhance plasticity which gradually leads to the recovery of connections in damaged neuron networks.

Activity 10 Antidepressants and neurogenesis

Allow 5 minutes

On this view, what is the significance of the results obtained by Santarelli et al. (2003) in the previous section, showing that antidepressants are ineffective if neurogenesis is suppressed?

Answer

The results are significant because they suggest that neurogenesis is essential to the action of antidepressants. Castre´n suggests the new neurons are essential as they help ‘repair’ damaged networks in the brain, in this case in the hippocampus, so the networks can function properly again.

One way of looking at the role of BDNF, then, is that it is not levels of BDNF as such that are important, or even that BDNF promotes neurogenesis. According to the network hypothesis, BDNF’s effects on behaviour will depend on *where* in the brain it is active, and which networks it therefore affects.

6 Genes and environment: bringing it all together

Earlier in this OpenLearn course you saw that heritability values suggest that genetic and environmental factors both affect whether people develop mental disorders. Identical twins share the same genes, but if one identical twin develops schizophrenia, there is just a 50–70% chance of the other one developing it too. This suggests a role for the environment in determining behaviour. On the other hand, it is also clear that experiences, or environment, alone cannot explain the aetiology of disorders. For instance, stressful or traumatic events can trigger clinical depression. But not all people who suffer such events become seriously depressed.

Thus, how an individual looks and behaves, including whether or not they have a mental disorder (their phenotype), is the product of an interaction between their inherited genetic make-up (their genotype) and environmental factors. Increasingly, psychologists are coming round to the idea, well-established amongst developmental biologists since the 1950s, that there is no question of it being 'nature versus nurture' – nature (our genotype) is in intimate interaction at all levels with nurture (our environment) to produce us (our phenotype) (See Box 2).

By environment we mean all the things outside our genes that can interact with them. This could be the environment of the cell in which the gene resides; it could be the environment in your mother's womb, where you could hear her heartbeat, and where chemicals from her blood passed into your blood. It could be the way in which you were treated as a baby, or the infections that you caught and the kind of food that you ate.

You might be wondering how such things could possibly interact with our genes, which are safely enclosed in the cells in our bodies. This is a very good question. In some cases, there is data to suggest that gene–environment interactions may be important, but it is not yet known how any effects are actually brought about. In other cases, an understanding of what may be happening in gene–environment interactions at the molecular level is beginning to emerge, though the picture is still far from complete. We consider some studies that are shedding light in this very important and exciting area in Box 2.

Box 2 Nature–nurture, diathesis–stress, gene–environment: what's the difference?

The short answer is that there is none. All these ideas or formulations address the same issue, the interaction between some kind of 'predisposition' – represented by nature, the diathesis (which is often seen as a pre-existing vulnerability), or a gene, and something outside the predisposition that interacts with it – represented, respectively, by nurture, a stressful environment or stressor, and the environment. Is it useful to have three different models of much the same thing? Quite possibly, the idea of nature – nurture is rather vague and bucolic, and while it might be good for arguments in the pub, it does not allow much precision in the discussion.

The greatest precision is allowed by the gene–environment model – there is no question here about what 'nature' might be. It is the activity of a gene. However, this precision itself could be a limitation in some respects, as becomes clearer when we consider the diathesis–stress formulation (Nemeroff, 1998). In essence this is a model that postulates

interaction between biological factors and environmental factors. The term ‘diathesis’ is used to mean an inborn, genetic vulnerability or a predisposition to a particular disorder. The model assumes that exposure to a stressful environment can trigger behavioural disorder in an individual who is vulnerable, while individuals who are not vulnerable may experience similar stressors and not succumb. It allows some precision; however, it appears that the usage has evolved to allow changes in the phenotype – for instance, due to early animal handling or child abuse – to become diatheses themselves. Thus ‘neuroticism’ could be seen as a diathesis for the development of emotional disorders – although neuroticism itself may be a product of gene–environment interactions and hence a phenotype. As you will by now have realised, it is not easy to draw clear lines in this area!

6.1 The serotonin transporter gene and vulnerability to stressful life events

One approach that genetic epidemiologists initially took was to see if mood disorders such as depression could be linked to the kinds of genes people carry. (Genetic epidemiologists are epidemiologists who study the role of genetic factors and their interactions with environmental factors in the occurrence of diseases or disorders.)

As you have seen previously, serotonin (also known as 5-HT) has been the focus of much attention as a modulator of mood, and a lack of serotonin has been suggested as a factor in the development of depression. (5-HT (5-hydroxytryptamine) is the chemical name for serotonin, so 5-HTT is the ‘serotonin transporter’: the second T stands for ‘transporter’.) Indeed, selective serotonin reuptake inhibitors (SSRIs) are widely used as ADMs. Thus a protein that is involved in serotonin reuptake, the serotonin transporter protein coded for by the *5-HTT* gene, has attracted much interest from genetic epidemiologists.

Before going any further, it would be a good idea to read paragraph 1 in Box 3, to understand what genes are and how they work to produce proteins. (You do not need to read paragraphs 2 and 3 just yet; you will directed to read these in a later section.)

Box 3 Genes, gene expression and epigenetic mechanisms

1. The human body contains around 100 trillion cells. Most cells contain an enclosed central area, the nucleus, which contains structures called chromosomes. In humans the nucleus typically contains 23 pairs of chromosomes. One chromosome in each pair is from the mother while the other is from the father. Each chromosome contains a long strand of DNA (short for deoxyribonucleic acid – you do not need to remember this!). The DNA contains the code for genes, written in chemical ‘letters’. Genes are the templates for proteins – that is, they contain instructions for putting together protein molecules from building blocks called amino acids. (You read about an amino acid, tryptophan, in Section 4.3) Protein molecules are vital to life – they build and maintain our cells, including our neurons, and hence our brains and bodies.
2. To have an effect on the phenotype, a gene must actually be used to make the protein it codes for, a process called gene expression. A cell does not use every gene it contains to make a protein. Almost every cell in an individual contains the same genes, but different cells express different selections of genes. Such

selective gene expression is what makes a muscle cell (for example) different from a neuron. The genes that are not expressed are said to be 'silenced'.

3. The main way to silence a gene is to physically block access to it so that the protein it codes for cannot be made. Methyl groups (a kind of chemical present in the body) are often used by cells to create such a barrier and block access to genes, a process called methylation. Access to a silenced gene can also be restored. Sometimes this can be done by removing the obstructing methyl groups (i.e. by demethylation). At other times it can be done by adding another chemical, acetyl groups, that facilitate greater access to genes. This process is known as acetylation. Such 'silencing' and 'de-silencing' mechanisms are examples of epigenetic mechanisms. The word 'epigenetic' means 'above or beyond genes' and is used to refer to the way the expression of genes can be altered as described above.

The *5-HTT* gene codes for the serotonin transporter protein – that is, it provides cells with the 'instructions' needed to make the protein. As a serotonin transporter, the protein is responsible for the reuptake of serotonin into the presynaptic cell after it has been released into the synaptic gap to signal to the adjacent neuron (recall Figure 9).

The number and activity of the serotonin transporters determines the length of time that serotonin will remain in the synaptic gap before reuptake into the presynaptic cell. The gene for the serotonin transporter comes in two variants, a short form (s) and a long form (l). Each person carries two copies, or alleles, of the gene, one from each parent. The 's' version produces less of the functional protein than the 'l' one.

- As mentioned above, each individual carries two alleles, one allele ('s' or 'l') from the father and one ('s'or'l') from the mother. What possible combination of alleles (or genotype) could an individual have?
- The combinations are ss, ll or sl.

Genetic epidemiologists wondered if carrying one of the forms, 'l' or 's', made people more likely to develop depression. However, doing epidemiological studies correlating the carrying of one or other of the *5-HTT* gene variants with the occurrence of depression failed to show a link.

Caspi et al. (2003) wondered if taking into account the level of stress people had experienced would clarify the picture. They determined which allele combinations were carried by each of the 847 participants in a long-term study (the Dunedin study, which followed participants from birth), along with the number of major stresses they had experienced. When participants were 26 years old, the researchers evaluated how many stressful events they had experienced in the last 5 years, and whether or not they had depression. Caspi et al. (2003) found that people with either one or two short alleles (i.e. 'sl' or 'ss') were significantly more likely to develop depression following stress than people with two long alleles ('ll') (Figure 13a).

- Did it matter how many stressful events participants had experienced in the last 5 years?
- Yes – 5-HTT genotype was associated with likelihood of depression only if three or more stressful events had occurred (Figure 13a).

Similarly, the researchers found that those who had experienced childhood maltreatment between 3–11 years were significantly more likely to be depressed between 18–26 years if they had the 'ss' or 'sl' genotype than if they had the 'll' genotype. There was no effect of 5HTT genotype if maltreatment had not occurred (Figure 13b).

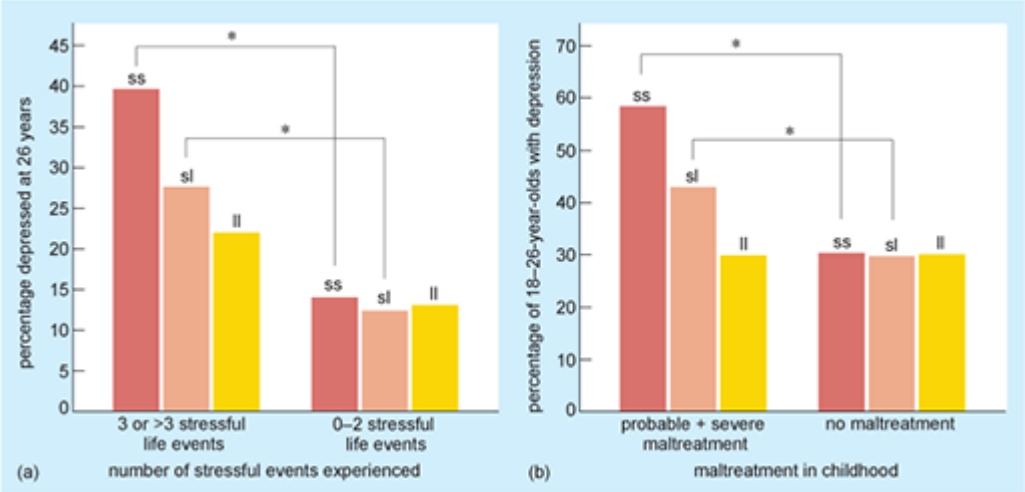

Figure 13 5HTT genotype (ss, sl or ll), the number of stressful life events and incidence of depression (a) Depression at age 26 years as a function of the number of stressful life events experienced between 21–26 years and 5HTT genotype. Those with ss or sl genotypes who experienced 3 or >3 stressors were statistically significantly more likely to be depressed at 26 years than those with similar genotypes who had experienced only 0–2 stressors; (b) Depression between 18–26 years as a function of level of maltreatment in childhood and 5HTT genotype. Those with ss or sl genotypes who experienced childhood maltreatment were statistically significantly more likely to be depressed between 18–26 years than those who were not maltreated in childhood. * denotes a statistically significant difference.

The importance of this study lies in its demonstration that genetic factors may not directly 'cause' disease, but may instead *mediate* responses to environmental factors such as stress (Caspi et. al. 2003).

- More than two-thirds of people apparently carry at least one short allele of the *5-HTT* gene. Does this mean they are all likely to get seriously depressed?
- No, carrying the 's' allele itself does not mean you are likely to get depressed. What it does mean is that the chances of getting depressed may be higher compared to people who have two long alleles ('ll'), if a person with two or one short alleles has many stressful experiences.

While an effect of carrying these combinations might exist (though the results of studies to replicate this finding are mixed to date – Risch et al., 2009; Hammen et al., 2010), it is not known how the effects might come about.

- The ‘s’ allele of the *5-HTT* gene causes decreased production of the functional protein – that is, fewer serotonin transporters are produced. What might happen if fewer serotonin transporters are available?
- The rate of reuptake of serotonin might be reduced, since these transporters are involved in reuptake of serotonin.

However, successful treatment of depression has often involved serotonin reuptake inhibitors, so it is puzzling that decreased production of the transporter responsible for this reuptake seems to exacerbate depression. It is evident that much is still unclear about precisely how serotonin or serotonin reuptake inhibitors might act to affect mood.

6.2 Genes, environment and development

Caspi et al.’s (2003) results suggest how gene–environment interactions (sometimes written as GxE interactions) might help explain the incidence of some disorders such as major depression, though the precise mechanisms involved (i.e. exactly how the two interact) are not known. However, understanding of genetics has recently undergone a profound paradigm shift in the light of evidence that the environment can affect the working of genes in ways that were thought impossible in the recent past.

To have an effect on the human phenotype a gene must be used to make a protein, a process known as gene expression (paragraph 2, Box 3). Scientists have recently shown that gene expression can in effect be switched on and off through epigenetic mechanisms (paragraph 3, Box 3).

It is important to note that the genes themselves (that is, the DNA, and the codes it provides for making proteins) are not changed by the action of epigenetic mechanisms – the genes remain exactly the same. Many common environmental factors or experiences are now known to trigger epigenetic mechanisms, including diet and exercise.

What is it that changes, then, when epigenetic changes occur? Think of a factory with lots of machinery for manufacturing different kinds of chocolate. If one of the machines is switched off, then that kind of chocolate is no longer produced. The machine is still there, unchanged, and it has not lost the capacity to make this particular chocolate, but it cannot make the chocolate because it is switched off. In this analogy, the machine is the equivalent of the gene or the genetic code for making a particular protein, and the epigenetic change is the equivalent of the switch – it can switch genetic machinery for making particular proteins, on or off.

6.3 Epigenetic effects and human mental disorders

McGowan et al. (2009) looked at post-mortem hippocampal tissue from humans, comparing three groups: (i) suicide victims with a history of child abuse; (ii) suicide victims without a history of child abuse, and (iii) non-suicide controls, people with no history of child abuse who had died suddenly.

The researchers found that *glucocorticoid receptor* (GR) gene expression in the hippocampus of abused suicide victims was lower than in the hippocampus of non-abused suicide victims or controls. In other words, glucocorticoid receptors are proteins made by the cells of the brain (neurons), so they are coded for by genetic information. The epigenetic mechanism silencing GR gene expression was methylation (Box 3). McGowan

and colleagues found higher levels of GR gene methylation in abused suicide victims than in non-abused suicide victims or in controls.

The effects of epigenetic modification in humans are undoubtedly hugely complex, as a great many genes besides the *GR* gene are known to be epigenetically modified by experiential factors. However McGowan et al.'s findings suggest that epigenetic mechanisms could be implicated in the long-term effects of adverse early experience on mental health in humans.

Activity 11 Genes and environment

Allow 5 minutes

On balance, does the evidence suggest that emotional disorders such as depression and anxiety are caused by genetic factors or by factors in the environment?

Answer

The weight of evidence suggests that both types of factors play a role. Combinations of genetic vulnerabilities and environmental factors may lead to the development of disorders. Environmental factors may also affect the sensitivity of systems such as the stress response system via changes in gene expression (epigenetic effects). Hence both genes and environment play a part in emotional disorders.

Conclusion

A major aim of this course was to shed some light on the aetiology of depression and anxiety. At the end of it you should have some idea of the complexity of this enterprise. We have focused on one of the best-studied and hence best-understood contributors to psychopathology – stress. This has biological, social and psychological significance, and its operation can be studied and understood at all these levels.

The clear message you should take away is that interaction between these levels is enormously important in aetiology. Biological factors, such as dysregulation of the HPA axis and its consequences, possible abnormalities in brain neurotransmitter systems, the effects of stress on the developing brain at different ages, and the kinds of genes that an individual carries, appear to play an important part in the development and maintenance of emotional disorders such as depression and anxiety. However, these biological factors cannot be divorced from factors that are thought of as psychosocial, such as abuse in childhood, or stressful events and how we perceive them. This is very evident from the most recent developments in genetics, which show how, via epigenetic processes, experiences are translated into the activity (or expression) of genes, which then modify the workings of the brain in ways that affect mood.

Research into epigenetic influences on mental health and ill-health is burgeoning and is likely to make a very significant contribution to our understanding of aetiology in the years to come. If so, it should also help clarify how existing treatments, both pharmacological and psychotherapeutic, for emotional disorders work, or suggest new approaches that would work more effectively.

The HPA axis is overactive in those with depression and anxiety, suggesting a role for chronic stress. Elevated levels of glucocorticoids such as cortisol and corticosterone, resulting from chronic stress, have toxic effects in some areas of the brain and promote neurogenesis in others.

The monoamine hypothesis of mood disorders has been influential in trying to explain the causes of depression. However the picture is now more complex and the view of a simple chemical imbalance as a cause of depression is outdated.

Hypotheses such as the neurotrophic hypothesis and the network hypothesis have been developed to try to account for the complex effects of antidepressant treatments on the brain.

The life-cycle model of stress links brain development with stress effects over the lifetime.

The cognitive approach concentrates on particular ways of thinking and how these cause and sustain depression.

Genetic and other vulnerabilities (also called predispositions or diatheses) can interact with environmental factors, which include psychosocial stressors such as stressful life events and early life stress (including child abuse) to cause emotional disorders such as depression.

Epigenetic processes add another layer of complexity to the interaction between genes and environment. There is increasingly evidence of the importance of epigenetic processes in the aetiology of mood disorders.

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