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AN INTRODUCTION TO STRESS & HEALTH

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THE NATURE OF STRESSORS

Monday morning

Can hardly get myself out of bed. It's just way too early. Why do they have classes at 8:30? It's inhuman. Well, I better move my butt. I've missed a couple of classes already and I'm pretty far behind, and sometimes I can't even figure out what the prof. is talking about. I borrowed some notes, but I might as well be reading hieroglyphics. I wish I had the time to go through the book, but between working at the restaurant at night and meeting with Jesse on weekends, there don't seem to be enough hours in the day. I can't put Jesse off any longer as I'm sensing annoyance because I'm never around. I really don't want to end up being dumped. Until I met Jesse, I felt pretty alone and didn't have much of a social group to hang with. Aw hell, I can't think about that now. The clock's ticking and those two essays and the class presentation are due soon. I don't even know where to start. It almost seems as if my profs are colluding against me. The exam schedule is nuts. My two toughest exams are on the same day, and then I've got six days to study for that no-brainer course that is easier than what we took in high school. I've also got to get home before the exams to see Dad. He didn't sound good last time I spoke to him and Mom. I really miss them, and I think they're not telling me everything about Dad's heart problems. I don't even know where to begin. I just want to stay in bed and cover my head.

There are certain topics that encourage opinions from everybody and their cousin, and on which people seem willing to make statements with absolute certainty regardless of their knowledge of the subject. It's unlikely you would overhear casual conversations regarding topics in physics, such as quark-gluon-plasma or the space and time continuum. However, you might catch snippets of conversations about how to fix the ailing economy (opposite opinions all being dogmatically pushed), about how badly international affairs have been bungled by this or that political party, and about the stresses of modern life. Here, people often divide into two camps. There are those who view modern life as a grind with a variety of stressors appearing everywhere, exacerbated by work/school and unsupportive friends. Others, in contrast, believe that stressors of modern life are vastly exaggerated and that the daily challenges that people are said to experience are something of a fiction, or perhaps it's something that only others need to endure. In short, stress is something everybody talks about with the view that they have special insights into the topic.

Learning objectives

This chapter will introduce you to some basic concepts, with the goal of familiarizing you with key variables that influence the impact of stressful events. So, if you do get into a conversation regarding the impact of stressors, your opinions will be scientifically based. To this end, we will cover:

- a description of what a stressor comprises and the various forms they come in;
- analyses of the attributes of a stressor that result in it having greater or lesser effects;
- how stressors are assessed in a laboratory or real world contexts, including analyses of stressors that appear to be nothing more than minor inconveniences, or stressors that represent life-changing events;
- the individual differences that influence vulnerability to the effects of stressors, or imbue resilience needed to overcome potential adverse consequences of stressful experiences.

Stressful events are linked to a wide range of mental health conditions and are among the prime suspects in the provocation of several physical illnesses. For this reason, it's important to learn how to recognize and deal with stressful events that entangle us every day (have you noticed that it's a jungle out there?), and major life stressors that most of us will invariably encounter at some time or other.

Did the text in the box at the outset of this chapter sound at all familiar? And if it did, upon finding yourself in a similar situation would you do anything about it or would you just hope everything would get better eventually? As we said in the Preface, this book might not help you solve your specific problems (does anybody ever read a preface?). However, it will provide you with information about stress and coping processes, and insights into a constellation of psychosocial, experiential,

and developmental factors and how these relate to a wide variety of illnesses that have been associated with stressful events. You'll learn about various aspects of our biological defense systems, and some of the consequences of not keeping stressful events in check. In essence, the book's core goal is to give you a comprehensive and integrated understanding of stress processes and their relation to health. What we want to emphasize is not only that these various elements are all important facets of human psychology, but that stressful events can have consequences that you might never have considered. Beyond having immediate effects on well-being, stressful experiences can mark you for decades. In fact, the stressors you encounter, depending on when they occurred and how severe they were, can have intergenerational effects.

Some basic definitions and concepts

It's a good idea to begin by defining some key terms so that we're all on the same page. For starters, what do we mean when we use the terms 'stress' and 'stressor'? This sounds fairly mundane, doesn't it? Nevertheless, just humor us, and assume that differentiation of these terms might be useful. A 'stressor' is a stimulus or event that is *appraised* or perceived as being aversive and causes a 'stress response'. This stress response can comprise a series of behavioral, emotional, and biological changes aimed at maintaining well-being. Among other things, the stress response involves changes within the body that occur so that energy resources are directed towards the places they are needed, and away from processes that are not essential at the moment (e.g., reproduction, eating, digestion). Simultaneously, multiple brain regions are activated to help us appraise and then deal with the stressful event.

So, what exactly are these stressors? In fact, there is no easy definition of 'stressor', since appraisals of events may vary with contextual factors and change yet again over time, and they are interpreted differently across individuals. In much the same way, what constitutes a stressor may be highly subjective, and the individual differences that exist can be fairly pronounced. Events or stimuli that are stressful to one individual might not be similarly appraised by a second. In effect, one person's poison is another person's meat. For example, jumping out of a plane (with a parachute, of course) might be exciting for some, whereas it might be exceptionally distressing for others. Even if two people appraise a stressor similarly, they might display different emotional reactions. But even if their emotional reactions were the same, they might use different methods of coping with the stressor. Finally, the fact that individuals' appraisals, coping, and emotional responses are similar doesn't mean that their biological responses will be the same, and hence different psychological outcomes (including pathologies) might evolve over time.

Individual differences in stress responses might come about because of several factors. We'll go through each of these, and revisit them in ensuing chapters, as they have important implications for the development of stressor-induced biological and pathological outcomes. Obviously, assessing the link between stressful encounters

and the emergence of psychological or physical disturbances isn't easy, but the research that has been conducted has made significant progress and has resulted in the development of effective strategies for preventing illness and treating pathology.

Characterizing stressors

Even at this very early point you've learned something important about stressors. First, not all stressors have the same impact and, second, individuals differ remarkably with respect to how they appraise stressful events and how they respond to them. You've also learned that there are multiple factors responsible for these individual differences. Figure 1.1 depicts several of the numerous variables that influence the impacts of stressors on psychological and physical disturbances. Some of these factors might reflect characteristics of the stressor itself, whereas others might be related to features of the individual and their experiences, their appraisal and coping methods, and diverse psychosocial influences.

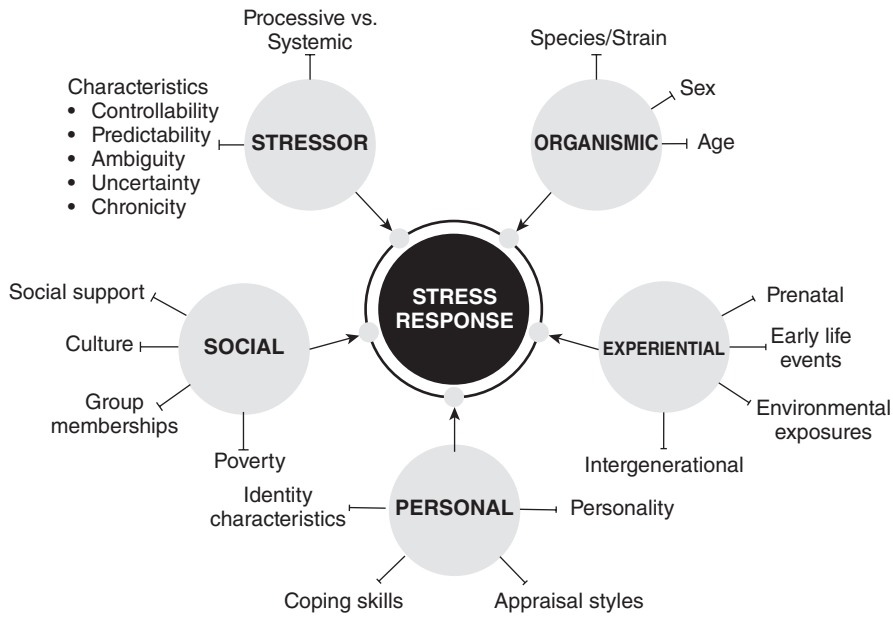

Figure 1.1 Factors that affect the reactions to stressors

Types of stressors

Stressors generally come in multiple forms, and they don't necessarily result in identical outcomes. A stressor that involves information processing (e.g., asking ourselves 'Is that dog drooling and does that glare and posture mean it's dangerous?',

or 'Does this guy with the mask covering his face seem like a mugger, or is he protecting himself from catching a virus?') is referred to as a *processive* stressor. Understanding the challenge (stressor) involves several complex cognitive processes that engage numerous brain regions. These include neural circuits responsible for executive functioning to enable appraisals and decision-making (e.g., prefrontal cortex; anterior cingulate cortex), memory processes (e.g., hippocampus and several cortical brain regions), and those involved in anxiety and/or fear responses (e.g., prefrontal cortex, amygdala, bed nucleus of the stria terminalis, and hippocampus). Broadly speaking, processive stressors can be of a purely psychological (psychogenic) nature, or of a physical nature (termed 'neurogenic' stressors), such as those associated with certain illnesses or painful stimuli (e.g., burns). Not surprisingly, psychogenic and neurogenic stressors may elicit similar outcomes in some respects but, as we will see, they can have several very different consequences.

Systemic stressors represent another type of challenge that doesn't involve information processing in the same way, but may nevertheless influence stress-related biological systems. Such stressors might include, but are not limited to, marked changes of glucose concentrations in our blood (as in diabetes), or the presence of inflammation or the production of certain proteins evoked by inflammation (as occurs with heart problems). In these instances, we might not be processing the information with the question 'Is this a threat to my well-being?', as we do when confronted by some processive stressors, but our body might interpret these challenges as threats and send messages to the brain so that certain actions are taken to meet the immediate needs. For instance, the pain associated with a broken bone (a neurogenic processive stressor) might make us more cautious and protective of the injured area, and thus increase the likelihood that it will heal properly. In a similar way, the fatigue and achiness associated with influenza (a systemic stressor) pushes us into bed so that we can rest and thus recuperate more readily. The behavioral changes that occur in response to processive or systemic insults involve the integration of several biological and cognitive systems. It seems that multidirectional communication occurs to coordinate responses between various facets of our brain, peripheral nervous system, hormonal systems, and the immune system.

Psychogenic stressors

Different types of stressors (psychogenic vs. neurogenic vs. systemic) do not necessarily lead to identical outcomes. For example, in rodents, a purely psychogenic stressor, such as being exposed to predator odors, gives rise to neurochemical changes within the brain that are different in several respects from those elicited by a neurogenic stressor (a painful stimulus). In fact, even among psychogenic stressors, marked differences occur as a function of the specific stressor encountered. Those psychological stressors that reflect innate challenges (e.g., predator odors) instigate neurobiological changes that are distinguishable from those elicited by conditioned or learned stressors, such as cues that had previously been associated with a neurogenic stressor. In light of the specific neural circuits activated by these

stressful events, it might be expected that they would be associated with the emergence of different behavioral outputs or pathophysiological processes and might require different strategies to attenuate the negative reactions that might occur (Anisman et al., 2018).

At one time scientists thought that we had a 'stress center' in our brain, just as it was mistakenly thought that there was a discrete 'pleasure center'. The neural circuitry associated with stressors is much more complex; we do not have 'a' stress system, but instead there appear to be multiple pathways that respond preferentially to different types of stressors (Merali et al., 2004). When we examine these systems from a perspective relevant to humans, this complexity takes on more tangible meaning and significance. For example, some stress responses reflect outcomes associated with something that has already happened (the loss of a loved one, a business failure, a hurricane, or being ostracized by your friends). In contrast, other challenges might entail future threats (waiting for biopsy results), which might involve the engagement of very different brain pathways.

One can intuitively appreciate that some stressors, particularly those that involve interpersonal events (e.g., the death of a loved one), might favor certain types of responses and lead to depression, but these processes might be distinct from those involving adverse achievement-related events (work-related stress), although these too can favor depressive affect. As we'll see later, varied forms of stigmatization and racism can promote severe psychological and physical disturbances, which might emanate from the activation of other (or additional) processes. Moreover, gender differences appear to exist with respect to the types of stressors that lead to pathological outcomes. In this regard, psychosocial stressors may have more dramatic effects in females than in males, whereas those related to economic problems have more profound effects in males, varying with age (Hu et al., 2021). Other stress responses, especially those that involve uncertainty and are of an anticipatory nature (e.g., imminent surgery, anticipation of an upcoming exam or public speaking, an imminent tax audit, the chance of seeing the bully in the schoolyard), are likely to be accompanied by anxiety (Starcke & Brand, 2016). Still other types of stressors, notably those that are ambiguous in nature (e.g., the 'possibility' of a terrorist attack, or a pilot announcing that 'we have to return to the airport' without further explanation), might be accompanied by disorganized cognitions while the situation plays out.

Some stressors involve an evaluative component (e.g., public speaking or asking questions in class, a job interview), a social component (e.g., a fight with your best friend), one that involves a degree of embarrassment (e.g., certain visits to the doctor), and some that instigate particularly aversive emotional responses (e.g., shame, humiliation). Some psychological stressors may have profound effects, but their actions are fairly transient, whereas others, especially those encountered early in life, may be remarkably powerful, so much so that they can have lifelong effects, even resulting in earlier mortality (Rod et al., 2020). Clearly there are many types of psychogenic stressors, and while they might instigate some common stress responses, their unique features are likely to elicit variations of appraisals, emotions, biological reactions, and psychophysiological outcomes.

Neurogenic stressors

Physical stressors can be brief (stubbing your toe), moderate in duration (e.g., a slight burn, a back strain, or a slightly sprained ankle), they can be persistent (e.g., sustained or recurrent migraine headaches), or they can be both persistent and intense (severe neurological pain, injuries sustained from accidents, or the pain associated with certain diseases, such as rheumatoid arthritis and cancer). There's little question that the more intense stressors call upon an incredible portion of a person's psychological and physiological resources. As well, these neurogenic stressors typically don't appear in isolation of psychogenic challenges. Whether these entail financial difficulties brought about owing to physical illness, repeated trips to doctors or hospitals, loss of employment, having to rely on others, or the anticipation that the distress will continue, it seems that complex multidimensional factors are often at work. As a result, diverse psychological processes might be necessary to cope with these multipronged insults. Often, our abilities may simply be insufficient to deal with events, and external mechanisms that enable us to withstand them (e.g., our social support resources) may become essential.

Systemic stressors

Psychogenic and neurogenic stressors are in some sense tangible (i.e., we can see or feel them), but we can encounter stressors that we might not be conscious of, and hence we might not be aware that we are experiencing strain. Thus, we typically wouldn't think of them as stressors. Nevertheless, surreptitious challenges, such as immune activation, should be considered as stressors given that they elicit a cascade of biological changes that in many ways are akin to those associated with psychogenic and neurogenic insults. Among other things, systemic stressors may affect neuroendocrine functioning, brain neurochemical processes, and could elicit several depression-like behavioral changes (Anisman et al., 2018). However, because we might be unaware that something is happening in our body that might adversely affect us, there is seemingly no opportunity to take steps that might facilitate coping with the challenge. From this perspective, systemic stressors reflect silent, insidious attackers that can have negative repercussions for well-being beyond their potential direct effects. We'll be dealing with this in considerable detail later (see Chapter 6), but for the moment just keep in mind that stressors aren't always obvious but may nevertheless have serious consequences.

Stressor characteristics

Each stressor that we encounter may have unique elements and thus may have very different repercussions. For example, let's consider one broad stressor category, that of being ill, and examine the various elements that make up this type of challenge. An illness can be a brief one (a bad case of the flu, or appendicitis requiring

surgery), or one that is less intense, but can still wreak havoc on a person's general well-being owing to the condition lasting for some time, and there are some illnesses that are chronic and/or progressive (get worse over time). Some illnesses might allow individuals to function normally despite the symptoms being exceptionally disturbing (e.g., tinnitus), whereas in other instances (e.g., arthritis, lupus erythematosus, Parkinson's disease) the features of the illness might interfere with multiple aspects of daily life. There are also illnesses, such as type 2 diabetes, that necessitate changes in lifestyle, and can have drastic long-term implications for further diseases, but early on might have few discernible negative effects. Worst of all, for the patient and the family members, are disturbances that rob you of yourself (Alzheimer's Disease), illnesses that might or might not lead to death (cancer, heart disease, HIV), or those that are physically incapacitating (e.g., ALS, paralysis). Some illnesses 'just show up' without any apparent cause, whereas others occur because of traumatic events (a head injury) stemming from one's own behaviors (engaging in certain sports), the actions of others (drunk or incompetent drivers), or acts of nature (flood, hurricane, earthquake). In each instance the illness trajectory may vary over months and years, and the needs of affected individuals might differ accordingly. The psychological aspects related to the illness, attributions regarding the cause of the illness, as well as the extent to which the illness *allows* the engagement of effective coping strategies all differ with the individual's condition.

Severity

Because each stressor has distinct characteristics, it is difficult to compare whether one stressor is more severe and debilitating than another. This is made still more difficult as our perception of stressors may be influenced by the context in which they occur and may vary over time. There are stressors that simply can't be compared to one another in terms of their relative severity (e.g., the death of a child vs. dealing with a severe incapacitating illness) as they are so entirely different on multiple dimensions and are often so severe that comparisons become meaningless. Nevertheless, most people would agree that some stressors are more profound than others (e.g., the loss of a loved one vs. getting a parking ticket), and thus most of us could guess that such stressors are apt to have greater pathophysiological consequences.

Controllability

The notion that control over one's destiny is important in determining psychological health has been around for a long time and there is no question that, under most conditions, uncontrollable stressful events have more profound adverse health consequences than do controllable experiences. Experiments conducted more than 40 years ago documented one of the best-known phenomena in stress research. It was shown that animals exposed to an escapable stressor (a shock to their feet), or

that had not been stressed at all, subsequently displayed proficient performance in a test where they were required to escape from a stressor. However, animals that had been exposed to an uncontrollable stressor (a foot shock that they could not escape) later exhibited profound behavioral impairments in an escape test where an active response would have terminated the stressor. In these studies, the animal in the 'uncontrollable' stressor condition received the stressor at the same time and for the same duration as the animal in the escapable shock condition. However, unlike the animals that were exposed to an escapable stressor, those in the uncontrollable condition were unable to control stressor termination. Instead, stressor offset occurred whenever animals in the escape condition made an appropriate response. Thus, animals received the same duration of the stressor, but differed with respect to the psychological dimension of having control over its termination (this is referred to as a 'yoked' paradigm). As only animals in the uncontrollable condition later showed impaired performance, it was concluded that it was not the stressor itself that was responsible for the behavioral impairments. Rather, the animal's inability to exert control over stressor termination resulted in cognitive changes that were crucial in determining whether or not the adverse effects of the treatment would become apparent (Maier & Seligman, 2016).

In describing the characteristics of animals who performed poorly in this paradigm, it was indicated that they did not make overt attempts to avoid or escape the foot shock. Instead, they seemed to passively accept the stressor. Indeed, when an animal made an occasional escape response, this was not predictive of further escape attempts. Cognitive processes were thought to occur whereby they *learned* that their responses were unrelated to outcomes ('nothing I do matters'), and as they had learned that they had no control over the situation they stopped trying to escape. They had learned that they were *helpless*. If animals were initially trained to make an appropriate response and then exposed to the uncontrollable situation, they did not display behavioral disturbances when subsequently exposed to a controllable stressor. Having first learned that they control their destiny, these animals were essentially *immunized* against the effects of the uncontrollable stressor.

NASTY LITTLE CREATURES

For some time it was thought that ulcers were caused by stress. However, it seems that the bacterium *Helicobacter pylori* is responsible for ulcers (Marshall & Warren, 1984), and in recent scientific discussions the contribution of stressful experiences has taken a back seat. To make the point concerning their hypothesis, which most scientists had dismissed, Marshall drank a brew of *H. pylori* to demonstrate that this bacterium would, indeed, cause ulcers. It would, after all, have been tough to get experimental participants for this study or even to get the study through an ethics review panel. For their work in identifying *H. pylori* as the main culprit responsible for peptic ulcer disease, Marshall and Warren received the 2005 Nobel Prize in Physiology or Medicine. Despite strong evidence supporting *H. pylori* in ulcer formation, stressful events and this bacteria may act synergistically

(Continued)

to promote ulceration. Indeed, over the last two decades it has become apparent that the gut is inhabited by trillions of microorganisms that can be beneficial to health. However, factors that cause an imbalance of these microorganisms (called dysbiosis), including stressful experiences and poor nutrition, can promote a wide range of physical and psychological illnesses (Cryan et al., 2019).

The behavioral disturbances elicited by uncontrollable stressors have been seen across a variety of species, but in rodents it is typically seen only in certain situations. It seems that when the stressor is administered to rodents, the high degree of reactivity that is elicited favors an appropriate escape response being emitted (i.e., running from one chamber in which the stressor is administered to an adjacent 'safe' chamber) and thus potential behavioral deficits are obfuscated. However, if the escape response required a motor response that was relatively difficult to accomplish or if an active response had to be maintained for several seconds before successful escape was possible, then performance deficits could be elicited. Such findings gave rise to the suggestion that performance disruption was not a reflection of a cognitive disturbance, such as helplessness, but instead stemmed from brain biochemical changes that hindered the rodents' ability to maintain prolonged or complex active responses (Anisman, 2009).

Failure experiences in humans may have effects vaguely reminiscent of those associated with uncontrollable stressors in animals. For instance, university students exposed to unsolvable problems subsequently displayed impaired performance in a problem-solving task, as did depressed students who had not been exposed to the unsolvable task. Although these outcomes have often been attributed to learned helplessness, there are other explanations that might have little to do with helplessness. For instance, a mismatch between the participant's expectancy regarding their performance and their failure to meet this expectancy might have induced frustration that was responsible for the subsequent impaired performance. As well, an uncontrollable stressor may promote a constellation of hormonal and brain neurochemical changes that undermine effective behavioral responses being initiated and maintained, which can lead to pathological outcomes (Anisman et al., 2018). The differing positions notwithstanding, since these early studies much has been made of the importance of stressor controllability in determining later psychological and physical disturbances.

Stressor predictability, uncertainty, ambiguity, and black swans

The impact of stressors on well-being is influenced by their predictability, uncertainty, and ambiguity. There are occasions when the occurrence of stressors is very predictable, but there are also those when stressors are entirely unpredictable, and our responses in these situations are likely to be quite different. Who among us would have predicted that a pandemic, such as COVID-19, would hit and would

have such disruptive effects,[1] or that an earthquake or tsunami would hit a particular region, causing the deaths of thousands upon thousands of people? In contrast, tax time is a stressor, particularly for accountants or those who owe the government a lot of money, and its occurrence is predictable (the behavior of governments may not always be predictable, but you can count on them being systematic when it comes to collecting taxes).

Uncertainty is related to unpredictability, but they can be distinguished from one another. We all will die eventually (that is a certainty), but when this will happen is often unpredictable. Essentially, when we talk about predictability, it is usually in the context of events that will happen; it is simply a matter of knowing when they might happen, whether there will be a warning of their occurrence, and on what schedule they might occur (e.g., a single event, repeated events, events that occur intermittently). Uncertainty, in contrast, deals with events that might or might not occur (e.g., will a new variant of COVID-19 virus end up creating a more destructive pandemic). When there is uncertainty about the occurrence of a stressor, individuals may take on a cavalier attitude that essentially comprises 'whatever happens, happens'. Others, however, seem to have great difficulty dealing with uncertainty, and for these individuals their stress reactions could potentially be pathogenic.

Another similar construct is that of ambiguity. We say that a situation is ambiguous when the stimulus context does not provide sufficient information, or provides multiple but inconsistent bits of information, so that it becomes difficult to determine whether and when the event might occur. For example, ambiguity exists when one has a set of symptoms, but they do not form a coherent pattern that allows for a firm diagnosis.

An old proverb has it that '*mann tracht un gott lacht*', literally translated as 'man thinks (plans) and god laughs'. On a daily basis, most individuals typically behave as if the events in their lives are predictable, that they can reasonably anticipate what the future holds for them, and that they even have some control over their lives. Even though most of us know that this sense of control is an illusion, many of us operate as if we have some say regarding what happens to us: we have expectations for the future, and planning is viewed as necessary given our apparent need for order and predictability. Thus, it shouldn't be surprising that adverse events that are unpredictable are generally viewed as being more unpleasant than predictable events, and are more likely to be associated with disturbed brain neuronal functioning, the excessive activation of some stress hormones, and altered immune functioning (Anisman et al., 2018).

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[1]To be clear, there had been repeated warnings of an imminent pandemic, and the mantra was frequently repeated that 'it wasn't a matter of if, but when'. Not to pat ourselves on the back, but we were among the many that issued these warnings (see discussion in Anisman, 2021), and based on our research of earlier pandemic responses, we also predicted that vaccine hesitancy would be a major issue that would need to be confronted (Taha et al., 2013). Collectively, we had been preaching to the choir. Political leaders that could have made a difference weren't listening.

So, what is it about the unpredictability and uncertainty regarding bad events that makes them especially aversive? To a significant extent, what differentiates predictable vs. unpredictable events is the anticipatory period. When we know that an event will happen at a particular time, there may be great anxiety about the impending event, and waiting itself, coupled with the probability of events occurring during specified periods, may be stressful. Yet knowing that the event will or is about to happen gives us the opportunity to prepare or adjust our behaviors and expectancies. Unpredictable events, however, don't allow us to prepare in a similar manner, and we may be on edge for extended periods of time. Most people are familiar with the first part of Franklin D. Roosevelt's statement in relation to the Great Depression (1929–1933), but less familiar with the second part; 'the only thing we have to fear is fear itself – nameless, unreasoning, unjustified terror which paralyzes needed efforts to convert retreat into advance'. This very well describes the response to unpredictable, ambiguous, but potentially very stressful situations: irrational, inappropriate, and immobilizing behaviors that reflect our inability to appraise and cope with situations, so that our ability to strategize becomes entirely ineffective.

As with unpredictability, in most situations uncertainty is seen as being more aversive than is certainty. However, there are times when this isn't the case. For instance, some people who are at risk for a genetic disorder, such as Huntington's Disease, might want to know whether they carry the gene for this illness, and hence will invariably be affected. These individuals don't want to live in suspense, essentially with a sword hanging over their heads, and choose to know whether they carry the gene. Others, however, would rather not know and appear to be able to vanquish these thoughts so that their daily routine is not affected. It seems that individuals differ in their *intolerance for uncertainty*. The level of uncertainty that can be tolerated is a trait that individuals bring into situations that involve an ambiguous or uncertain component. High intolerance for uncertainty has been found to be associated with anxiety regarding daily stressors, and the desire to reduce uncertainty predicted elevated information seeking (Rosen et al., 2007).

The co-existence of ambiguity and uncertainty are frequent aspects of our experiences, and they are known to promote anxiety. Consider what your own reactions to ambiguous symptoms of an illness might be (e.g., 'Is this lump something I should worry about?' 'This feeling in my chest seems like indigestion, but it might be a heart attack. What do I do?'). Confirmation of an illness, in turn, might lead to further uncertainties pertaining to the illness and its prognosis ('What are the odds that the treatment will work?'), and the availability of a competent and experienced medical practitioner ('Does this doctor have the experience and skill needed?').

From what has been said to this point, it's clear that unpredictability, uncertainty, and ambiguity can be exceedingly stressful. But there is also a different spin that can be applied regarding the role of uncertainty in the context of serious illnesses. Uncertainty involves two distinct appraisal processes, namely *inference* and *illusion*. If uncertainty exists, then individuals can reconstrue a largely negative situation (inference) to extract a glimmer of hope despite the odds (illusion).

Because uncertain situations are vague and changeable, when events start spiraling downward (e.g., when all treatment efforts to stall the progress of a cancer have failed), individuals can capitalize on uncertainty so that their appraisals take on a positive hue, no matter how limited this might be. Uncertainty, essentially, allows a person to expect the worst, but hope for the best.

Unpredictable and uncertain events obviously have the potential for turning our lives upside down. The death of loved ones, sudden illness, catastrophic natural disasters are all events that we know are possibilities, but we really don't expect them to happen to us. Yet the probability of dying of heart disease is about 31% and that of cancer is about 21–22% (although survival rates have been increasing for several cancers), Type 2 diabetes occurs in about 8.5% of individuals and is climbing, autoimmune disorders occur at 3.1%, and then there's kidney, pancreatic, or liver disease, and serious automobile accidents that lead to severe disability or death occur at a rate of about 1.7% each year. There is also a chance of being hit by lightning or the possibility of being in a plane crash (although these are rare events, for the person hit by lightning or the people on the plane, such probabilities simply don't count). The point of all of this is simple. We might not know how we'll fare in the future but given the number of bad things that can happen to us, and the additive probabilities of these events, we can pretty much count on not getting away untouched. We don't know whether, how, or when we'll encounter these nightmares, but it's almost a certainty that we'll encounter some bad dreams.

ILLUSIONS AND DELUSIONS OF CONTROL

It seems that for many of us, there is a need to maintain a semblance of control over our own destinies. Even when a situation is entirely unpredictable and individuals have absolutely no control over the outcome, those who are self-assured are more likely to choose to exercise their own judgment in determining that outcome. The fact is that when situations are unpredictable and when outcomes are entirely out of our control, our participation in decision-making (e.g., how to treat an illness) is not that far removed from that of engaging in a game of chance (e.g., tossing a coin). For example, when given the opportunity to play a game of chance (say roulette) where individuals either have absolutely no control over outcomes or are allowed to 'pay' a premium to press a button to stop the wheel (in this instance they have a semblance of control insofar as the wheel will stop, but they have no control with respect to where the ball lands), they will more often pick the latter. Similarly, when people buy lottery tickets, they often prefer to choose their own numbers rather than have a series of numbers generated through a computer (as if they have a divine connection with the odds maker in the sky, which the computer, of course, doesn't). It seems that some people feel that they (or others) are endowed with a trait of being lucky ('I'm a lucky person', as opposed to 'This was my lucky day'), and so might get involved in events that involve high risks (e.g., gambling) that they believe don't apply to them because they are, after all, lucky. There are others who develop an 'illusion of control by proxy' wherein they find a 'lucky person' to buy their lottery tickets for them. One wonders whether stock-market players, at least to some extent, are affected by some of these characteristics.

Some time ago Taleb (2007) introduced the 'black swan theory' to explain irrational behaviors that people often endorse in the context of making decisions. Essentially, from Taleb's position, there are events that occur very infrequently and are essentially unpredictable and have a major impact on the individual (or society, or the economy). These events often have people rationalizing, in hindsight, that it might have been predictable if only the right data had been available. For instance, could we have predicted 9/11 and the ensuing stock-market catastrophe; or the earthquake in Japan and resulting tsunami that had the potential to produce a nuclear meltdown? Probably not, but it can be argued that even though any single event is an outlier (a black swan), there are so many possible things that could go wrong that one or more of these will eventually occur. Black swans don't simply refer to 'major' events like a 9/11, a crash in the housing market, or the possibility of another war breaking out somewhere (the latter aren't really black swans given how frequently these occur globally). There are human tragedies that can also occur, such as being diagnosed with a rare disease, sitting at an outdoor cafe and having part of a building suddenly collapse with you as collateral damage, or a piece of space junk re-entering the atmosphere and taking direct aim at your house. We can't know what will befall us, as there are simply too many 'unknown unknowns'; so many that the odds of dodging all of them are slight. However, they can and do occur, and their ramifications can be enormous.

THE BRAIN'S RESPONSE TO KNOWING AND THE UNKNOWABLE

Given that we often find ourselves in situations in which the information available is ambiguous and making decisions entails a degree of risk (e.g., the stock markets), there has been increasing interest in determining which brain regions might be engaged for decision-making under such conditions. For instance, which brain regions are activated under conditions that involve risk (i.e., the outcome probabilities are known), ambiguity (there is a lack of *information* about outcome probabilities), or ignorance (the outcomes were completely unknown and even unknowable)? It was observed that relative to the risk situation, ambiguous information provoked especially marked activation of certain brain regions (inferior frontal gyrus and posterior parietal cortex), and this same outcome was apparent when participants were presented with non-useful information (the ignorance context) (Bach et al., 2009). Using a similar paradigm, marked individual differences could be detected in the neural processes activated in relation to risk and ambiguity (Blankenstein et al., 2017). Perhaps specific cortical brain regions are activated in an effort to make sense of this situation. In essence, the brain doesn't like uncertainty and tries to set things in order. It has been suggested that the individual differences observed in these situations might be related to differences in intolerance for uncertainty, and it is important to consider this variable in assessing neural systems that are involved in decision-making.

Chronicity

There are stressors that, unfortunately, must be endured on a chronic basis: these can be psychosocial or family-related issues, financial impositions, health problems, discrimination or stigma, or a combination of different factors. When stressors are chronic, do not vary much from day to day, and occur on a predictable basis (termed 'homotypic' stressors), we are often able to adapt and perhaps even take charge of our situation. Sometimes, however, the stressors experienced might be chronic, intermittent, unpredictable, ambiguous, and uncontrollable, and vary across days (referred to as 'heterotypic' stressors), making it difficult to establish adequate coping methods, or even to take preparatory steps to enable effective coping. Under such conditions, the usual adaptation that occurs in response to homotypic stressors might be less likely to develop (Anisman et al., 2008). Thus, persistent stressors, such as acting as a caregiver (e.g., for a parent with Alzheimer's or a child with exceptional needs), or dealing with chronic illness or financial problems, each of which involves multiple challenges that might change from one day to the next, might strain an individual's ability to cope effectively and might lead to psychological or physical disturbances (Del-Pino-Casado et al., 2019).

Chronic unpredictable stressors needn't be severe to elicit pathophysiological outcomes. Studies in animals showed that a regimen that comprised a series of mild uncontrollable stressors was effective in this regard (Willner, 2016), although this outcome was not universally observed, tending to appear more readily with somewhat stronger stressors. The chronic mild stress model, perhaps because it has a degree of intuitive appeal (i.e., it 'sounds' right), has received wide recognition and attention, but it seems that the effects of stressor treatments depend on several other factors, such as previous stressor experiences, genetic factors, and the coping styles adopted.

Allostatic overload

In recent years, the concepts of allostasis and allostatic overload have evolved to explain the impact of severe or chronic stressors. Under normal conditions biological changes occur to meet the ebb and flow of environmental demands, thus maintaining stability within the organism. This essentially describes homeostasis. In response to strong or sudden stressful challenges, greater and more rapid biological changes are instigated to restore and maintain stability, which we refer to as allostasis. As adaptable as humans and animals might be, when a strain on the system is excessive, adaptive biological systems might eventually become overly taxed, or specific biological systems excited for excessive periods, resulting in *allostatic overload*. Under these conditions the organism may become ill or more vulnerable to the negative impact of new stressors that might be encountered (McEwen & Akil, 2020).

Measuring stressors

We all seem to know what we mean by a stressor, but for experimental purposes we need to be able to distinguish between different types of stressors and how intense these stressors are perceived to be. Later, we'll be discussing individual differences in how stressors are appraised and perceived, but for the moment we'll examine how stressor experiences are measured, and a few of the limitations of these procedures.

Major life events

Stressful events are known to promote psychological disturbances, and severe stressors are more likely to do so than are relatively mild stressors. In an effort to analyze the impact of stressors, several scales have been developed to predict the relations between stressors and the occurrence of illness or disturbed quality of life. One approach is based on the notion that a stressor ought to be considered in terms of the social adjustment that is required to deal with it (e.g., the Social Readjustment Scale: Holmes & Rahe, 1967). Others simply focus on major life stressors that have been encountered over a set period of time (e.g., six months or one year), basing relative severity on responses from a normative group of participants (Paykel et al., 1971). Other questionnaires focus on particular types of events, such as traumatic experiences that might have occurred at some specific time over the course of the life span (e.g., the Traumatic Life Events Questionnaire; Kubany et al., 2000), or particular emotional-cognitive responses reflective of pathological conditions such as posttraumatic stress disorder (PTSD; the Impact of Events Scale, Weiss & Marmar, 1997). There are scales that deal with specific types of stressors ranging from psychological abuse to breast cancer and other types of challenges.

These scales share certain key attributes (they do, after all, give us an idea of what an individual has experienced), and they share several deficiencies. First, an evaluation of the distress experienced by an individual over some set period of time is implicitly or explicitly based on scaled scores. For instance, in the Social Readjustment Scale, 'death of a child' receives a score of 100, 'trouble with in-laws' gets a score of 29, 'changes in work hours' a score of 20, 'revisions of personal habits' 24, and 'pregnancy' is scored as 40. So the combination of getting pregnant, changing our personal habits, altering our work hours, and having issues with our in-laws is worse than having our own child die. That doesn't make a lot of sense, does it? Furthermore, certain items on the list seem to have a positive valence (e.g., an outstanding personal achievement), others a negative valence (e.g., the death of a close friend), and still others depend on the individual's perspective (e.g., a major change in responsibilities at work, such as a promotion, demotion, or lateral transfer). So, the scale doesn't necessarily reflect adverse events, but instead deals with 'life changes' that might or might not be interpreted as stressors. Of course, the scales don't consider the context in which a stressor had occurred. For instance, the death of a loved one is typically a severe stressor, but it might vary as a function

of whether the deceased person had been going through a severe illness or had died suddenly in an accident.

A further problem with each of these approaches is that they ask individuals to report on events that had previously occurred, and hence are subject to 'retrospective bias'. The way individuals interpret or even remember the past may be colored by how they feel at the moment. If an individual is feeling really great, then past negative events might not seem so bad and they might not even recall that certain adverse events had ever occurred. In contrast, if the individual is currently dejected, then all events in their past may be perceived as the slings and arrows of outrageous (mis)fortune and they might even dredge up events that were insignificant at the time. Further to this, when individuals are ill they often want to know why this occurred. Is it something they did, or something that somebody else did? Or is it just bad luck? In the case of people who are depressed they might be looking for causes and might attribute their depression, sometimes inappropriately, to specific past events. In short, as most defense and prosecution lawyers know, we can't be trusted to recall our past experiences accurately.

Daily hassles

One typically presumes that the more intense the stressor the more profound the consequences. To a certain degree this is certainly accurate. But what are the consequences of those day-to-day annoyances that can really bug you, especially when they occur repeatedly or are superimposed on the backdrop of other ongoing stressors (it's not from nowhere that we have expressions such as 'the straw that broke the camel's back')? Most of us know the experience of having to deal with a new stressor when we're in the midst of dealing with an earlier challenge; our immediate response when this occurs is something like 'Oh no! Not now'. It's hard enough to deal with one event, but when coping resources must be redirected to a second, even if it's a trivial one, our abilities to deal with these situations may become stretched. Most of us must deal with multiple concurrent challenges at some time or other. For some, juggling different tasks is so much part of their repertoire that they can't see how anyone would ever have a problem in this respect. For others, however, juggling multiple demands is exceptionally difficult, taxing their resources, and ultimately leading to illness.

Hassles can be a pain and even small increases in these experiences may result in individuals being more prone to illness and mood disturbances. The relations between daily hassles and pathology are evident across a range of illnesses, including depression, irritable bowel syndrome, and diabetes (e.g., Piazza et al., 2019), although this doesn't necessarily mean that the hassles caused the pathology, as those who are already ill may be more sensitive to day-to-day annoyances. Nevertheless, these seemingly inconsequential stressors, when they continue for long enough, can have a cumulative effect.

The formal publication of the Hassles and Uplifts Scale (Kanner et al., 1981) provided an instrument to show that hassles were related to poor well-being. Since the initial publication of this scale, other similar instruments have been developed for specific groups (e.g., caregivers) or circumstances (e.g., transition to university). Investigations using daily hassles scales typically report an overall score, but it may well be that specific types of hassles are more germane to some individuals than to others. Thus, analyses might be considered in terms of the different types of challenges experienced (e.g., partner, friends, and family hassles, as well as those that are related to home, work, health, and financial strains). This hasn't been widely done, but if it was, then we might see that illness varies as a function of both the severity and type of the stressor encountered, and that certain illnesses are more closely related to particular types of hassles.

In their original report, Kanner et al. outlined some of most frequent hassles and uplifts reported. These included concerns about weight, health of family member, too many things to do, misplacing or losing things, and physical appearance. This paper was published about forty years ago, but some of those same hassles are still pertinent. Today, however, we might find that frustration with our computer, loud people talking on cell phones, emails from work when you're at home, junk emails, and misinformation that inundates us on the internet as being especially annoying. Clearly the nature of the daily hassles we encounter has changed over time. In addition, some hassles might be relevant to the population at large, but might not be at the top of the list for individuals dealing with particular issues, such as caregivers, or people dealing with an illness. When hassles are superimposed on major life stressors, then we're dealing with exponentially greater problems.

Prospective analyses

To overcome some of the limitations associated with retrospective analyses, several researchers attempted to obtain confirmation of stressful experiences by interviewing friends and family members. Although, at first blush, this might seem reasonable, such reports can reflect the observers' own spin or bias, and hence can be just as flawed. Besides this, stress, like beauty, is ultimately in the eye of the beholder, and it's hard to know what a particular person feels by asking someone else. Judicial courts don't allow witnesses to testify about what was happening in the mind of someone else, and researchers are equally skeptical of this approach.

Ultimately, the best way to evaluate the relations between stressful events and later outcomes is by *prospectively* assessing stressor experiences and then relating them to specific outcomes, such as aspects of health. This entails following individuals for lengthy periods (often many years) and then determining whether stressful experiences predict later development of an illness. Not unexpectedly, this can be an onerous task that takes an awfully long time to complete, and participant loss (referred to as subject attrition) can be very high. Thus, one might end up with only those participants who are most dedicated to the project, so that the data collected

are not representative of individuals in general. If the study is relatively short term, say for a matter of weeks or even a couple of months, a diary approach can be used. This can be conducted using a format in which participants answer a brief set of questions at the end of each day (or week) describing what they've experienced. This requires that the investigator meet with participants and form some sort of relationship with them so that they will be motivated to engage in the study on a daily basis. As useful as this approach might be, its use in long-term studies is obviously limited by logistical considerations.

In addition to assessing perceptions of events that participants had experienced some time earlier, scales have been developed to evaluate overall reactions to more recent stressor experiences (Perceived Stress Scale; Cohen et al., 1983). This scale, which is the most frequently used to evaluate the stress load that individuals are experiencing, has been correlated with various psychopathogies. Shortened forms of this scale have been developed so that it may be useful in tracking people's stress perceptions over the course of persistent stressors, such as during the COVID-19 pandemic (She et al., 2021).

Vulnerability and resilience

To this point, we've focused on the different characteristics of stressors that could potentially influence behavioral or physiological outcomes. Of course, these features are only a few of the many factors that influence how stressors affect us. To a considerable extent, previous life experiences, characteristics of the organism (animal or human), and personality variables determine the nature of the stress responses that occur. In the next section we'll focus on the influence of these variables. In assessing these factors, we will not only think about what makes us vulnerable to pathological outcomes related to stressful experiences, but also what goes into resilience in the face of different challenges.

In the context of illness, vulnerability refers to the susceptibility of a person (or a group, or even a whole society) to increased psychological or physical poor health in response to environmental or social challenges. Resilience, by contrast, refers to factors that limit or prevent these events from having adverse effects or, more often, resilience refers to the ability to recover from illness. Vulnerability and resilience aren't necessarily at opposite ends of a continuum. The absence of factors that increase vulnerability doesn't necessarily imbue resilience. A person can, theoretically, have many factors that engender stressor resilience, but a single catastrophic vulnerability factor might be sufficient to undo all that fitness. For example, how often have you heard of a person being perfectly healthy who suddenly died? It took only one malfunction, an aneurysm or a pulmonary embolism, for instance, to undo all that was 'healthy' about that individual. In this regard, one could take the view that stressors act on weak links within a system. After all, the proverbial chain is only as strong as its weakest link.

For an individual to be resilient, numerous ingredients might have to come together in exactly the right amounts. It was suggested that neural mechanisms related to reward and motivation (hedonia, optimism), responsiveness to fear and fear-related situations, and adaptive social behaviors (altruism, bonding, and teamwork) all acted to influence character traits that affected resilience to severely traumatic events (Southwick & Charney, 2018). Another view has it that resilience increases with greater tenacity, trust in one's instincts, acceptance of change, control, and spirituality. Still another perspective attributes resilience to the ability to adapt and be flexible to changes, the ability to problem solve, and possessing a positive outlook on life. No doubt, other resiliency factors, including early experiences and genetic influences, contribute to the ability to withstand the potential for stressors to create harm. Conversely, certain characteristics might enhance well-being even in the presence of factors that would otherwise increase vulnerability to pathology. For instance, an individual with many factors that make them vulnerable to stress-related pathology may overcome challenges by having an excellent social support network, spending time in nature, or perhaps by espousing a spiritual belief that allows them to endure the worst challenges. Several factors that seem to make individuals resilient in fending off or preventing the adverse effects of stressors have been identified (see Figure 1.2), but it's certainly the case that there are enormous differences across individuals in this regard.

Most studies that assessed the relationship between stressful events and pathology have addressed questions related to what makes us ill and what characteristics of individuals are most likely to favor illness. Much less information is available regarding what makes us resilient. Where we most often encounter this topic is in considering the resilience of some people in coping with illness, and the findings from such studies have been especially informative. There are some who, in the context of serious illnesses, are particularly resilient and can maintain, or regain, their mental health readily. Among individuals who have previously encountered a severe illness, the cognitive restructuring that might have occurred (e.g., finding meaning in their illness, which we'll come back to in Chapter 2) may have facilitated their ability to appraise and cope with the subsequent stressor. In other instances, however, previous stressful experiences might not have served in this capacity, but instead acted against well-being. Having gone through a traumatic experience, individuals might simply be too worn down or they may be sensitized so that later stressors in the form of severe illness might simply be too difficult to handle.

Resilience in relation to illness can be influenced by several personality characteristics, such as self-efficacy, self-esteem, internal locus of control, optimism, mastery, hardiness, hope, self-empowerment, determination, and acceptance of illness. Knowing this, unfortunately, isn't going to be of much help in advising anyone how to deal with illness as we can't easily get people to develop better self-esteem or greater hardiness. However, the way individuals appraise and cope with their illness may have profound repercussions for their well-being. Specifically,

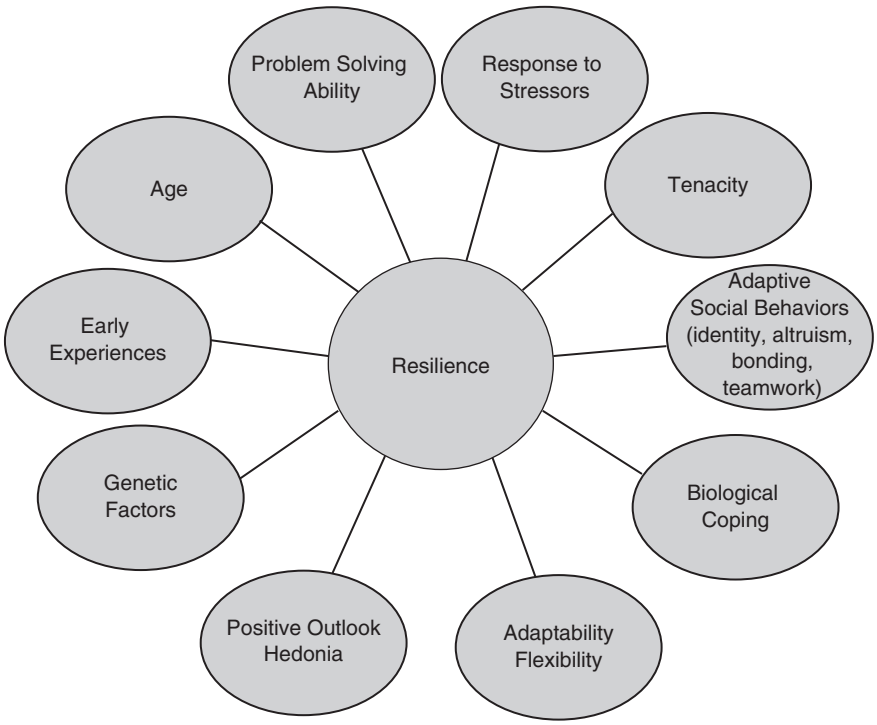

Figure 1.2 Numerous factors might be important in preventing the development of stress-related pathology. These range from personality characteristics, genetic factors, social, cultural, and environmental resources, and a variety of experiences. Some, but certainly not all, of the important ingredients are provided in Figure 1.2. The effectiveness of these resilience factors is likely dependent on the stressor situation, will vary over time as the stressor is experienced, and will also vary across individuals.

positive cognitive appraisal, spirituality, and active coping, which are considered in Chapter 2, were associated with resilience, and these attributes can be promoted with proper training (e.g., using cognitive behavioral therapy or mindfulness training as described in Chapter 12).

In addition to individual difference characteristics, resilience can be attributed to a constellation of processes that reflect a positive social orientation, such as altruism, social bonding, and adaptive social behaviors. In this regard, resilience has been tied to having a strong social identity, being positively connected to others, and having an effective social support network. Socio-ecological frameworks for understanding resilience to some groups, such as Indigenous People, have further emphasized culture, spirituality, and connections to the land. In essence, resilience can entail a relational process involving the interplay of individual, social, cultural, and environmental factors (Liebenberg et al., 2015).

Genetic factors

Years ago, an introduction to genetics entailed a description of Mendelian inheritance (that stuff about pea plants), and most of us came to believe that we inherited certain genotypes (specific genes we received from our parents), which then affected our phenotype (how we looked or behaved). At the same time, it was acknowledged that inheritance could be incomplete, and hence we might not be exactly like either of our parents on any given domain. So, unlike pea plants, people aren't simply tall or short, green or yellow, round or wrinkled: there are all sorts of variations in between. A second premise that was drilled into us was that whatever genes you inherited were those that you were stuck with forever, and that was that. A third premise was that, for some unknown reason, genes could interact with the environment, but nobody ever explained how or why this could happen.

In the past few decades, a revolution has occurred within molecular biology, medicine, and neuroscience. Scientists not only unraveled the genome, they found ways of modifying genes and identifying how genetic changes occur naturally or in response to environmental factors, including stressful events. It is now known that the potential actions or effects of genes can be suppressed by environmental triggers or specific experiences, and consequently might promote (or limit) pathology. In addition, many subtle mutations or variants occur within genes (referred to as 'polymorphisms') that can have profound effects on pathology.

SO, WHAT'S THIS STUFF ABOUT GENES CAUSING BEHAVIOR?

There is this notion that genes cause behavioral phenotypes. That seems pretty vague; it's as if you inherit some gene or set of genes, *et voilà* a behavior appears as if by magic. Moreover, it's often thought that the effects of genes are immutable. In fact, however, the job of genes is to produce proteins, including hormones, peptides, enzymes, and receptors that, in turn, influence behaviors. The effects of these genes aren't immutable but are influenced by environmental factors that moderate how they are expressed. So, you might have genes that dispose you to particular characteristics, but whether these characteristics are expressed can be influenced by day-to-day events or those that occurred way back, even when you were just a fetus.

The chromosomes inherited from parents comprise a lengthy DNA strand that comprise many genes. These genes are composed of strings of nucleotides, which in sets of three (a codon) make up amino acids that form lengthy chains. In DNA, these nucleotide bases (guanine, adenine, cytosine, and thymine) reflect the gene playbook. In essence, when strung together the nucleotides, like letters of the alphabet, form words that become paragraphs, which provide the instructions (or blueprints) for the formation of each phenotype expressed by individual humans.

Using the DNA as a template, RNA is formed through a process called *transcription*. The messenger RNA (mRNA) produced through this process is then decoded or *translated* so that a specific amino acid chain, or polypeptide, is created that will produce a protein (e.g., an enzyme, a hormone, or a receptor). When the characteristics of the DNA are altered, as occurs when even a single nucleotide is changed, the message that's delivered can potentially change and have significant consequences.

The genes on a DNA strand are interspaced by a bunch of additional nucleotides, much of which we know little about. But, in this pile of 'junk DNA' we also find strands that precede the gene. These are known as 'promoters' or 'promoter regions' (there are other names used as well, such as 'response elements') that are thought to act as activators or repressors. Essentially, the promoter serves as an instruction manual for the gene that follows it. These promoter regions can tell a gene when to turn on or off, or even when to interact with other genes. Importantly, environmental events, including stressors, influence these promoters by affecting other chemicals present in cells as well as extracellularly, which can then affect the influence of the gene on neurobiological processes that come to affect behavior.

Genes, therefore, have the potential to affect behavior in one way or another (e.g., increasing certain proteins that favor a disposition towards behavioral phenotypes, such as depression or anxiety), but don't directly cause the behaviors. Ultimately, what we do is dictated by much more than just our genes. Face it, whether it's God or Nature, neither fully transcribes our lives before we are born. That would be pretty boring. Instead, we're faced with multiple paths that can be taken, ways to deal with environmental and social challenges, and these affect the way genes get to express themselves.

Approaches in humans

Many studies have shown that genetic factors might be related to various psychopathological states. These studies have included pedigree analysis in which a particular phenotype has been traced through families to identify the presence of particular genes. Other studies compared pathology in monozygotic and dizygotic twins (identical vs. fraternal twins) to determine the degree to which a particular phenotype was inherited or induced by environmental factors. In some cases, comparisons were made between identical twins who were reared together or apart, although as we'll see later these studies were often fraught with difficulties. In more recent years, one of the most common approaches has involved the identification of particular genes or gene polymorphisms in relation to the presence of pathological states. In some instances, this has entailed finding a sample (cohort) of affected and non-affected individuals (who have, or do not have, a particular phenotype or a family history for a particular phenotype), and then doing whole genome analyses to see whether there is a match between the presence of certain genes or mutations and the appearance of a pathology. The idea was that if we could identify the gene associated with an illness, then determining what proteins this gene is responsible for making (e.g., levels of hormones and immune factors) would facilitate the development of treatments to attenuate or prevent pathology.

It sounds simple enough to find a proper cohort and then do the genetic analysis. However, if it were that simple, then many of the problems in the field might already have been solved. First, the diagnosis of an illness needs to be correct, which isn't always a simple matter as different illnesses have overlapping symptoms. Second, just because individuals have similar symptoms doesn't necessarily mean that these stem from the same underlying biological causes (including genetic and biochemical processes). Two individuals can come to have a particular

chemical modification, but this might have involved different routes (much in the same way as your bank account can be low either because you're spending too much, not earning enough, a bank error, or unknown to you someone had been removing money from your account). Finally, there are potentially many mutations that can occur across the genome (more than a single mutation can also appear on any given gene), and most of these will be entirely unrelated to the pathology being studied. As a result, a huge number of participants is needed to do the studies appropriately. In retrospect, it is understandable that the data from studies that had been conducted were not particularly reliable, probably because so many mutations occur concurrently and due to the small numbers of participants used. What is clear, however, is that for certain pathologies, as well as the underlying biological processes, the expression of genetic effects was not always evident. However, in many instances, the contribution of genetic factors was apparent in the presence of particular challenges, such as life stressors.

Approaches in animals

Studies conducted using rodents have made it clear that genetic factors are fundamental in determining several stress responses and the pathological outcomes associated with stressors. In this regard, several approaches can be adopted to evaluate these relationships. A first step that is often taken is the use of inbred strains that naturally differ with respect to a given phenotype and genotype. Mice of a given inbred strain are genetically identical to one another and differ from those of other inbred strains. The genetic variation between strains is then related to neurochemical or hormonal differences in response to stressors. Of course, simply because a strain is high (or low) with respect to both a given behavioral outcome and particular biological change doesn't mean that these factors are connected. But as described in the box below, this observation can be followed by further analyses.

GENETIC ANALYSES IN PAST DECADES

There are occasions in which it might be suspected that the effect of a stressor is determined by the genetic backdrop upon which it is superimposed; that is, having a particular gene doesn't cause the development of a particular psychological or physical illness, but it might be 'permissive' in that it allows for stressors to have adverse effects. There are some fairly simple, if somewhat tedious, laboratory manipulations that can be conducted to evaluate these possibilities.

When mice of two inbred strains are crossed, the offspring (referred to as the F1 generation) will all be genetically identical to one another. For example, one parent might be dominant for both components of a gene (AA), whereas the other parent may be homozygous recessive (aa). As the offspring inherit one gene from each parent, they will necessarily be Aa. With respect to another gene, both parents may be BB, and so the offspring will necessarily be BB. The same will apply to every gene and hence all F1 animals will be identical to all others. When we cross two F1s, we can then begin to see differences in the genotype: the offspring of an Aa x Aa cross can potentially carry the AA, aa, or Aa combination. Within this F2 generation (also referred to as the 'first segregating generation')

we can determine whether a particular genotype and phenotype are linked to one another (either in the absence of a stressor or following exposure to a stressor). For instance, if every mouse that inherited the AA genotype exhibits a particular phenotype, and every mouse with the aa genotype exhibits a different characteristic, then the genotypes and phenotypes might be related. This doesn't mean they are causally linked, as this is once again simply a correlation between variables. However, if those mice that exhibit a given phenotype do not carry a particular genotype, then we would know with a fair degree of certainty that these genotype, and the phenotype are unrelated.

There are occasions where a single gene can have more than a single phenotypic outcome. This is referred to as 'pleiotropy'. Pleiotropy can occur because genes on a chromosome are inherited as a group (termed 'linkage') or because one phenotype (e.g., a biological change) may directly or indirectly lead to a second phenotypic change. Assessing genes across successive crosses allows us to see whether certain characteristics always appear together (e.g., Does a certain chemical always end up being present in conjunction with a particular heart problem? Does having a certain coat color predict the occurrence of epilepsy?). In effect, we could develop 'biomarkers' that predict later disease occurrence.

As well, one could determine whether genetic influences interact with maternal factors in determining outcomes. As we have just learned, all F1s of inbred strains are identical to one another. If a particular trait is entirely due to genetic factors, then it shouldn't matter who their mother is (i.e., from one strain or the other). However, F1 mice can be produced where the dam (mother) is a member of a particular strain, whereas in another cross the dam is of the alternative strain (referred to as a 'diallel cross'). In this instance the F1s will be genetically identical, but if they differ from one another on some phenotype, then we'd likely ascribe this to characteristics of the mother.

With the remarkable advances in our understanding of molecular biological processes and the related technologies, newer and more sophisticated methods have been developed, including those in which the genome of specific strains of mice can be engineered (transgenic mice). Thus, one can assess the effects of stressors on a particular outcome in the presence of a specific genotype. For instance, a gene can be deleted from (knock-out) or added to (knock-in) the genome of a mouse, and then bred so that numerous identical mice are obtained. This allows for analysis of the role of a particular gene or small set of genes in relation to specific pathophysiological outcomes, and how stressors influence vulnerability to pathology. So, if one believes that stressors cause a rise in chemical X, which then promotes depressive-like symptoms, then strains can be developed that lack the gene responsible for producing chemical X and thus determine whether the depressive-like behaviors are prevented. Conversely, mice can be developed that overexpress the gene that determines the presence of chemical X, with the expectation that depressive-like features would be more prominent. In theory, this approach is potentially revealing and might prompt important hints for human pathology. Yet, as most complex human pathologies likely involve many genes, the effectiveness of this approach is necessarily limited, and certainly doesn't reflect the full spectrum of a disorder. Furthermore, in mice born with a particular gene deleted, there is a fair possibility that other genes may compensate for the deleted genes.

With respect to the latter issue, approaches have been developed so that the gene deletion will occur at specific times in life (thereby limiting the adaptations that could occur through early development). The possibility of using this 'conditional knockout' in relation to pathology has been very exciting, and opportunities exist to assess the combined role of more than a single gene.

More recent approaches have entailed the use of CRISPR-Cas9 technology, and variations of this procedure allow for aspects of a gene to be deleted or inserted and then observing changes of pathological conditions (Jinek et al., 2012). This breakthrough method has met some challenges (e.g., the occurrence of unwanted outcomes, notably 'off target' effects on the genome), but increasingly sophisticated methods are being developed to enhance the accuracy of the procedure.

The key point is that when these genetic approaches are coupled with the analysis of stressor effects (and other factors that may favor the provocation of behavioral disturbances) and experiential factors (e.g., early-life experiences), it may be possible to identify the array of variables that contribute to stress-related disturbances. This approach can also be used to identify the relative contribution of different biological processes to specific features (symptoms) of illness and may ultimately provide biomarkers that can be used to predict an individual's vulnerability (or resilience) to disease states.

The data supporting genetic involvement in stress-related pathology are overwhelming and have been fundamental in the development of new targets for the treatment of several illnesses. One can't say, however, to what extent genetic and environmental factors influence pathology as, among other things, their relative contributions likely vary with the specific disease being assessed. Understandably, most of the molecular genetic analyses that have been conducted have involved animals (primarily mice), and studies of the interactive effects of stressors and genes in affecting illness in humans have been more limited. Nevertheless, as we'll see, when these factors were examined concurrently, the results obtained were impressive.

Precision medicine

Before closing off this section one further issue ought to be introduced. Because of the diversity of symptoms associated with most psychiatric disturbances, the variability in the effectiveness of pharmacological treatments of such disorders, and the presumed array of neurochemical and hormonal processes that might underlie them, it was suggested that analyses of these illnesses might not be best served by assessing them as syndromes. Instead, it might be more useful to consider specific *symptoms* of a disorder in relation to certain genetic components and neurobiological processes that might be related to the efficacy of treatment responses. This is not an easy thing to do, but calls for this approach have become more common, and it has led to the idea that rather than treating all individuals diagnosed with a syndrome in a particular way, it would be propitious to identify the biological and behavioral characteristics of each person, and then to apply 'individualized' treatments.

Most often this is referred to as *precision medicine*. This might be expensive in the short run, but more economically sensible over the long term.

Personality

We all know those individuals who, given the least encouragement, seem to turn into Henny-Penny shouting that the sky is falling, whereas others, in contrast, seem stoic even under the worst of conditions. As we've already seen, there are several factors that make us different from one another. An important set of characteristics engendering diversity of responses to stressors concerns personality attributes. There appear to be relatively stable features of individuals that are important in determining whether they will be more or less vulnerable or resilient to the impact of stressors. Certain personality traits might influence the stress process by affecting the way we appraise or cope with stressors. Others might make us more sensitive or reactive to stressors, and there seem to be characteristics that are instrumental in getting us into aversive situations (e.g., high-risk takers). Many of these factors may have evolved through the parenting individuals received, the socialization that occurred in early life including cultural values and expectations, experiences that shaped particular responses, and it is possible that genetic factors also contribute.

One of the best studied views of personality has comprised the analysis of the Big Five or Five Factor Model. This conceptual framework has a lengthy history that culminated (more or less) with the model provided by Costa and McCrae (1992). The Five Factors include Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. One could argue that each of these dimensions could influence stress responses indirectly, but it is Neuroticism (or emotional stability), which reflects a disposition to experience unpleasant emotions readily (anger, anxiety, depression, or vulnerability), that seems most closely related to stressor reactivity. In this regard, some of the questions from the Big Five Factor inventory ('I get stressed out easily'; 'I worry about things'; 'I get irritated easily') tell us this factor is indeed targeted at stress-related reactivity.

Of course, the Big Five represents only one perspective concerning the personality dimensions that might influence the stress response. In fact, because of the broadness of this framework, it isn't clear that it is the best approach to evaluate predictors of stress reactivity, and numerous other factors have been proposed that are viewed as personality-based moderators of the stress response. Of these, *resilience* has received increasing attention, although it is not considered to be a trait. Resilience is seen as a process (or a constellation of factors) leading to changes that make individuals better able to deal with stressors or to bounce back from the adverse effects otherwise elicited by stressful experiences. Based on the many components that influence the stress response, it can be deduced that there are certain characteristics that lead to an individual being more or less resilient, taking into account that stress responses are governed by multiple contextual factors.

Not surprisingly, individuals who approach situations with an upbeat and optimistic outlook will have a very different view of a situation compared to individuals who enter it with a pessimistic perspective. Scheier and Carver (1985) developed the Life Orientation Test (LOT), which was later revised (LOT-R), to measure the attributes of personality that make up optimism/pessimism. Based on studies using this measure it was shown that optimism/pessimism represents a personality trait that was associated with stress reactions and the ability to meet the demands of severe life challenges. Optimism/pessimism influenced how individuals deal with breast cancer in women and radical prostatectomy in men, moderated hormonal changes and immune responses ordinarily elicited by stressors, and was related to stress reactions, such as burnout (e.g., Carver & Connor-Smith, 2010).

As in the case of optimism, an individual's *self-efficacy* (the belief that tasks can be accomplished and difficulties resolved through one's own efforts) can act as a moderator of the stress response, and thus influence well-being. Likewise, *locus of control* may influence how individuals appraise or respond to stressful events. Specifically, those with a high internal locus of control tend to believe that events in life arise primarily because of their own behaviors and actions, whereas individuals with a low internal locus of control generally think that fate, chance, or powerful others determine what events they encounter. These characteristics may influence how individuals interpret or appraise situations and their own abilities to deal with them, and thus will affect psychological stress responses (we'll be coming back to this in Chapter 9, when we discuss depressive illness).

There are many personality factors that play into how we deal with stressors, and only a small number of these have been mentioned to this point. Numerous volumes have been written on this issue and trying to cover this broad field wouldn't do it any justice, certainly not in just a few pages. As we move forward, however, the contribution of several of these many personality traits will emerge, but the important message here is that you should not assume that the things that bother you, and the way you think stressful issues should be dealt with, necessarily apply to everyone.

Age

An individual's age has a lot to do with how they react to stressors emotionally and physically, and whether pathology will arise. In their thoughtful review, Lupien et al. (2009) indicated that regardless of whether stressors occur prenatally, during infancy, childhood, adolescence, adulthood, or in those who are aged, profound brain changes and mental health conditions can emerge. These outcomes, as already mentioned, can reflect the interaction with genetic and psychosocial factors, but the nature of the pathology that emerges may be dependent on the timing of the stressor experience.

Prenatal experiences

Stressors experienced during pregnancy may have effects on the fetus that will be manifested at various times following birth. In humans, the offspring of mothers who experienced chronic or severe stress during pregnancy subsequently exhibited cognitive, behavioral, and emotional problems during both childhood and adulthood. However, studies that evaluated these relations in retrospective analyses were troubled by some of the factors typical of self-report studies. Moreover, prospective analyses of children born following natural disasters were confounded by changes in quality of life that extended well beyond the primary stressful period (e.g., multiple financial and health repercussions). This, however, does not belie the fact that the severity of natural disasters was a strong predictor of mental health conditions among pregnant and postpartum women, which was related to health outcomes in the offspring.

The fetus's intrauterine environment might profoundly influence its brain development, and hence stressful events that influence this prenatal environment may have repercussions that carry through postnatal periods. For example, stressful events give rise to elevated levels of a stress hormone (corticotropin releasing hormone) within the placenta, ultimately affecting the fetal brain. In addition, among rodents, the offspring of mothers that were stressed during pregnancy showed elevated activity of the stress hormone corticosterone when they encountered stressors postnatally (Grundwald & Brunton, 2015). Furthermore, these experiences influenced neurochemical receptors present within the hippocampus, a brain region that is fundamental in regulating biological stress responses and cognitive functioning. It might be particularly relevant that the effects of maternal stressors have profound effects in female offspring and might be an important element responsible for differences between males and females in the development of stress-related pathology. Chapter 12, which largely deals with the intergenerational transmission of trauma effects, provides a lengthier discussion of prenatal stressor effects.

Early postnatal experiences

Stressors can profoundly affect children, and events early in life may subsequently affect biological responses to stressors in adulthood (see Chapters 4–6), and encourage psychological disturbances, such as depressive and anxiety disorders, and substance use disorders (Chapters 9–11), and may even have effects that are manifested across generations (Chapter 12). There are a wide range of stressors that infants and children can experience, ranging from physical, psychological, or sexual abuse, through to neglect or socioeconomic difficulties (poverty). However, children may not appraise specific challenges in the same way that adults do and therefore it is sometimes difficult to discern how they are being affected by adverse events (e.g., Gruhn & Compas, 2020). In addition, the social, cognitive, emotional, and tangible resources to deal with stressors are not as well developed in children as they are in adults. Thus, it can reasonably be expected that stressful events might have marked

immediate effects on children's well-being, and the notion is intuitively appealing that stressors experienced early in life would have repercussions on long-term well-being.

Studies conducted by Harlow in the 1950s revealed that monkeys raised in isolated environments later became asocial and had vastly deficient parenting skills. It has likewise been known for decades that raising children in deprived environments, as in the case of hospitals or orphanages where they were not stimulated by touch or caress, gave rise to frequent psychological and physical disturbances and exceptionally high levels of infant mortality. In fact, marked behavioral and biological disturbances are seen even when humans or rodents are brought up in environments that are not nearly as severe as those experienced by children in orphanages or monkeys in Harlow's studies. Early experiences, and in particular maternal care and factors related to socioeconomic status, most certainly influence developmental trajectories and ultimately adult behaviors (Shonkoff et al., 2009). Among other things, children from a nurturing early-life environment were subsequently found to have a hippocampus that was larger (by about 10%) than children from a less nurturing environment (Luby et al., 2012), which could have enormous repercussions for stress responses and mental health, as well as learning and memory processes. Furthermore, stressful early-life experiences have been associated with greater adult anxiety and depression, and have been implicated in the development of a variety of diseases of aging, such as vascular disease and autoimmune disorders, and premature mortality.

Re-programming biological functions and epigenetic processes

To account for why early events might have repercussions many years later, it was proposed that psychological stressors result in the programming of various types of biological signals, including those that involve hormonal and immunological processes. The biological changes driven by adverse early-life experiences give rise to several behavioral and cognitive changes (e.g., high threat vigilance, mistrust of others, disrupted social relations, disturbed self-regulation, and unhealthy lifestyle choices) that might engender further stressors or result in these individuals being highly reactive to threats. These behavioral factors, and the stress reactions they elicit, might exacerbate already disturbed hormonal and immunological functioning associated with the early experiences, and eventually might culminate in pathology (Lautarescu et al., 2020).

In considering the effects of stressful early-life experiences, one should not just focus on severe cases, such as abuse. Indeed, simply having an inattentive or neglectful parent can have profound and lasting repercussions on cognitive functioning and on vulnerability to stress-related disturbances. Studies with rodents indicated that early-life neglect (during the initial ten postnatal days) may engender disturbed adult behavioral and biological functioning, whereas stimulation enhanced an animal's ability to contend with later stressor experiences. In this regard, it seems that if pups had an attentive mother who cared for them well (in the case of rodents,

this involves lots of licking and grooming of pups), then these animals grew up to be relatively resilient in the face of stressors (Kaffman & Meaney, 2007). In contrast, stressors experienced early in life, including insufficient maternal attention, was related to the later development of diverse psychological disturbances (Turecki & Meaney, 2016).[2] Essential questions that have emerged have been concerned with which neurobiological processes are involved in these outcomes, and whether the adverse effects of early adverse experiences can be reversed, or if there are variables that may compensate for poor parenting.

In their influential review and commentary, Shonkoff et al. (2009) indicated that numerous diseases that appear in adulthood, including psychiatric disorders, diabetes, heart disease, and various immune-related disorders, might have their roots in childhood stressor experiences. They suggested that the cumulative effects of life stresses contribute to allostatic overload that might eventually lead to pathology or, alternatively, that stressful experiences in childhood may become biologically 'embedded' (either through processes that cause the actions of certain genes to turn off or via sensitized biological responses) so that their consequences might appear years later. These investigators distinguished between 'tolerable' stressors that, with appropriate social support, might allow individuals to learn how to cope with such events, from those described as 'toxic' stressors (extreme poverty, psychological or physical abuse, neglect, maternal depression, parental substance use, and family violence) that are more likely to lead to pathology. In effect, there are challenges that are basically part of growing up that have positive effects as they allow individuals to learn how to appraise and cope with events properly. However, there are also 'toxic' challenges that no one should have to endure.

EPIGENETIC PROCESSES

A fairly hot topic for many years has been the possibility that stressful events (as well as other factors) may affect the expression of genes, without altering the sequence of amino acids that make up these genes. This has been termed 'epigenetics', which essentially refers to changes in gene expression that result in a phenotypic change, but without fundamentally altering the underlying DNA sequence (Szyf et al., 2016). The silencing of genes through epigenetic changes may come about when certain portions of DNA become methylated, which entails a process in which methyl groups are added to genes, thereby modifying their function so that specific phenotypes may be altered. Epigenetic changes can likewise occur through processes related to DNA being wound around histones, which allow a lengthy DNA strand to fit into the nucleus. Should the DNA be wound too tightly, important genes may be less accessible, thereby preventing gene expression. In addition

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[2]In most species, infant care is conducted by the maternal parent, although there are exceptions in which both parents contribute. In humans, parental responsibilities are often shared, families may comprise same-gender parents, and in some cultures extended families or communities may play a key role in infant care. Under these circumstances, it might be expected that solely considering maternal behaviors may not fully represent the environment of the infant that influences well-being.

to epigenetic changes, after DNA has been transcribed to RNA, gene expression can be influenced through 'post-transcriptional gene regulation' in which small non-coding RNA (microRNAs) can silence RNA thereby affecting phenotypic outcomes. While distinct from epigenetic actions, microRNAs have been related to the development and progression of some diseases.

Epigenetic changes promoted by environmental and experiential factors can occur at any time of life, but the early-life period is especially sensitive in this regard so that the expression of genes are suppressed. This gene suppression could affect whether certain neurochemical processes are operating appropriately, and hence could have effects with respect to how individuals deal with stressors, or they could have effects directly on processes that lead to illness. Importantly, these epigenetic actions could persist over the course of an organism's life and could be transmitted across successive generations (if the epigenetic change occurred within the germline, i.e., the sperm or ova), hence affecting the biological and behavioral processes of the children and grandchildren of the individual that had initially been affected.

Epigenetic changes contribute to some forms of cancer, as well as autoimmune disorders, such as rheumatoid arthritis, and adverse early-life experiences (abuse or neglect) might have long-term consequences owing to epigenetic changes. In this regard, analyses of the brain tissue of depressed individuals who died by suicide revealed epigenetic changes in the genes associated with stress-relevant neurochemical responses among those individuals who had experienced early-life parental neglect (McGowan & Szyf, 2010). Much less studied has been the possibility that epigenetic alterations could have beneficial effects on the offspring by silencing genes whose activation might otherwise produce negative outcomes.

To a certain extent the focus on epigenetic changes associated with early development have overshadowed events that occur in older age, which is also a highly vulnerable period for the development and progression of varied illnesses. As individuals age the accumulation of epigenetic changes, like that of mutations, can have pronounced effects on health. In fact, environmental challenges and stressors may affect biological aging, and an older age may influence the actions of these challenges that can influence stress buffering processes (Barrere-Cain & Allard, 2020). Given the involvement of aging processes in the emergence of so many diseases, much greater attention ought to be devoted to environmentally and experientially determined epigenetic factors that contribute to pathology.

Transitional periods

In addition to prenatal and early postnatal periods, there are other developmental times during which an organism might be especially sensitive to stressors. These include phases of life that are referred to as transitional periods. We all go through events in life that involve change or transitions that call upon our adaptive resources. Entering kindergarten, for instance, is one of these life transitions. You're suddenly a big boy or big girl, having graduated from daycare, but then you find yourself in a new social context, where it's not just you and your family members anymore. Likewise, entering high school, college, university, or the workforce is an exciting major life transition during which we might experience insecurities and

may be particularly vulnerable to the adverse effects of stressors. Leaving home, living with someone else, getting married (or divorced), moving cities and retirement, represent life transitions, and at these times responses to stressors might be altered (Rudolph et al., 2021).

In rodents, the juvenile (early adolescent) period spanning postnatal days 28–35, is exquisitely sensitive to stressors and has protracted ramifications on vulnerability to the stressor-provoked neurochemical and behavioral changes that occur in adulthood (Albrecht et al., 2017). The sensitivity of this developmental phase may be related to reorganization of many neurotransmitter systems that occur at this time. As well, it is a developmental phase during which rodents display increased socialization (play) with conspecifics and increased independence from the dam. Stressors in the form of social instability encountered at this age may influence brain development, particularly the hippocampus, and thus may affect some forms of memory in adulthood, including those associated with fear. Moreover, as adults, these rats exhibited elevated levels of the stress hormone corticosterone and reduced numbers of receptors in the hippocampus that are sensitive to corticoids, likely owing to epigenetic variations (Chaby et al., 2020). Interestingly, in both rodents and humans, the adolescent period is one during which fear responses are especially difficult to overcome. Once an anxiety or fear response is established it may persist even after the danger is no longer present, and among adults with fear-related disorders, about 75% of cases have their roots in anxiety that developed at earlier ages. These fear responses are not immutable, as they could be attenuated with appropriate treatment; however, this was more difficult to achieve in adolescent rodents and humans.

Adolescence in humans is a period in which individuals are highly focused on 'fitting in', developing an adult-like identity, finding a peer group that will accept them and with whom they feel comfortable, showing interest in a sexual partner, and even concerns about events that they will be facing some time down the road. These issues become particularly acute as many young people move from secondary school to college or university, as this transition requires considerable adaptation in the face of psychosocial and environmental changes. During this stage of life, particularly if it involves moving out of the family home or to a different city, many individuals leave behind long-standing social networks and form new ones, including changes in their romantic relationships, and efforts to gain social, economic, and emotional independence. In effect, just when young people are expected to establish their independence, they encounter a transition replete with factors that destabilize their support systems. Adolescents may struggle with a collision between expectations of autonomy and contending with a series of novel and stressful experiences that would be best met with the support of others.

Given the distress associated with transitions into adulthood, a considerable number of young people experience clinical levels of major depression, dysthymia (i.e., chronic low-grade depression), and anxiety disorders that were estimated to be as high as 25–40% across many countries. Moreover, many may have undiagnosed or subsyndromal symptoms of depression and anxiety that could reflect

the antecedent conditions of major depression. Thus, although the transition into adulthood can be seamless and exciting, for some it is a challenging process that feels overwhelming and every day is filled with hardships. The recognition of this problem has resulted in many universities and colleges instituting programs to diminish distress amongst students, as well as to determine which individuals will be at greatest risk of faring poorly.

Older age

Before starting a discussion of stress and aging, we need to distinguish what we mean by aged or aging. For those born in the mid-portion of the preceding century when the mean life span was somewhere around 75 for females and 70 for males, someone at retirement age (65) was considered to be fairly old. With changes in lifestyle (diet, exercise) and medical treatments, life expectancy has increased appreciably, and 65 is hardly seen as 'old', and certainly not by others who are about that age. Still, being old is no picnic and has significant downsides. With age comes decaying biological systems so that disease states generally become more common: neurodegenerative and cardiovascular illnesses appear; kidney, liver, and lung diseases are on the horizon; and metabolic disorders become much more common. Whether an individual ages 'successfully' or not depends on complex interactions that involve genetic factors, earlier experiences, environmental influences, concurrent morbidities, and the ability to cope with stressors.

Studies in rats point to yet another age-related factor that interferes with well-being in association with stressors. In older rats, the release of several brain neurotransmitters, such as norepinephrine, as well as the stress hormone corticosterone, is elevated under basal conditions (as it is in humans) and increases appreciably in response to acute stressors. However, normalization (the return to basal levels) may take longer to occur than it does in younger animals. It is thought that hormonal and neurochemical responses elicited by stressors are of adaptive value, but once the stressor terminates, things ought to return to normal relatively quickly. The sluggish normalization of neurotransmitter release and corticosterone levels in older individuals might have some unfavorable repercussions.

A good conceptual framework to use regarding stress and aging is that of allostasis and allostatic overload (Goldstein, 2011). Let's face it, the wear and tear on a 70-year-old person (like a 70-year-old car) will be much greater than the load that has been put on a much younger person or car. The greater the strain an individual had encountered previously, and the greater the challenges they are currently undergoing, the more likely it is that the car bumper will fall off. However, as individuals age, vulnerability to pathology might not only stem from decaying biological processes but might be a result of the dwindling availability of resources that lend themselves to effective coping, including the reduced availability of social

support from family and from friends who might not be able to help (or who might have predeceased them). Of course, on the other side, with age may come wisdom, including learning better coping strategies, and how to appraise situations and put them into perspective.

Case study 1.1

Scamming older people

When Julia A, who had just celebrated her 67th birthday, arrived home from work, her 77-year-old husband, Mel, was giddy with glee. He had received an email indicating that his lost cousin in Russia, Yvegeny A, had died suddenly and he was the only known living relative. He stood to inherit millions and all he had to do was front the legal costs that amounted to $2,000. She told him that this was a scam and that he was behaving foolishly, but he was adamant that it might not be since he had relatives in Russia with whom he hadn't had contact in decades.

The next day, Julia received a similar email but in this case the death was a cousin, Giorgio A, who had lived in a small Italian village. Again, she and Mel could inherit millions and all they had to do was cover legal fees in advance. Upon getting home she presented her still very happy husband with the email she had received assuming this would open his eyes. Instead, he was over the moon delighted, saying, 'How lucky can a guy get. I've won the lottery twice.'

Although elderly, Mel had been functioning perfectly well on a day-to-day basis, even if he seemed to be experiencing mild cognitive decline. Since this gullibility was out of character for Mel, who tended to be on the frugal side and wouldn't send cash to anyone in advance, Julia was concerned and thus consulted with a family friend who was a gerontologist who specialized in dementia.

She was informed that mild cognitive deficits, or specific components of cognitive functioning that emerge with age, may make older individuals more vulnerable to deceit. Scammers know this and thus older people are often targeted over the phone or internet. The gerontologist had indicated age-related loss of neurons might make some people injudiciously trusting or, phrased differently, that they lost their ability to 'doubt' information that would ordinarily appear suspicious. It seems that with age, a region in the brain associated with appraisals and decision-making, aspects of the prefrontal cortex, may undergo changes for the worse. Even among otherwise intelligent people, when the brain dysfunctionality occurred, individuals had trouble in the effortful process necessary for disbelief, and hence they were more likely to be the victims of fraud. Being scammed is embarrassing and stressful for anyone, but for the elderly it's yet another slap in the face that highlights their limitations.

Julia was relieved that Mel wasn't necessarily at an early stage of Alzheimer's disease. Of the many illnesses faced by older people, one of the most dreaded is dementia. The loss of self and the indignities that can be experienced in relation to many diseases are often

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beyond what anyone envisions for themselves. However, Julia's fears weren't entirely eliminated as she also learned that among the elderly, further cognitive decline could be linked to stressful experiences. A prospective study among elderly individuals conducted over just two and a half years revealed that protracted, highly stressful experiences were associated with increased conversion from individuals exhibiting mild cognitive impairments to moderate levels of dementia. There had been indications that cognitive deficits and 'tau pathology' (a substance implicated in Alzheimer's disease) are influenced by cumulative stressor experiences (Sotiropoulos & Sousa, 2016).

For some 'seniors', particularly those who've aged successfully (healthy in body and mind), this time of life can be wonderful. For many others, however, aging is the pits, and they certainly don't refer to it as 'the golden years'. Besides being accompanied by health problems and repeated visits to different doctors, aging is associated with difficulties getting around, change of life purpose, the loss of friends (through death or translocation), the dispersal of family members, and diminished coping resources. In fact, loneliness, which is stressful for individuals of any age, is often notable in the elderly as their social network might have dissipated, and certain types of stressors produce especially marked physiological changes (e.g., cardiovascular responses) relative to those apparent at earlier ages. Beyond these stressors, older individuals might suffer multiple indignities, including stigmatization and unsupportive interactions (often being patronized, talked down to, dismissed, made to feel invisible, or made to feel like a burden). In light of these factors, it seems that the coping strategies endorsed by older individuals might shift away from those that reflect a sense of control over their own lives, to those that are reliant on others. Is there any wonder that depression rates in older people are as high as they are?

Sex and gender

Certain illnesses, such as mood disorders and autoimmune disorders (those in which the immune system turns on the individual, as in the case of multiple sclerosis, lupus erythematosus, and rheumatoid arthritis), occur more frequently in women than in men. In the case of major depression, the ratio is about 2:1, and posttraumatic stress disorder (PTSD) that develops in response to traumatic events occurs more frequently among females than males. These gender and sex differences might occur for any number of reasons, including differences in the stressors actually experienced, greater stress-relevant neurochemical disturbances in females, the influence of particular sex hormones, socialization processes that promote certain behavioral styles being adopted, the endorsement of less adaptive coping strategies to deal with stressors, or other psychosocial factors that favor the development of illness. To the extent that sensitivity or reactivity to stressors differs between sexes, one might expect to find that the treatment of stress-related

disorders would likewise differ. In discussing the neuroendocrine effects of stressors (Chapter 5), we'll see that hormonal responses differ appreciably in relation to sex, which may have significant ramifications for the development and progression of diseases. Despite these inequities, on average, women still outlive men just as they did fifty years ago, although the gap has been closing. This is not simply due to a bias regarding who is in the workforce, as the same statistics are apparent in both industrialized and non-industrialized countries.

HOW COME WOMEN LIVE LONGER THAN MEN?

The greater life span of women relative to men has been observed globally (Ortiz-Ospina & Beltekian, 2018). This difference may be related to sex hormones, notably estrogen and testosterone, that affect immune functioning so that females may be better equipped than males to fend off certain illnesses (e.g., colds and influenza) (Shepherd et al., 2021). Relatedly, the hormonal consequences of women having two XX chromosomes, whereas men have an X chromosome replaced by a Y, may influence vulnerability to non-communicable diseases (Anisman & Kusnecov, 2022), thereby affecting longevity (Sampathkumar et al., 2020). Alternatively, differences in several lifestyle factors may converge to produce the gap, as might the greater disposition of men to engage in risky behaviors. Moreover, men are less likely to seek medical attention in response to signs of non-communicable diseases (e.g., heart disease, cancer) that are highly linked to mortality (Thornton, 2019). There doesn't seem to be a single cause for the sexual dimorphism related to life span; it may be significant, however, that the gender gap has narrowed from 5.2 years to about 3.6 years and it is expected that difference will continue to diminish, especially with the adoption of healthier lifestyles and improved therapeutics.

Previous experiences and sensitization

There is no question, as we've seen in our discussion of early-life events, that an individual's previous experiences may influence responses to later stressor encounters. It's not simply a matter of our memories of previous experiences influencing our responses to stressors, which we hear much about, usually in the context of 'triggering events' that instigate adverse psychological responses. The characteristics of the neurons themselves may have changed, so that the response to later stimulation is enhanced, which is referred to as 'sensitization'.

Studies in animals indicated that the brain's neurochemical changes exerted by acute stressors can be induced more readily if they had previously encountered stressful experiences (Anisman et al., 2008). As we'll see later, stressful events might come to change the characteristics of neurons so that they become more responsive (or, conversely, less responsive, which is termed 'desensitized' or 'down-regulated') to later challenges. There are several ways by which sensitized responses can develop, and many biological systems are subject to this effect. One of these concerns changes of neuronal plasticity, which refers to the ability of the synapses to change, or the

connection between neurons to change in strength as a result of experiences. Plasticity is a fundamental feature of the brain that is required for, among other things, learning and memory, and sensitization is an instance of this neural plasticity. However, when we deal with this phenomenon, it should be considered that processes responsible for the sensitization of a given neurotransmitter system may differ from those associated with a second transmitter system. For instance, it is possible that sensitization of some systems may involve altered expression or sensitivity of relevant receptors, whereas in other systems this may involve the synergistic (multiplicative) effects of two or more biological substrates. Importantly, the effects of stressors on these neuronal responses may persist for lengthy times following a stressor event, and it is possible that sensitization processes contribute to the long-term influence of stressors on psychological states.

Based on such findings, it has been maintained that the biological processes that promote depressive illness may evolve over time with repeated stressor experiences and recurrent depressive episodes. With each stressor experience, or with each episode of depression, the stressor severity needed to elicit the depressive mood becomes smaller, until eventually very little is needed to encourage a depressive state. There have, indeed, been numerous reports showing that although the first episode of depression is preceded by fairly strong stressors, less severe stressor experiences may cause illness recurrence. In fact, among individuals who experienced recurrent episodes of depression, very mild stressors were needed to re-induce the depressive state, and even reminders of stressful experiences were sufficient to produce this outcome (Post, 2021).

In addition to sensitization of biological systems, how we appraise (evaluate) the world around us can be influenced by our previous stressor experiences. For example, it isn't hard to imagine that if individuals encounter a stressor that traumatized them, later reminders of these same experiences will have profound psychological and physical repercussions. This also applies to adverse experiences that occurred in early childhood. Children who experience a trauma will, as adults, be much more likely to develop depressive illness (Martínez et al., 2021), and importantly this is apparent even when statistically controlling for the family and contextual factors that have been associated with depressive illness. This effect of early-life adversity is not limited to young children, having similarly been observed in women that had experienced physical or sexual abuse in adolescence. It might be that when certain stressors are encountered, they cause changes in numerous aspects of an individual's life, altering the trajectory of life experiences (friendships and other support networks, coping processes, lifestyles, general world view, and even the propensity for further stress encounters), culminating in a greater vulnerability to psychological and physical illness.

Stress generation

Stress generation refers to occasions wherein individuals, because of their circumstances, may bring stress onto themselves. This doesn't mean that we should blame the victim for finding themselves in adverse situations. Instead, it means

that sometimes, through any number of factors, specific events result in a proliferation of consequences. For example, a person might lose their job, and as a result can't pay their rent and so lose their home. They might start 'couch-surfing', but slowly their friends no longer respond well to them. Or some people make the wrong decisions or choices in an effort to cope with the event, creating even greater challenges. Depressed individuals, by their behaviors, are thought to be a particularly vulnerable group for stress generation (Liu & Alloy, 2010). For instance, one partner in a romantic relationship may find it challenging to deal with the other person's depressive state (poor mood, negativity, and aggressive behaviors that might occur). This may therefore potentially lead to the dissolution of the relationship because the partner no longer knows how to cope with the situation. Essentially, the depressed partner, by engaging in negative behaviors (often these involve behaviors of a dependent nature), may have contributed to the break-up and the loss of an important relationship that they relied on as a stress buffer. Likewise, the depressed individual, whose symptoms might include apathy and withdrawal, may alienate their co-workers, and ultimately find themselves struggling at work. Stress generation is more common among those high in neuroticism (emotional instability), which is not surprising as their emotional sensitivity might provoke interpersonal conflicts. It has been reported that perfectionism contributed to interpersonal stressors, as did sociotropy (a characteristic in which individuals exhibit high levels of dependence and an excessive need to please others). This is in line with the perspective that individuals whose self-esteem is based largely on their relationship with others place themselves in a situation where interpersonal conflicts will occur, which might thereby contribute to stress generation.

In a sense, stress breeds stress. In some instances, by their behaviors and attitudes, individuals make their worst fears turn into reality. Let's have a look at one example where this appears, namely that of dating abuse, which occurs in about 20% of dating relationships among university-aged individuals (the abuse goes in all directions, as people of all genders report psychological abuse). Significantly, women who had previously been abused were reported to be at increased risk of being in subsequent abusive relationships. Among undergraduate women, about 70% of those who encountered dating abuse reported a previous assaultive experience (childhood assault, assault by a previous partner), whereas only about 25% of those in non-abusive relationships had such a history (Matheson et al., 2007). It was not a matter of women who experienced abuse generally being more likely to encounter traumatic experiences, as other forms of trauma (e.g., accidents, witnessing violent events, and the death of someone close to them) were not more common among abused women. Instead, it seemed as if an experience of abuse that occurred earlier in life effectively set in motion a cascade of changes that favored later stressor encounters and increased vulnerability *to the effects* of those stressors, which provoked depression and PTSD. What exactly this process entails isn't known. It is possible that the initial abusive experience engendered a set of beliefs and learned coping responses that facilitated women's ability to endure or tolerate their abusive situations, or alternatively the experience may have undermined their

confidence to leave a bad relationship. Additionally, early abuse experiences may have limited the development of social and emotional skills, which diminished the ability to appraise and respond appropriately to emotionally charged stressor situations. In view of the relations between dating abuse and earlier abusive experiences, increased incidence of stress generation, diminished self-esteem and self-worth, depression, and PTSD, it would be inappropriate to consider an adult experience in isolation from other factors that might be tied to stress generation.

Conclusion

Stressors come in multiple forms and vary across numerous dimensions. The extent to which stressors affect our well-being is related to the nature of the stressor and the psychological attributes of that stressor, such as the controllability, predictability uncertainty, and ambiguity of stressors or threats of impending stressors. As well, the impact of stressors may be governed by the chronicity of stressor experiences as well as stressors that had previously been encountered (e.g., early in life). Individual difference factors are likewise fundamental in determining to what extent a stressor might have severe adverse consequences. In this regard, genetic make-up, age, gender, and personality factors are effective in moderating stress responses.

Stressful events are common life experiences whose effects can be negligible and brushed off readily, or they can be extremely severe, affecting individuals for years and across generations. Numerous factors can contribute to our vulnerability to stressor-elicited illnesses, and likewise being resilient in the face of severe stressors and pathology involves complex interactions between a constellation of variables. To a significant extent, however, the impact of stressors will be determined by how they are viewed or appraised and how individuals cope with them. If there's a single take-home message, it's that stressful events and their effects are not only complex, but that there are marked inter-individual differences in their effects. What might be stressful to you might be a walk in the park for someone else, and conversely someone else's greatest distress may be a mild annoyance for others. Without considerable experience (and perhaps not even then), don't presume to understand another person's stress responses.

Suggested readings

Lupien, S.J., McEwen, B.S., Gunnar, M.R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*, 434–445.

Southwick, S.M. & Charney, D.D. (2018). *Resilience: The Science of Mastering Life's Greatest Challenges*. Cambridge, UK: Cambridge University Press.

McEwen, C.A. & McEwen, B.S. (2017). Social structure, adversity, toxic stress, and intergenerational poverty: An early childhood model. *Annual Review of Sociology*, *43*, 445–472.