Although the field of neuroscience has historically focused on disease, impairment, disability, and the harmful effects of stress and trauma, the growing field of positive neuroscience focuses on studying what the brain does well. Positive neuroscience is a blend of positive psychology and neuroscience, and positive neuroscientists are interested in the neural mechanisms that serve to enrich a person’s life and potentially provide a buffering effect against negative

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psychological functioning (i.e., depression, anxiety, and other mental health disorders). In this chapter, we focus on the neurobiology, as well as other biological mechanisms, that underpin several positive psychological traits. The commonalities among the brain regions involved in the various psychological traits are striking; for example, the anterior cingulate cortex is implicated in empathy, resilience, optimism, creativity, spirituality, wisdom, and social decision making. Similar commonalities are found among the genetic markers and among the blood and saliva markers involved in the various positive traits. To emphasize these commonalities, we have chosen to organize this chapter by biological mechanisms instead of by positive psychological traits. Specifically, we discuss the following three biological mechanisms: 1) the neurocircuitry of the positive psychological traits with the most empirical support, including empathy and compassion, resilience, optimism, and creativity; 2) the genetic bases of positive psychological traits; and 3) blood and saliva biomarkers associated with positive psychological traits.

Neurocircuitry of Positive Psychological Traits

Measurement of Brain Function

Many studies on positive neuroscience use advanced neuroimaging tools, such as functional magnetic resonance imaging (fMRI). fMRI can be used to measure brain activity during tasks thought to directly measure a particular psychological trait (e.g., measuring empathy by showing the participant a video of someone suffering) or to monitor brain activity during emotional or cognitive tests (such as a facial affect matching task) known to activate the brain regions of interest, which can then be examined for correlations with positive psychological traits outside of the scanner. Furthermore, a more traditional neuropsychological approach has also been used to understand the neurological impairments and/or changes in positive traits after neuronal injury.

Another approach examines the potential therapeutic effects of brain stimulation on improving positive psychological traits. Transcranial direct current stimulation uses static direct electrical currents to stimulate the brain. It is safe, painless, noninvasive, and inexpensive. Novel work by Professor Snyder and colleagues at the Centre for the Mind in Sydney, Australia, has demonstrated that by using transcranial direct current stimulation to “turn off” certain parts of the brain, other skills such as problem solving, insight, and creativity can be enhanced (Chi and Snyder 2012). These various techniques for measuring the neural mechanisms of positive psychological traits have helped scientists discover brain regions implicated in several positive psychological traits, as described in the subsequent section “Empathy and Compassion” (and shown in Figure 13-1 later in this section).

Empathy and Compassion

Empathy

A general consensus in the literature on the neurocircuitry of empathy is that of shared networks or shared representations. This theory posits that sharing the emotions of others activates neural structures similar to those activated by experiencing the same emotions firsthand. Empathic responding appears to be context specific and dependent on information available in the environment. The anterior insula and medial and anterior cingulate cortex have frequently been implicated as being consistently activated in empathy. At least two forms of empathy have been identified: affective-perceptual (feeling with) and cognitive-evaluative (perspective taking) components, with these dimensions thought to have overlapping but nonidentical neural bases. In a meta-analysis of the relevant fMRI literature, Fan et al. (2011) found that the left anterior midcingulate cortex was activated more frequently when a person was engaging in the cognitive-evaluative form of empathy, whereas greater activation in the right interior insula was found when a person was engaging in affective-perceptual empathy. The left anterior insula was active in both forms of empathy, and the researchers concluded that the bilateral insula, dorsal anterior cingulate cortex, anterior midcingulate cortex, and supplementary motor area form a core neural network of empathy. This core neural network was observed when research participants were empathizing with a variety of different emotions, including pain, fear, disgust, anxiety, and happiness, implying that this neural network is relevant to empathy in general and is not emotion specific. Other brain regions that have been implicated in the empathy network include the anterior temporal cortex, sensorimotor cortex, the inferior frontal gyrus (IFG), the prefrontal cortex (PFC, including medial orbitofrontal PFC, dorsomedial PFC, and dorsolateral PFC), the superior temporal sulcus and gyrus, and temporal-polar and temporal-parietal cortex areas.

Brain activity during emotion processing appears to change with age, with older adults demonstrating less neural activity with negative stimuli, a positivity bias for remembering positive information better than negative information, and an ability to ignore irrelevant negative stimuli. Researchers call this the “emotion paradox in the aging brain” and interpret the age-related brain changes to emotional responding as improved emotional control and regulation in late life (for a comprehensive review, see Mather 2012). Our group examined the neural correlates of emotional and cognitive empathy in healthy older adults (mean age = 79) and found more deactivation in the bilateral amygdala and right insula during a working memory task among older adults with higher levels of affective-perceptual empathy (Moore et al., in press). We also found greater bilateral
insula and right frontal activation during a response inhibition task and greater midline precuneus activation during an affective facial matching task in older adults with higher cognitive empathy. Our preliminary findings speak to the possibility of differential relationships for the different forms of empathy in old age and provide support for the emotion paradox theory.

Compassion

The neural circuitry of compassion is less well understood. Compassion can be defined as an outward behavioral response of empathy, with the intention of reducing another's perceived suffering. Given that having an empathic response is a precursor to compassionate behavior, it is probable that empathy-related neural processes are activated during personal experiences of compassion. In one of the few fMRI studies specifically examining neural activation during the experience of compassion, Simon-Thomas and colleagues (2012) found that when they induced compassion in their undergraduate research participants during scanning, the midbrain periaqueductal gray was activated. They also found that self-reports of compassion were related to activation in a region near the periaqueductal gray and in the right IFG.

Central Function of Brain Regions Involved in Empathy and Compassion

The anterior insula and anterior and midcingulate cortex have consistently been shown to be involved in experiences of direct pain. The same regions are activated when one takes the perspective of another person and feels someone else's pain, which lends support to the shared-network perspective on empathy. Empathy-related insular and cingulate activity may represent a link between interoceptive (data from within the body, such as blood oxygen levels, muscle tension, and blood pressure) and exteroceptive (data from the outside world) stimuli, but this proposed linkage is speculative at this time.

Resilience

The study of the neurocircuitry of resilience has received considerable attention in the scientific literature. Scientists have attempted to elucidate both the psychological and the neurobiological underpinnings of resilience, which has been difficult given the complex nature of this construct. To date, neuroimaging studies of resilience have focused on brain regions involved in emotion and stress regulation circuitry. Other regions believed to be critical to resilience include pathways involved in attention, learning and memory, speed of recovery from stress, positive versus negative outlook, response to fear, and adaptive social behaviors. Across review papers, the PFC has consistently been implicated as a critical brain region for resilience. The PFC is involved in intentional emotion regulation, which can help with the self-regulation of stress. Inhibition of subcor-
tical regions by the PFC is heightened among depressed individuals, which can result in a reduced capacity to regulate stress-related emotions.

Evidence also shows a role for the insular cortex in resilience. At the OptiBrain Center at the University of California, San Diego, cognitive neuroscientists have conducted multiple studies examining the neural pathways believed to be critical to resilience in elite athletes (e.g., Olympic athletes, marines, adventure racers). Elite athletes are thought to have unrivestiment brains and therefore have been able to provide researchers with insight into optimal resilience performance. Paulus and colleagues’ work at the OptiBrain Center used fMRI methods to probe interoceptive distress (e.g., the sensation of increased difficulty breathing in air) in elite athletes and “normal” participants and found group differences in resilience in the insular cortex, with the elite athletes having an attenuated insular cortex activation during an aversive experience (Paulus et al. 2012). Similar insular patterns were found by this research group in elite military personnel, providing evidence for the role of the insular cortex in handling stress, or, said another way, having resilience under extreme environmental conditions. The literature has mixed evidence for the role of the hippocampus, amygdala, anterior cingulate cortex, hypothalamic-pituitary-adrenal (HPA) axis reward circuitry, and somatic nervous system in resilience.

Overall, the literature points to a relationship between resilience and core emotion-processing regions (i.e., amygdala, insula) in younger adults. In an unpublished study examining the association between resilience and emotion processing among older adults, we did not find any relationship between resilience and amygdala or insular cortex response. However, dorsolateral PFC response was greater in high-resilience older adults, indicating that older adults who are more resilient may have more dorsolateral PFC responses during an affective task, whereas their younger counterparts may have more amygdala and insular responses. Whether these differences are reflective of cognitive coping strategies, changes in emotion regulation, other processing differences, or are simply due to sampling differences is currently unknown.

Optimism

The majority of studies examining the neurocircuitry of optimism have been done exploring the optimism bias. The optimism bias is defined as the tendency for people to overestimate the likelihood of experiencing good events in their life and to underestimate the likelihood of experiencing bad events. In the Affective Brain Lab at the University College London, Sharot and colleagues found that trait optimism was related to enhanced activation in the rostral anterior cingulate cortex (rACC) and that the optimism bias was also related to enhanced activation in the rACC as well as the amygdala (Sharot et al. 2007). They also found a strong correspondence between brain responses in the rACC and
amygdala when people were imagining future positive events and less correspondence of brain activation between these two structures when people were imagining future negative events. In another study, Sharot et al. (2011) found activation of the left IFG among optimists and pessimists alike when responding to positive information. However, when responding to negative information, the right IFG of more optimistic people was less likely to respond than the right IFG of less optimistic and pessimistic people. The researchers interpreted these findings as the brains of the optimistic people failing to integrate undesirable information about the future, which is related to increased happiness and well-being. In other words, the brains of optimistic people appear to be wearing "rose-tinted glasses."

Given what researchers know about the emotion paradox of the aging brain, older adults would be expected to demonstrate a greater positivity bias in their brains compared with younger adults. Chowdhury et al. (2013) examined age-related neural differences in response to biases about future negative events (termed an "update bias"). Compared with the younger adults, the older adults exhibited a greater update bias, and this update bias was related to activation of the dorsal anterior cingulate cortex in the older group but not the younger group. In a study examining individual differences in optimism among older adults, we found that older adults who had greater optimism showed reduced activation in their fusiform and frontal regions when viewing fearful faces (Bangen et al. 2014). These results may reflect a decreased salience of negative stimuli and/or better emotion regulation in optimistic older adults.

Creativity

Because of the complexity (and perhaps vagueness) of the construct and measurement difficulties in laboratory environments, the neural underpinnings of creativity are largely unknown. In a review of 72 experiments, Dietrich and Kanso (2010) found creative cognition to be broadly divided into three categories: divergent thinking, artistic creativity, and insight. Inconsistent findings were found for divergent thinking and artistic creativity, but for both creative constructs it is evident that no single brain region is sufficient. In terms of divergent thinking, defined as coming up with multiple solutions to a problem, the only consistent among neuroimaging studies was a finding of diffuse prefrontal activation. Studies examining artistic creativity have generally found activation in the motor and temporoparietal regions. Imaging studies examining the neural mechanisms of insight (also known as having an "aha" moment) have been more reliable. The researchers did not find support for right brain dominance despite a popular belief that "right brain thinking" underlies insight. There is convergent evidence for the involvement of the superior temporal gyrus and the anterior cingulate cortex in insight. The superior temporal gyrus appears to help with successful solutions of problems by making remote verbal associations, whereas the anterior cingulate cortex appears to help with cognitive flexibility. The role of prefrontal regions in moments of insight is unknown.

Much of what is known about creativity in the brain comes from lesion studies. The most compelling studies have come from patients with localized lesions to their left language areas, including the left IFG, left temporoparietal region, and left inferior parietal lobe. These regions are largely responsible for logical thinking, verbal communication, and comprehension, and theory posits that these regions may be inhibiting the formation of creative thought. By inactivating these regions and their potential inhibitory links to other parts of the frontal cortex, some think that the right PFC has an enhanced ability to generate novel creative thoughts and solutions. Examples of acquired savant syndrome in patients with lesions to these regions date back to the 1970s, with patients developing extraordinary artistic, mathematical, and memory skills. It is interesting to consider that "exceptional abilities" may lie in all of us but are being inhibited by the logical and verbal centers in our brains. However, we must also consider what costs might come from disabling these abilities in the hopes of unlocking hidden creativity.

Other Positive Traits

The neurocircuitry of other positive traits, including spirituality, humor, wisdom, and social decision making, has been studied in enough depth for at least one review paper to have been written on each trait. A summary of the brain regions that have been implicated in each of these traits is provided in Table 13–1. We chose to report findings from what we deemed the most comprehensive review paper for a particular trait. Empathy, resilience, optimism, and creativity are also included in the table for comparison purposes. Additionally, the numbering system that is used in Figure 13–1 is cross-referenced in Table 13–1 to highlight the overlap between traits in the regions noted in the figure. Interestingly, as Table 13–1 shows, considerable overlap occurs among the regions thought to be involved in these various traits. Please note, however, that support is mixed for these traits, and the brain regions presented have not been consistently found across studies.

Summary of Brain Regions Involved in Neurocircuitry of Positive Psychological Traits

Although the neurocircuitry of the various positive psychological traits we have described varies depending on the specific trait, the population, and the methods used to measure them, considerable overlap in the brain regions involved exists. Figure 13–1 depicts a broad neural model of positive psychological traits.
### Table 13-1. Summary of brain regions with general support for positive psychological traits

<table>
<thead>
<tr>
<th>Frontal and prefrontal cortex</th>
<th>Temporal lobe</th>
<th>Limbic system</th>
<th>Parietal lobe</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empathy</strong></td>
<td></td>
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</tr>
<tr>
<td>Dorsolateral PFC [4]; dorsoomedial PFC [1]; supplementary motor area; inferior frontal gyrus; medial orbitofrontal PFC</td>
<td>Insula [5]; anterior temporal cortex; superior temporal sulcus and gyrus</td>
<td>Anterior cingulate cortex [1]; anterior midcingulate cortex</td>
<td>Temporoparietal junction [6]; sensorimotor cortex</td>
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<tr>
<td><strong>Resilience</strong></td>
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<td><strong>Optimism</strong></td>
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<tr>
<td>Inferior frontal gyrus</td>
<td>Pusiform gyrus</td>
<td>Anterior cingulate cortex [1]; amygdala [3]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Creativity</strong></td>
<td></td>
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<tr>
<td><strong>Spirituality</strong></td>
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<tr>
<td>Dorsolateral PFC [4]; ventromedial PFC [4]; ventromedial PFC [2]; medial orbitofrontal cortex</td>
<td>Insula [5]; ventromedial temporal lobe; middle temporal cortex</td>
<td>Anterior cingulate cortex [1]; posterior cingulate cortex; amygdala; nucleus accumbens and striatum</td>
<td>Temporoparietal junction [6]; posterior superior parietal lobule; medial parietal cortex; inferior parietal lobule; angular gyrus</td>
<td>Brain stem</td>
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<tr>
<td><strong>Humor</strong></td>
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<tr>
<td>Inferior frontal cortex</td>
<td>Insula [5]; posterior temporal cortex</td>
<td>Amygdala [3]; hippocampus; parahippocampal cortex; nucleus accumbens and striatum</td>
<td>—</td>
<td>Midbrain</td>
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<tr>
<td><strong>Wisdom</strong></td>
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<tr>
<td>Dorsomedial PFC [1]; ventromedial PFC [2]; medial PFC; inferior frontal gyrus; medial orbitofrontal cortex</td>
<td>Superior temporal gyrus</td>
<td>Anterior cingulate cortex [1]; posterior cingulate cortex; amygdala; nucleus accumbens and striatum</td>
<td>Parietal association cortex</td>
<td>—</td>
</tr>
<tr>
<td><strong>Social decision making</strong></td>
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<tr>
<td>Dorsolateral PFC [4]; ventromedial PFC [4]; dorsomedial PFC [1]; ventromedial PFC [2]; frontal pole, inferior frontal cortex, medial orbitofrontal cortex</td>
<td>Insula [5]; superior temporal gyrus</td>
<td>Anterior cingulate cortex [1]; amygdala [3]; posterior cingulate cortex; nucleus accumbens and striatum; caudate nucleus</td>
<td>Temporoparietal junction [6]; inferior parietal cortex</td>
<td>—</td>
</tr>
</tbody>
</table>

**Note.** Numbers in brackets correspond to brain regions denoted in Figure 13–1. Dashes indicate a particular region is not involved in the neurocircuitry of a particular trait. PFC = prefrontal cortex.

Figure 13–1 shows six brain functions seen across the various traits: 1) dorsal medial PFC and the dorsal anterior cingulate cortex (intentional and automatic emotion regulation and self/other pain avoidance motivation), 2) ventromedial PFC (automatic emotion regulation), 3) amygdala (emotion identification), 4) dorsolateral PFC and ventrolateral PFC (intentional emotion regulation and cognitive reappraisal), 5) anterior insula (self/other awareness of subjective state), and 6) temporoparietal junction (self/other distinction processes and theory of mind). As can be seen, the majority of the neural circuits for positive psychological traits lie in the PFC and the interplay between the PFC and structures of the limbic system. The PFC, particularly the ventrolateral PFC, is what scientists believe makes humans different from their closest nonhuman (i.e., primate) relatives. As the following clinical vignettes demonstrate, damage to the PFC can cause significant personality and behavioral changes. However, it is highly likely that it is not just the PFC that makes human brains unique but, rather, the communication between the PFC and other brain regions. The brain networks that we have described in relation to the various positive psychological traits include integration of neural activity of higher-order cortical brain regions with lower-level sensory and motor regions, which can result in advanced emotional functioning, adaptive responses to stress, and novel and complex goal-directed problem solving. There is clearly much researchers still do not know about the brain systems involved in positive psychological traits. However, science is continuing to make considerable advances in understanding the neural circuitry of the brain (see the Human Connectome Project Web site, www.humanconnectomeproject.org), which will hopefully continue to lead to novel targets for enhancing quality of life.

Illustrative Vignettes

Positive psychological characteristics are typically considered to be traitlike in nature and rather stable over time. They do not generally fluctuate on the basis of mood, stress levels, or changes to one’s external environment. However, these characteristics may change in people with long-lasting health problems or acute infection (such as a state of delirium) and in people with brain lesions. The involvement of particular brain regions in these acute changes is additional evidence for the centrality of some regions to the expression of these positive traits.

Clinical Vignette I

At age 48, Martin, a married and formerly successful, responsible architect, was let go from his job for progressive troublesome behavioral changes, namely, obsessively shutting off the lights in the offices of his coworkers. His new obsession with conserving energy was pervasive, and he also went around his home turning off all the lights and made his wife stop the car ignition at stop signs and stop
lights. Martin also became obsessed with license plates, trash on the side of the road, and consuming excessive amounts of candy, and at age 49, Martin was diagnosed with psychosis. He continued to develop additional obsessions and rituals, including fixations on killing ants, his own hygiene (including shaving and showering five times per day despite wearing the same clothing every day), and food, to the extent that he was consuming so much food and soda his wife was forced to put a lock on the refrigerator. Martin also developed personality changes. He became disinhibited, impulsive, and mildly apathetic and had inappropriate manners. He began calling people names and developed a serious dislike for people who were overweight and for people with tattoos. According to his wife, Martin had a loss of empathy and was unable to connect with other people's emotions as he was previously able to do. For example, she stated that when she would cry, he would not show any emotional response but would tell her in a neutral voice not to cry and to be happy. He also reportedly failed to show an emotional response when his 1-year-old baby fell.

Neuropsychological testing, conducted when Martin was 50, revealed significant impairment in the frontal executive domains, yet his memory and visuospatial function were relatively spared. Functional brain imaging showed hypometabolism in the frontal lobes. At that time, Martin was accurately diagnosed with behavioral-variant frontotemporal dementia, and his bizarre behaviors, neuropsychological functioning, and personality changes progressively worsened over time.

Clinical Vignette 2

Julia, a 48-year-old woman with brain cancer, underwent two right frontal craniotomies with tumor resections over the course of 8 years. The tumor recurrence after the first surgery was more invasive than the original tumor and had infiltrated the patient's bilateral frontal lobes and anterior temporal lobes (right more than left), as well as the right frontal horn of her right lateral ventricle. Following the second surgery, Julia denied any changes to her cognitive functioning (except diminished concentration, which she attributed to poor sleep), personality, or everyday functional behaviors. She also denied any past or present depression or anxiety. However, according to Julia's daughter, her mother had changes in cognition, personality, and behaviors after the second surgery. Julia's daughter stated that her mother had been experiencing confusion, language problems (repetitive speech), and memory problems, such as forgetfulness and getting lost in familiar places. Additionally, her daughter reported significant personality changes and stated that her mother become more dramatic and prone to yelling and verbal altercations when she became frustrated and that she was "short-tempered" and "sometimes mean." Collateral information was obtained from a close friend of Julia's, who stated that the patient's personality changes began 1 year before the first tumor was diagnosed. According to the friend, Julia's personality changes progressed over the years and had worsened since the second surgery. Primary changes included verbal and physical aggressive behaviors and frequent threats to harm others. The friend described an incident in which Julia, unprovoked, became enraged with her hair stylist while getting her hair done and stabbed the stylist in the leg with a pencil. Another time, the police had to be called to resolve a dispute between Julia and her roommate. Julia's friend also reported changes in short-term memory and executive functions (i.e., decreased multitasking, poor planning, and reduced judgment).

Neuropsychological testing revealed relatively intact executive functions and some impairment in learning and memory. Clearly, however, the personality and social changes caused by the tumor were leading to the greatest impairments in everyday functioning in this patient.

Genetic Bases of Positive Traits

Another approach to understanding the biology of positive traits is through examination of their genetic associations. Genetic markers can both identify individuals who are more likely to display a specific psychological trait and point to the potential etiological pathway that may lead to the development of the trait. Cumulatively, the range of genetic studies examining positive traits suggests that these traits likely have a moderate to strong genetic basis. The consideration of the genetic underpinnings of positive psychological traits is a new area of research, and only a few studies conducted to date have addressed these issues. Furthermore, positive traits are typically considered in the context of examining a specific psychiatric disorder or a specific genetic marker, rather than the trait itself being the focus of the investigation. Even if genetic markers are identified, it is not yet clear that such markers are both sensitive to and specific for positive psychological traits. Definitions of positive traits themselves vary, and thus, the phenotype under investigation can vary across studies of the same positive trait. More broad-based, non-hypothesis-driven, agnostic genome-wide association studies (GWASs) targeted to understanding the genetic basis of positive traits are rare.

Heritability of Genetic Traits: Twin Studies

Twin studies are one way to understand the extent to which a trait is heritable by comparing the trait in monozygotic (MZ) versus dizygotic (DZ) twins. Approximately 50% of the genome is shared in DZ twins, whereas the genome is shared entirely in MZ twins. Factors that are more concordant in MZ twins than in DZ twins may have a stronger genetic basis, whereas factors associated with similar rates of concordance in MZ and DZ twin pairs suggest that there are both genetic and environmental factors at play. Estimates of the genetic heritability of positive traits using twin studies have suggested 31%–36% heritability for resilience to stressful life events (Amstadter et al. 2014) and for optimism (Mosing et al. 2009); the heritability of empathy may be as high as 46% in some age groups (Knafo et al. 2008), and heritability may be 30%–40% for subjective well-being. Overall, these studies suggest that there is a considerable genetic contribution to a range of positive traits.
Candidate Genetic Markers and Positive Traits

Inferences about the genetic basis of positive traits often come from studies of candidate genetic markers. One genetic risk factor associated with the development of psychopathological response to stress is the serotonin transporter promoter polymorphism (5HTTLPR). Therefore, several investigators have considered it to be an ideal target for studying the genetic basis of several positive traits, particularly resilience. The short or deletion form (the S allele) is associated with reduced transcription and reuptake efficiency within the serotonergic system, whereas the long form (the L allele) is considered to confer increased resiliency and thus is protective against negative outcomes such as depression and anxiety in the presence of stress. In a sample of 423 undergraduates, Stein et al. (2009) found S allele carriers had reduced resilience to stress, whereas carriers of the L allele had higher levels of resilience, suggesting that a more efficient serotonergic system may confer increased resiliency to stress. This genetic marker was not found to be associated with resilience in an older adult sample, suggesting the association of 5HTTLPR with resilience attenuates with age (O’Hara et al. 2012). Additional candidate genes found to be associated with different aspects of resiliency include the monoamine oxidase A (MAOA), neuropeptide Y (NPY), brain-derived neurotrophic factor (BDNF), corticotropin-releasing hormone receptor 1 (CRHR1), FK506-binding protein 5 (FKBP5), 5HTTLPR, catechol O-methyltransferase (COMT), and nerve growth factor inducible (NGFI-A) genes.

Although the physiological basis of positive traits can be indicated by their genetic basis, their biological basis can sometimes be the starting point for understanding their genetic underpinnings. Oxytocin is one hormone documented to be involved in positive traits such as good social communication skills and has been associated with increased levels of trust and generosity. Many investigators have suggested that genetic variation in the oxytocin receptor gene (OXTR) may play a role in empathy modulation. Located on 2q25, OXTR spans 17 kb, contains four exons and three introns, and has many polymorphic sites. Several studies have identified various single nucleotide polymorphisms (SNPs) or haplotypes (combinations of polymorphisms) associated with different types of empathy (e.g., Wu et al. 2012). Because OXTR has also been associated with levels of optimism, this gene may play a key role in the regulation of many positive traits.

Another candidate marker for positive traits is calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C), with Strohmaier et al. (2013) finding that genetic variation in CACNA1C was related to lower levels of optimism as well as resilience. CACNA1C is a member of a family of genes implicated in calcium channels and is considered to be key for normal function of both heart and brain cells. However, although findings are mixed, many investigations have found CACNA1C to be associated with a range of psychiatric disorders, including schizophrenia, depressive disorders, and bipolar disorders. This finding raises a critical issue pertinent to understanding the genetic basis of positive traits. It may be that any genotype associated with a negative outcome, such as a specific psychiatric disorder, will likely have a genotype that is also associated with positive traits that characterize the absence of the disorder. As such, these genetic markers may be nonspecific for positive traits per se but are associated with a range of positive traits by virtue of not being associated with the negative traits integral to mental health disorders. For example, in our own investigation (O’Hara et al. 2012), the 5HTTLPR L allele was not associated with resilience but was instead associated with better cognitive performance and self-rated successful aging. Thus, resilience may actually be a proxy variable for cognitive function, with which the 5HTTLPR L allele is well documented to be associated. In another investigation, our group found decreased neuroconnectivity among 5HTTLPR S allele carriers (Waring et al. 2013), suggesting a neurobiological basis for increased resilience. Indeed, it is interesting to note that other candidate genes found to be associated with resilience, including BDNF and COMT, have been implicated in brain neurocircuitry that is thought to subserve emotional regulation and other potential aspects of positive psychological traits. Because candidate genetic marker studies of positive traits are often conducted only in the context of psychiatric disorders, the interpretation that researchers can make with respect to their true association with positive traits is limited. Non-hypothesis-testing, agnostic, data-driven GWAS investigations of positive traits are required to more fully understand if there are specific markers that have high penetrance for specific positive traits, but to date, such investigations are few in number.

Multigene Association Studies

McGrath et al. (2013) performed a GWAS of the mental and physical components of health-related quality of life across diagnosis (1.6 million SNPs), adjusting for psychiatric symptom severity. After controlling for diagnostic category and symptom severity, they found that the strongest evidence of genetic association was between variants in ADAM metallopeptidase with thrombospondin type 1 motif, 16 (ADAMTS16) and physical functioning, but no other positive markers were identified. In one of the few other investigations to explore a range of genetic markers associated with positive traits, Rana et al. (2014) examined 426 women from the Women’s Health Initiative study. On the basis of a literature review, they examined 65 candidate gene SNPs judged to be related to predisposition to resilience and optimism. Following correction for type I errors, they found no significant associations of resilience and optimism with any of the specific gene SNPs in single-locus analyses. The authors concluded that positive psychological traits are likely to be genetically complex, such that many loci,
rather than one specific gene or SNP, have small effects that contribute to the
phenotypic variation.

**Blood- and Saliva-Based Biomarkers**
**Associated With Positive Psychological Traits**

When one scans the literature on the topic of blood- and saliva-based biomarkers of positive psychological traits, one finds that the domains of resilience, optimism, and well-being have been the most heavily researched. The next most frequently researched topics are compassion and mindfulness, happiness, spirituality, and gratitude. Biomarkers examined in the context of these traits have focused on telomere protection of the chromosomes; autonomic measures, including catecholamines and cortisol; and commonly measured biomarkers of inflammation such as interleukin-6 (IL-6) and C-reactive protein (CRP).

**Resilience**

In terms of resilience, telomere length, considered a proxy for cellular aging, and telomerase, the enzyme that regulates telomere length, have received the most empirical attention. Resilience is associated with less HPA axis activation to stress. In turn, greater stress (in terms of both early life stress and the chronicity of stress) is associated with shorter telomere length. Epel et al. (2006) describe resilience as a composite of multiple factors such as psychological stress resilience, healthy lifestyle factors, and social connections and show that higher resilience is associated with longer telomere length and that each aspect of resilience acts as a protective factor from stress-induced telomere shortening. One of the routes through which stressors affect telomere length and telomerase activity is through autonomic activation as seen via elevated catecholamine and cortisol levels.

**Optimism and Well-Being**

Like individuals with high resilience, individuals with more optimism show less HPA activation in response to stressors (e.g., Lai et al. 2005). Similar findings have been reported for inflammatory biomarkers. Brydon et al. (2009), for example, examined linkages between dispositional optimism and the immune system in healthy young men and found that optimism was inversely related to IL-6 levels, such that men with higher optimism showed reduced IL-6 responses to acute stress independent of resting IL-6 levels, BMI, age, or depression. Similar findings with IL-6, as well as links between optimism and general immune responsiveness and antioxidant levels, have been reported in the literature.

A unique study on this topic of biomarkers and well-being also examined if ill-being showed biomarkers distinct from those of well-being. Among the measured biomarkers were endocrine (i.e., cortisol, epinephrine, norepinephrine, dihydroepiandrosterone sulfate (DHEA-S) and cardiovascular (i.e., high-density lipoprotein [HDL] cholesterol, total/HDL cholesterol, systolic blood pressure, waist-hip ratio, glycosylated hemoglobin) markers. Well-being was found to be significantly associated with lower cortisol, epinephrine, and norepinephrine levels. Further analysis revealed that higher personal growth and purpose influenced daily slopes of salivary cortisol (Ryff et al. 2006).

The relationship between optimism and well-being is not always straightforward, however. It has been described as a complex relationship that is dependent on the duration and type of stressor involved and is potentially influenced by gender, such that not all studies report a protective effect of optimism on stress-induced immune changes. Studies on healthy elderly men and postmenopausal women, for example, have not found any significant associations between telomere length and optimism or have found that the effects are restricted to women (O’Donovan et al. 2009).

**Compassion and Mindfulness**

Studies on the domains of compassion and mindfulness examine not only existing trait levels but also levels influenced by the practice of different forms of meditation. A meditation practice that fosters compassion, for example, has been shown to influence stress-induced IL-6 levels, with the effects being dependent on the degree of engagement with the practice. In these studies, individuals who regularly practice compassion meditation and/or participate in compassion training have lower IL-6 responses to stress (e.g., Pace et al. 2009). Similarly, individuals who have high trait self-compassion have lower resting CRP levels.

Mindfulness has received increasing attention over the past decade because of the increase in research on mindfulness meditation techniques. Some research suggests that mindfulness influences the endocrine response to stress such that individuals with higher mindfulness show lower cortisol levels in acute stress conditions (Brown et al. 2012). We conducted an exploratory study in healthy individuals to examine different components of mindfulness in relationship to inflammation and found that the mindfulness components of observing and nonreactivity were associated with lower IL-6 levels.

**Happiness**

In heart failure, a condition with marked severe and chronic inflammation, patients with more positive affect show lower levels of tumor necrosis factor (a), soluble tumor necrosis factor receptor 2, and IL-6 (Brouwers et al. 2013). Such effects
of happiness on inflammatory profile have also been reported in healthy individuals, with those having more happiness showing lower levels of interferon-γ. In addition, several studies have examined the HPA axis in the context of happiness. In the large Whitehall II study of nearly 3,000 individuals, for example, more positive effect was associated with lower cortisol levels (Skeie et al. 2008).

**Spirituality and Gratitude**

The potential effects of spirituality and religiousness on health and mortality have been actively researched for decades. Only a small subset of those studies, however, have examined potential biomarkers associated with such effects. Similar to individuals in studies on resilience and happiness, individuals who report greater spiritual wellness have lower levels of CRP (Holt-Lunstad et al. 2011). This effect might be mediated by lower stress and HPA activation because several studies showed that higher self-reported spirituality or well-being is associated with lower cortisol levels. These findings have been reported in various other populations, including healthy individuals, people living with HIV, and military veterans with posttraumatic stress disorder. Some of the authors of this chapter have been studying inflammatory profiles in different stages of heart failure development. We have found that in patients with New York Heart Association stages II and III heart failure, those with high trait spirituality and high trait gratitude have lower levels of the cardiac biomarker soluble ST2, which is a member of the IL-1 receptor family and is secreted by cardiac muscle cells under mechanical stress. Thus, heart failure patients with more trait spirituality as well as more trait gratitude show a more favorable profile of an important prognostic biomarker of heart failure.

**Interventions to Improve Positive Psychological Traits: A Biological Perspective**

The clinical implications for understanding the neurocircuitry, biomarkers, and genetics of positive psychiatry are vast. A better understanding of the biological mechanisms underlying positive psychological traits can lead to the development of novel interventions to alter and/or increase these traits. For example, methodologies to target specific neural circuits, including fMRI neurofeedback, mindfulness meditation, mental training exercises, and cognitive reappraisal training are promising noninvasive techniques that can possibly stimulate and strengthen emotion regulation. In particular, mindfulness meditation and cognitive reappraisals may be two methods that can be used to enhance resilience through the mechanism of enhancing PFC regulation of limbic and brain-stem systems. Interfering with certain brain circuits using magnetic stimulation might also be a way of influencing behaviors, such as the optimism bias. Novel pharmaceuticals or natural compounds may also be able to regulate executive and limbic function and may lead to increases in positive psychological traits. For instance, medications that improve regulation of the HPA axis and the sympathetic nervous system in response to stress may be able to improve function in the PFC and regulate limbic reactivity to stress, which could potentially lead to improvements in resilience. As another example, giving oxytocin to people while they are engaged in compassion training versus completing compassion training alone may serve to bolster the results of compassion training. To our knowledge, these therapeutic treatment targets have yet to be empirically tested, and they provide interesting avenues for future research.

**Summary**

In this chapter, we pull together the growing evidence for the biological basis of positive psychological traits. To date, the majority of clinical research has focused on identifying the neurobiology of these traits, but ongoing research on the genetic markers and blood and saliva markers involved in these traits is under way. There are exciting treatment opportunities to enhance positive psychological traits through our existing knowledge of the neurocircuitry, biomarkers, and genetics of positive psychiatry. However, a caveat is that current scientific assessment methods are limited to assessing these mechanisms from a single biological perspective (neurocircuitry, genetic, or blood and saliva markers), and integrated research is needed to develop novel interventions aimed at concurrently strengthening the neural networks and other biological mechanisms associated with positive psychological traits. An emerging trend in academic research has been to bridge the knowledge gap and share research across multiple disciplines, and multidisciplinary research teams of engineers, software architects, experimental psychologists, neurologists, physicians, and others are working together to design and implement novel approaches to capturing, storing, and analyzing data on biological mechanisms. These collaborative efforts will greatly enhance the ability to measure, and eventually improve, the biology of positive psychological traits.

**Clinical Key Points**

- Positive psychological traits are a function of various neural networks throughout the brain; these traits are not localized to discrete brain structures, lobes, or hemispheres.
• Research has shown that strengthening the neural connections between certain brain structures can improve certain traits (e.g., empathy, resilience), whereas suppressing the neural connections between structures may improve other traits (e.g., creativity).

• Data suggest that positive psychological traits likely have a moderate to strong genetic basis; however, literature is limited regarding specific genetic markers subserving these traits.

• Research has also demonstrated relationships between positive psychological traits and saliva- and blood-based biomarkers; particularly notable are reduced hypothalamic-pituitary-adrenal axis activation and reduced inflammatory biomarkers responses to stress in individuals with greater positive psychological traits.

• Treatments aimed at strengthening these neural networks and other biological mechanisms, through either pharmacological or nonpharmacological means or a combination of both, have the potential to improve positive psychological traits.

References


Biology of Positive Psychiatry


Suggested Cross-References

Well-being is discussed in Chapter 6 ("What Is Well-Being?"). Chapter 7 ("Clinical Assessments of Positive Mental Health"), and Chapter 15 ("Positive Geriatric and Cultural Psychiatry"). Gratitude is discussed in Chapter 9 ("Positivity in Supportive and Psychodynamic Therapy") and Chapter 12 ("Integrating Positive Psychiatry Into Clinical Practice"). Resilience is discussed in Chapter 3 ("Resilience and Posttraumatic Growth") and Chapter 12. Spirituality is discussed in Chapter 2 ("Positive Psychological Traits") and Chapter 10 ("Complementary, Alternative, and Integrative Medicine Interventions"). Optimism is discussed in Chapter 2.

Suggested Readings

