Chapter 7
Neurobiology of Well-Being

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ABSTRACT

This chapter is designed to review much of the research on the neurobiology of well-being. A distinction between hedonic well-being and eudaimonic well-being is made. The brain reward center was discussed in relation to well-being, which was followed by an in-depth discussion related to drugs, neurotransmitters, and well-being. Neurochemicals related to hedonia and eudaimonia were then discussed, followed by another discussion on gene expression. Finally, brain structures involved in well-being were the discussed followed by concluding thoughts.

INTRODUCTION

Well-Being: Hedonic and Eudaimonic

There is a plethora of concepts directly related to the psychology of well-being, including but not limited to life satisfaction, domain satisfaction, positive and negative affect, emotional well-being, hedonic well-being, perceived quality of life (QOL), happiness, psychological well-being, eudaimonia, authentic happiness, flourishing, positive mental health, psychological happiness, prudential happiness, perfectionist happiness, the good life, etc. Philosophers and psychologists of well-being have much to say about these concepts and their meaning (Sirgy, 2012).

In a review of the literature on subjective well-being, Diener, Suh, Lucas, and Smith (1999) defined subjective well-being as a broad category of phenomena that includes people's emotional responses, domain satisfaction (satisfaction in important life domains such as satisfaction with family life, health life, work life, leisure life, social life, etc.), and global judgments of life satisfaction. Diener and his col-

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leagues added that each of these concepts should be studied separately, although the constructs often correlate substantially with each other.

Sirgy and Wu (2009) assert that true happiness occurs when an individual experiences satisfaction in terms of their basic needs (based on Maslow's hierarchy of needs), but also in terms of their growth needs (i.e., social, esteem, self-actualization, knowledge, and aesthetic needs). This type of satisfaction is referred to as eudaimonic or psychological well-being. Ryff refers to eudaimonic well-being as human flourishing. Ryff's construct involves six dimensions: self-acceptance, positive relations with others, personal growth, purpose in life, environmental mastery, and autonomy (e.g., Ryff, 1989, 2017; Ryff & Singer, 2008; Ryff et al., 2016). Whereas the hedonic approach to well-being focuses on pleasure attainment and pain avoidance (Kahneman, 1999), the eudaimonic approach focuses on meaning, self-realization, and purposefulness. Throughout this chapter hedonic well-being and eudaimonic well-being will be referred to as two major components that define overall well-being.

In sum, well-being is an umbrella concept that captures hedonic well-being and eudaimonic well-being. Hedonic well-being is the affective dimension that reflects preponderance of positive affect over negative affect. Eudaimonic well-being focuses on experiences related to personal growth and character development.

The Reward Center and Well-Being

What is the mechanism of action that produces pleasant emotions that result in hedonic well-being? The mechanism involves brain centers that reflect what neuroscientists refer to as "the reward system" (Wise, 1996). The seminal study demonstrating the presence of the reward circuit involved rats that pressed a bar to administer a brief burst of electrical stimulation to specific sites in their brains (Olds & Milner, 1954). Said behavior had no value to their survival (i.e., food) or to that of the species (i.e., sex), but resulted in compulsive repetition of bar pressing. This phenomenon has been referred to as "intracranial self-stimulation" or "brain-stimulation reward" (Wise, 1996).

Research investigating intracranial self-stimulation has identified several brain sites that are involved in the reward system. Some regions stand out more than others (e.g., the ventral tegmental area (VTA) and the medial forebrain bundle). Stimulation of these regions activates fibers that form the ascending pathways from dopamine-producing cells of the VTA that project to the nucleus accumbens (NAc), the amygdala, the hippocampus, and the prefrontal cortex (Advokat, Comaty, & Julien, 2014; Kolb & Whishaw, 2014; Rickard & Vella-Brodick, 2014). This system, referred to as the mesolimbic dopamine pathway, plays a crucial role in reward. Drugs of abuse activate this reward system either directly (e.g., cocaine) or indirectly (e.g., opium). Much evidence shows that increases in dopamine (a neurotransmitter) in this pathway are directly involved with positive affect (i.e., feelings of pleasure and even euphoria).

The mesolimbic system shows a marked increase of dopamine when animals are engaged in intracranial self-stimulation (Olds & Milner, 1954). The same system shows a marked increase of dopamine when animals engage in rewarding behaviors (e.g., feeding and copulation). The reward system also shows a marked increase in dopamine with all drugs taken for pleasure, such as amphetamines, opiates, barbiturates, alcohol, THC, PCP, MDMA, nicotine, and even caffeine (Kolb & Wishaw, 2014, p. 438). Other addictions, such as compulsive gambling, pathological overeating, and sexual addiction, have also been strongly correlated with changes in the VTA-NAc dopamine system (Nestler, 2005). Chronic dopamine activation diminishes endogenous dopamine release and causes down-regulation of dopamine receptors

which is a major aspect of drug tolerance (Volkow et al., 2005). Fewer dopamine receptors creates a "reward deficiency syndrome" that accounts for addicts' lowered responsiveness to natural rewards and predisposes addicts to seek out drugs to experience even normal levels of pleasure.

Other neurons interact with the dopamine-producing neurons in the VTA, and other neurotransmitters are involved in the increase of dopamine in the system as well. The endogenous opioid system (EOS) is one of the principal modulators of the mesolimbic dopaminergic reward circuitry (Mathew & Paulose, 2011). The use of acupuncture has been linked to the enhancement of endogenous opiates, resulting in pain relief from multiple disorders, surgeries, and diseases (Patil et al., 2016). The "runner's high" is an example of intense pleasure following the release of endogenous opiates (endorphins) during prolonged vigorous exercise (Gianoulakis, 2001). When observing individuals with borderline personality disorder (BPD), it is believed these individuals will go to any means to experience pleasure, regardless of the harmful effects that may accompany it, such as using whips to cause heavy bleeding to reach a heightened state of ecstasy (Gratz & Gunderson, 2006). This suggests a dysregulation in the EOS of individuals with BPD.

Heller et al. (2013) examined neural responses to positive stimuli and found links between sustained activity in the reward center (ventral striatum and dorsolateral prefrontal cortex) and higher eudaimonic well-being. In other words, participants with higher levels of eudaimonic well-being experienced sustained activation of the reward center in response to positive stimuli and lower levels of cortisol. Panksepp (2005) has argued that the brain reward center is the motivating force underlying growth needs or higher-order needs *a la* Maslow (cf. Silton et al., 2011). Specific areas of the limbic system (i.e., the reward center) may help actualize a diversity of internal wants and desires, thus motivating the individual to satisfy growth needs that lead to positive affect. On the other hand, the person that seeks to increase hedonic well-being by using drugs regularly will experience lower life satisfaction because of the tolerance that develops. The reasons are threefold and due largely to the changes in the reward center: 1) the reduction in dopamine and dopamine receptors in the VTA means that the person will feel less pleasure in general when the drug is not on board, and 2) they will need greater amounts of the drug to experience the original level of euphoria the drug produced, and 3) to satisfy the craving that results and the need for the euphoric effect, the person will spend greater time and resources engaging in drug seeking behavior, time and resources needed to maintain life quality in various life domains.

In sum, the brain center responsible for hedonic well-being reflects what neuroscientists refer to as "the reward system." The reward system involves several regions in the brain. Stimulation of these regions activates pathways from the VTA that project to the NAc, the amygdala, the hippocampus, and the prefrontal cortex (i.e., the mesolimbic dopamine pathway). Increases in dopamine in this circuit produce feelings of pleasure or positive affect. Sustained activity in the reward center is associated with higher levels of eudaimonic well-being and lower levels of cortisol. The brain reward center seems to be the motivating force underlying growth needs related to eudaimonia. The mesolimbic system is characterized by marked increases in dopamine with all drugs taken for pleasure, such as amphetamines, opiates, barbiturates, alcohol, THC, PCP, MDMA, nicotine, caffeine, and even compulsive gambling, pathological overeating, and sexual addiction. Other systems interact with the mesolimbic system such as the endogenous opioid system. Individuals seeking to increase hedonic well-being through drug use are likely to experience lower levels of life satisfaction because of the adverse effects of drug tolerance.

Drugs, Neurotransmitters, and Well-Being

Throughout the history of humanity, people have used drugs of all types to make them feel happy and numb the pain of life's adversities. Probably the most common drug is alcohol. Other drugs include opium (derivatives of opium include morphine and heroin), cocaine, amphetamines, benzodiazepines, and cannabis (THC). These, and many other drugs, stimulate the reward system and produce euphoria in the user, which makes these drugs key candidates for abuse.

Cocaine (a potent psychostimulant) can dramatically induce the release of dopamine (as well as norepinephrine, epinephrine, and serotonin). The net effect is heightened alertness, euphoria, lowered fatigue, decreased boredom, depressed appetite, and insomnia (Advokat, Comaty, & Julien, 2014). In 1884, Freud recommended using cocaine to alleviate depression and chronic fatigue. However, the rebound symptoms (once the drug leaves the system) are fatigue and depression (McKim & Hancock, 2013) making the therapeutic use of cocaine for depression ill advised.

Looby and Earleywine (2007) compared a large sample of people that had never used methamphetamine to a group that had used it at least once in the past year. They found that methamphetamine use decreased subjective well-being. It was also predictive of feeling more depressed and apathetic, less happy and having lower levels of satisfaction with life. This could mean that unhappy people seek out psychostimulants to self-medicate, or it could indicate that using methamphetamine produces depression, symptoms of which have been shown to be increased in methamphetamine users in other studies (e.g., Dyer & Cruickshank, 2005). While acute use may produce hedonia, it has long-term detrimental effects on well-being.

Opiates (morphine, codeine, and heroin) have euphoric effects. In small doses opiates decrease anxiety and reduce pain; higher doses can produce euphoria. The brain and body make their own opiate-like chemicals, commonly referred to as "endorphins" (endogenous morphine-like peptides). Endorphins control pain by stopping the flow of pain signals to the brain. Engaging in physical activities such as distance running could produce an "endorphin high."

Clearly, drugs that act on the reward system in the brain influence hedonic well-being (i.e., short-term positive and negative affect). However, do drugs affect other forms of hedonic well-being or eudaimonia? The answer is yes, drugs affect life satisfaction in a negative manner. Consider additional evidence:

- Focusing on substance abuse, a longitudinal study conducted by Bogart et al. (2007) clearly showed that the use of cigarettes and hard drugs at age 18 was associated with lower life satisfaction at age 29. In contrast, marijuana use and alcohol consumption at age 18 was not related to life satisfaction at age 29. Low income, poor health, and cigarette consumption in adulthood were determined to be mediators of the link between cigarette smoking and earlier hard drug use and lower satisfaction at age 29 (Bogart et al., 2007).
- A recent study (Khan & Shah, 2014) compared the subjective well-being of two groups of addicts, those who received drug-de-addiction treatment and those who did not. The study found that those who received treatment scored better on certain dimensions of subjective well-being (i.e., confidence in coping and perceived ill health). However, the two groups did not differ significantly on other dimensions such as general well-being, positive affect, expectation achievement congruence, transcendence, family group support, social support, primary group concern, inadequate mental mastery, deficiency in social contact, and negative affect (Khan & Shah, 2014).

- Quite a bit of evidence suggests that those with substance use disorder (SUD) and those seeking psychiatric treatment do not score as well on quality-of-life (QOL) measures as participants without a SUD or with no psychiatric condition (e.g., Donovan et al., 2005; Rudolf & Watts, 2002; Smith & Larson, 2003). Laudet, Becker, and White (2009) confirmed the finding but also found that QOL played a critical role in longitudinal remission. Higher QOL correlated with sustained remission. However, if QOL decreased during the measurement period it predicted increased vulnerability to substance use and relapse.
- Zullig et al. (2001) conducted a large study of public high school students and found that several drugs of abuse were correlated with a reduction in global life satisfaction (cigarettes and chewing tobacco, marijuana, cocaine, alcohol use, and steroids). In addition, the earlier the age at which they first used marijuana, alcohol, cocaine, or cigarettes, the stronger the association with reduced life satisfaction.

Research has also shown drugs such as opiates may activate both dopaminergic and nondopaminergic systems (e.g., Spanagel & Weiss, 1999). Such findings led to the development of the incentive-sensitization theory of addiction (Robinson & Berridge, 1993, 2003). This theory asserts that rewards involve two separate dimensions: "wanting" (which may be viewed as an incentive) and "liking" (which can be viewed as evaluation of the pleasant sensation). For example, a person may feel the desire to eat chocolate ("wanting"), and he may experience a pleasant sensation having eaten the chocolate ("liking"). The dopamine system seems to be related to both the "wanting" and "liking" components, whereas the "liking" component may also involve opioid and GABA (an inhibitory neurotransmitter) systems.

Another theory explained the role of dopamine in learning. More specifically, the dopamine system responds to the "unpredictability of rewards" (Berns et al., 2001) or errors in prediction (Schultz, 2002). That is, learning occurs when the reward is better or worse than expected. Learning does not occur when the reward matches expectations. Dopamine release is concomitant with learning. This learning is evidenced in brain plasticity involving significant neuronal changes—increased dendritic length and complexity in the nucleus accumbens and prefrontal cortex, as well as activity increases in areas involved in learning such as the hippocampus (e.g., Robinson & Berridge, 2001). Given the dopamine release in situations when expectations are negatively disconfirmed (worse than expectations), dissatisfaction may follow, and of course dissatisfaction is reflective of negative affect. Negative affect cannot be construed as "reward." Hence, neuroscientists now feel more comfortable using the term "reinforcer" rather than "reward." In other words, dopamine plays a crucial role in the "reinforcement" system (i.e., learning), as well as in the "reward" system.[1] In addition, large and fast increases in dopamine, such as those triggered by drugs, are associated with phasic dopamine firing in the brain, which conveys information about saliency as well as reward (Schultz, 2010). Therefore, when a person expects a certain euphoric high from taking a drug but the euphoria is lower because tolerance has developed, they will experience negative affect. This may contribute to the decreases in life satisfaction observed in those with substance-use disorder.

Based on the research related to drug dependence (e.g., Kalivas & Volkow, 2005; Kalivas et al., 2006; Volkow et al., 2005), the following theoretical notions concerning well-being can be extrapolated:

1. Humans possess a reward circuit that is activated by both drug and non-drug rewards. The most well-known reward circuit involves stimulation of neurons in the ventral tegmental area which project to and cause release of dopamine in the nucleus accumbens, amygdala, and prefrontal cortex. This produces subjective feelings of pleasure.

2. Thus, dopamine underlies the reward experience and promotes learning through brain plasticity. The projections, over time, facilitate brain changes (at the neuronal level) promoting learned associations with those behaviors perceived to have led to positive affect or the reduction of negative affect, as well as progressive tolerance to the substance, ultimately resulting in less pleasure. With repeated exposure to the drug, there is a transition such that activation begins to occur more in the dorsal striatum (the caudate nucleus) as opposed to the nucleus accumbens. This is thought to underlie habit learning, in which drug taking switches from a reward-motivated behavior to a behavior that is automatic, habitual, and even compulsive. This results in negative emotionality, but also higher drug craving (see Volkow et al., 2014 on marijuana abusers).
3. Although dopamine release in the nucleus accumbens is important for the association between the behavior and the reward to be established, repeated behaviors (i.e., habits) cause recruitment of the frontal cortex and involves glutaminergic efferents to the nucleus accumbens, amygdala, and hippocampus. Kasanetz et al. (2010) found that rats developing an addiction to cocaine via self-administration showed permanent impairments in long-term-depression in the nucleus accumbens, whereas those rats exhibiting controlled drug intake were able to recover this form of neural plasticity.
4. Habits then persist as a result of enduring cellular changes in glutamate neurons in the frontal cortex. These glutaminergic projections from the frontal cortex to the nucleus accumbens are involved in motivating the individual to maintain his/her habits. Interference with the glutamate pathway impairs the ability of the prefrontal cortex to mediate response inhibition and impulse control (one consequence of chronic drug use). There are increases in prefrontal cortex activity in response to the drug itself or to cues associated with drug use (e.g., Wang et al., 1999). Volkow et al. (2005) showed an increase in metabolic activity in the orbitofrontal cortex, anterior cingulate cortex, and the dorsal striatum with drug craving as well. As a result, the drug-addicted person cannot control the craving, the impulse to take the drug, or even to avoid seeking out the drug.
5. As such, the drug-addicted person cannot control the impulse to take the drug or even to avoid seeking out the drug. Drug-addicted individuals show an enhanced motivation to procure drugs; they will go to extremes to obtain drugs despite the adverse consequences. The drug seeking and drug taking motivational drives consume much time, energy, and resources undermining both hedonic and eudaimonic well-being.

In sum, drugs of abuse provide us with a window to identify neurotransmitters and brain systems involved in hedonic well-being. These drugs stimulate the reward system and produce short-lived positive affect (as well as reduce negative affect). In the long-term, these same drugs undermine feelings of well-being via multiple mechanisms. The neurotransmitters involved with these drugs include dopamine, norepinephrine, epinephrine, serotonin, glutamate, and endorphins, which are discussed next. Furthermore, the research shows that dopamine and glutamate play important roles in the experience of well-being, learning, habit formation, and drug seeking behavior.

Neurochemicals Related to Well-Being

With or without drugs, the preponderance of the evidence from neuroscience shows the major neurotransmitters implicated in positive affect include dopamine, norepinephrine, serotonin, and oxytocin, with cortisol being implicated in negative affect (Advokat, Comaty, & Julien, 2014). Discussion of these neurotransmitters in relation to well-being follows.

With respect to dopamine, much evidence from psychopharmacology suggests dopamine has a direct role in the experience of positive affect because it is the primary neurotransmitter for the reward system in the brain. The vast majority of activities people engage in for pleasure (e.g., eating, drinking, having sex, listening to music) influences dopamine neurons, specifically the release of dopamine in the NAc, which then projects up to the frontal lobes (Advokat, Comaty, & Julien, 2014). The net effect is not only feelings of euphoria but also arousal and quick thinking. Wenk (2009) uses the analogy of the gas pedal and race car to explain the adaptive function of dopamine. The brain is like the race car and dopamine is like the gas pedal. The brain feels euphoria when the gas pedal is pushed, one result of which is quick thinking. The forces of evolution have shaped the brain to enjoy working fast; the faster the better. Creatures that work faster and better are likely to survive and pass this trait to the next generation.

Studies focusing on dopamine have shown maternal separation leads to a lower density of neurotransmitter sites for dopamine (e.g., Brake et al., 2004). In actuality, dopamine and norepinephrine work together to allow the individual to experience positive affect. An insufficient amount of norepinephrine will lead to poor concentration, restlessness, and irritability (Mathew & Paulose, 2011). On the other hand, Davis et al. (2015) found an association between low eudaimonic well-being and higher levels of tumor norepinephrine in female patients with ovarian cancer. The authors also found an indirect relationship between eudaimonic well-being and psychological resilience, such that increased eudaimonic well-being appeared to improve physiological as well as psychological resilience in these patients.

Neurons that produce and release serotonin are located in the brainstem but project throughout the brain (Kolb & Whishaw, 2014). Serotonin is involved in wakefulness and modulates many psychological processes including sexual activity, aggression, sleep and body temperature. Serotonin is also implicated in the regulation of mood, anxiety, hostility, and depression. Low levels of serotonin may be the underlying cause of depression and aggressive actions (Coccaro & Kavoussi, 1997). Peirson and Heuchert (2000) found that higher levels of platelet 5-HT_2 receptors, corresponding to lower levels of serotonin (5-HT), were significantly correlated with depressed mood in college students. Although Peirson and Heuchert's participants were not diagnosed as depressed, the authors noted that clinically depressed patients also showed this effect in several other studies. One study (Flory et al., 2004) found that central serotonergic function measured by the peak prolactin response to fenfluramine was significantly related to positive mood averaged across seven days, but was not correlated with negative mood in a nonpatient sample of adults. The authors suggested that reduced serotonin may result in the absence of positive mood. Williams et al. (2006) found that whole-blood levels of serotonin were positively correlated with positive affect using the PANAS scale, but not with negative affect. A two-way interaction between serotonin synthesis and mood is also a possibility. Meaning that while mood may be influenced by serotonin level, it may also be true that the opposite occurs–serotonin level may be influenced by mood (Mathew & Paulose, 2011).

Turning to oxytocin, research has shown this hormone to be associated with childbirth and lactation, mother-infant bonding (Kendrick, 2004), stress, and the regulation of social behavior (i.e., Elkins, 2016). Early life experiences, such as child abuse or any childhood trauma, was negatively correlated with oxytocin levels, suggesting those early experiences can cause social deficits in the future. One study confirmed the use of oxytocin as a buffer against stress in pregnant women and showed it protected women who were of high stress from developing depressive symptoms, which, in turn, may have increased sensitive maternal behavior (Zelkowitz et al., 2014). Oxytocin has also been found to reduce symptoms related to alcohol withdrawal (Pedersen et al., 2013) and cannabis craving. The use of cannabis has been linked to stress, and a study involving marijuana-dependent individuals supported this idea. McRae-Clark et al. (2013) assessed a baseline using the Marijuana Craving Questionnaire (MCQ). The individuals were

then administered oxytocin or a placebo prior to a psychosocial stress task. Intensity of craving was assessed immediately after the task and also 5-, 35-, and 60-minutes post task. The overall results showed a significant reduction in craving of marijuana in response to the stressor in the group that was administered oxytocin. Another observation from the study was a lower anxiety response in the oxytocin group versus the placebo group (McRae-Clark et al., 2013). Oxytocin is also released during sexual orgasm (Huppert, 2009) and while experiencing feelings of trust (Kosfeld et al., 2005).

With respect to cortisol, studies have shown that exposure to stressors activates the hypothalamic-pituitary adrenal (HPA) axis and results in increased secretion of the stress hormone cortisol. Individual differences in emotional style (positivity versus negativity) modulate stress-induced elevations in cortisol (e.g., Jacobs et al., 2007; Polk et al., 2005; Pruessner, Hellhammer, & Krischbaum, 1999; Smyth et al., 1998). However, it is not only the absence of cortisol that is important, research has shown that it is the pattern of cortisol release and the recovery to baseline following stressors that correlates best with well-being (e.g., Steptoe, Gibson, Hamer, & Wardle, 2007; Ryff et al., 2006). Consider the Ryff, Keyes, and Hughes (2003) study as an example of how cortisol is implicated in eudaimonic well-being. The study compared US Blacks with Whites. Blacks were found to score higher on inventories of purpose in life and personal growth than Whites. Correspondingly, Blacks registered healthier profiles of diurnal cortisol (steeper diurnal decline) compared to their White counterparts.

Pressman and Cohen (2005) conducted a meta-analytic study establishing an association between trait positive affect and reduced release of stress hormones (e.g., cortisol, epinephrine and norepinephrine). In aversive situations, the amygdala sends signals to the HPA axis causing cortisol to be released from the adrenal glands. As such, people with a positive affective disposition tend to have lower basal cortisol levels compared to those with a negative affective disposition.

Several studies have shown that a pattern of cortisol secretion that involves a post-awakening peak and a 20-fold decrease later in the day is associated with high scores on measures of well-being (e.g., positive affect, optimism), but not with scores on measures of ill-being (e.g., negative affect, pessimism, anxiety, fear) (Lai et al., 2005; Ryff et al., 2006; Steptoe et al., 2007; Steptoe & Wardle, 2005). Individuals with a lower score on eudaimonic well-being experience increased activity in the HPA axis, which resulted in greater cortisol release (Heller et al., 2013; Lindfors & Lundberg, 2002). Thus, both positive and negative affect seems to be associated with the cortisol response, but they seem to be independent of each other. Excessive stress may result in wear and tear on the body and brain. This excessive stress can cause the HPA axis to remain activated because it is less able to shut itself off, which leads to an impairment in the immune system. This impairment may decrease well-being by making the individual more susceptible to illnesses, as well as depression and anxiety disorders (McEwen, 1998b; Walker & McGlone, 2013).

Having a social support system can serve as a buffer for this stress reactivity, which can aid in increasing well-being, therefore, decreasing the probability of illness. Studies confirming this theory demonstrated the decrease of cortisol responses when a significant other was giving social support in comparison to when a stranger was providing it (DeVries et al., 2003; Walker & McGlone, 2013).

Another method that may aid in reducing stress, which also inhibits excessive cortisol secretion, is prefrontal transcranial Direct Current Stimulation (tDCS). It involves the placement of two macro-electrodes on the skull in certain brain regions and sending a weak current between them. Austin et al. (2016) used the F3 and F4 brain regions, and applied it to healthy, early adult females to observe if there was a difference in psychological distress after tDCS. Typically, the F3 and F4 regions are used in the treatment of depression. The results yielded significantly less psychological distress from daily

stressors in the participants and a decrease in negative mood states (Austin et al., 2016; Siever, 2015). The Petrocchi et al. (2017) study involved only anodal stimulation, which is related to an increase in neuronal excitability and is followed by a decrease in GABA. They sought to find a correlation between heart rate variability and positive emotion in healthy individuals. This study placed an electrode on the left temporal lobe only. Researchers found one session of tDCS increased heart rate variability, and in return, this stimulation triggered soothing positive affect, which was associated with peacefulness, contentment, and well-being. Their study provided support for the effectiveness of tDCS on depression and other psychopathological conditions (Petrocchi et al., 2017; Stagg et al., 2009).

In sum, much of the evidence shows that the major neurotransmitters implicated in positive affect include dopamine, norepinephrine, serotonin, and oxytocin. Cortisol, on the other hand, is implicated in negative affect.

Gene Expression and Well-Being

Chronic stress or a major acute stressor (e.g., divorce) is highly correlated with clinical depression, especially for those genetically susceptible (Kanarik et al., 2011; van Praag, 2004). Kanarik et al. found that the Gsk3b gene (glycogen synthase kinase-3) was significantly down-regulated in the frontal cortex following chronic social stress in rats. This gene, Gsk3b, is inhibited by lithium, a mood stabilizing drug (Gould et al., 2007), as well as other antidepressants and atypical antipsychotics (Beaulieu, 2007). Kanarik et al. concluded that down-regulation of the Gsk3b gene is an adaptive response to severe stress. Kanarik and colleagues also found down-regulation of the Map1b gene in the frontal cortex and the hippocampus due to chronic social stress. The Map1b gene has also been implicated in neural plasticity (e.g., Nozumi et al., 2009; Kuo et al., 2009) and regulation of serotonin and glutamate receptors (e.g., Moritz et al., 2009; Sun et al., 2008).

Genetic susceptibility to stress can be inherited directly or promoted via epigenetics, an interaction between the environment and the genetic makeup. For example, Francis, Diorio, Liu, and Meaney (1999) found that rat litters receiving low maternal attention (specifically lower levels of licking and grooming the pups) were more fearful and showed a higher hypothalamic pituitary adrenal response to stress as adults than those that received high levels of maternal attention. The differences in maternal care caused glucocorticoid receptor (GR) gene expression changes in the hippocampus, which resulted in differences in hippocampal GR levels and glucocorticoid negative feedback sensitivity (Liu et al., 1997). Additionally, Weaver et al. (2004) found that the maternal behavior produced alterations of DNA methylation and chromatin structure. Relatedly, van Hasselt et al. (2012) examined the effect of maternal attention at the level of individual pups using a complicated cross-fostering system to ensure that the experience was translated through an epigenetic mechanism of inheritance. Specifically, the frequency of licking and grooming during the first postnatal week correlated with mRNA expression of the hippocampal GR gene and with the ability to induce long-term-potentiation in the dentate gyrus (associated with cognitive ability). These findings point to the possibility that the glucocorticoid receptor gene NR3C1 may be a key candidate in epigenetic investigations of stress and depression (e.g., Labonte et al., 2012; Perroud et al., 2011).

Research has also documented the effects of hedonic versus eudaimonic well-being in gene expression, specifically the conserved transcriptional response to adversity (CTRA). CTRA is characterized by expression of pro-inflammatory genes and antibody synthesis genes. For example, Fredrickson et al. (2013, 2015) found that hedonic well-being was associated with CTRA up-regulation (i.e., increased

expression of pro-inflammatory genes and decreased expression of antibody synthesis genes). In contrast, eudaimonic well-being was associated with CTRA down-regulation (i.e., decreased expression of pro-inflammatory genes and increased expression of antibody synthesis genes). The authors suggested that the immune system of the participants was more sensitive to the source of their happiness than their own conscious experiences. As such, eudaimonic well-being seems to be associated with health benefits related to gene expression not evident for hedonic well-being (cf. Cole et al., 2015). A similar study by Cole et al. (2015) found the same effect when they controlled for loneliness as a factor. However, when eudaimonia was controlled for in the data analysis, CTRA was less correlated with loneliness. Cole and colleagues concluded that social well-being could be compensated for by treatment aimed at increasing a person's sense of purpose in life.

In sum, gene expression seems to also play a role in both hedonic and eudaimonic well-being. Several gene alterations have been found to be correlated with depression and high levels of stress. Hedonic well-being seems to be involved in CTRA up-regulation, whereas eudaimonic well-being was associated with CTRA down-regulation. Mechanisms that may explain some aspect of the role of well-being in immune function.

Brain Structures and Well-Being

Huppert (2009) suggested that the individual differences seen in baseline activation in the prefrontal cortex corresponding to emotional style also correlates with adaptive cognitive and emotional responses in relation to psychological well-being. Several studies by Davidson and his colleagues (Davidson, 2004; Tomarken, Davidson, Wheeler, & Doss, 1992; Urry et al., 2004) have shown that activation in the prefrontal cortex (PFC) is asymmetrical and that higher baseline activation occurs in the left PFC in those with a positive, more resilient, affective style, whereas those with a negative affective style show higher baseline activation in the right PFC. Davidson (2004) states the mood of patients following damage to the left side of the PFC results in a greater incidence of depressive symptoms compared to damage to the right side. Consistent with these findings, Grajny et al. (2016) found that stroke damage in the left dorsolateral prefrontal cortex was associated with greater symptoms of depression. In addition, Turner, Cipolotti, Yousry, and Shallice (2007) found that in human lesion patients, damage to the left lateral PFC was associated with deficits in organization and strategy, whereas damage in the right lateral group caused failure of error detection and the checking system. Taken together this data suggests that the PFC is very much involved in both the emotional and cognitive aspects of well-being.

Stroke patients with damage to the left side PFC tend to experience more anxiety and depression than comparable right lesion patients (e.g., Robinson & Sztela, 1981; Starkstein et al., 1987). Similarly, patients with right PFC lesions tend to experience flat affect, implying that the right hemisphere based PFC is implicated for negative affect. Furthermore, much research using electroencephalographic methods supports the association between frontal asymmetry and positive affect and well-being (see Rickard & Vella-Brodick's literature review, 2014, pp. 443-445). The implication from these findings is the left PFC may be involved in approach-related, goal directed planning of actions, as well as positive affect; and conversely, the right PFC may be related to threat-related vigilance (see meta-analytic studies by Murphy et al., 2003; Wager et al., 2003). Additionally, interventions (such as mindfulness meditation) aimed at increasing well-being appear to increase left-sided frontal asymmetry, possibly by promoting emotion regulation (Brefczynski-Lewis et al., 2008; Davidson et al., 2003).

With respect to eudaimonic well-being, Urry et al. (2004) found that those with high eudaimonic well-being show greater left than right superior frontal activation in response to emotional stimuli after adjusting for reported levels of hedonic well-being. Van Reekum et al. (2007) examined amygdala activation in response to negative stimuli. The study showed that those who were faster to evaluate negative information also showed increased amygdala activation. However, the pattern of amygdala activation varied between high and low eudaimonic subjects. High eudaimonics were slower to evaluate negative information (showing reduced amygdala activation) as well as increased ventral anterior cingulate cortex activity—possibly evolved to deal with aversive stimuli (cf. Schaefer et al., 2013). Lewis et al. (2014) found an association between eudaimonia and insular cortex volume—those with higher well-being had greater volume of the right insular cortex gray matter. These data suggest that regulation of emotion via PFC inhibition of the amygdala may correlate with higher eudaimonic function.

Furthermore, research (Boyle et al., 2010, 2012) has shown that eudaimonic well-being is negatively associated with Alzheimer's disease and mild cognitive impairment. Specifically, purpose in life was found to significantly mitigate the effects of Alzheimer's disease pathology (evidenced by a global pathologic score and a measure of neurofibrillary tangles) on cognitive impairment. Additionally, Yu et al. (2015) have shown that greater purpose in life was associated with significant reduction of risk of cerebral infarcts (macroscopic infarcts caused by lacunar infarcts).

In sum, research indicates that expressions of well-being are associated with prefrontal cortex activity. Specifically, activation in the left PFC is associated with positive hedonic well-being, whereas activation in the right PFC is associated with negative hedonic well-being. The pattern is somewhat different in relation to eudaimonic well-being. Although individuals high in eudaimonia experience a similar pattern of activation in the left PFC, they are better in controlling their negative affect via PFC inhibition of amygdala response. Furthermore, high eudaimonic individuals are also less susceptible to cognitive impairment than their low eudaimonic counterparts.

CONCLUSION

Hedonic well-being was defined as an affective dimension that reflects a preponderance of positive affect over negative affect. In contrast, eudaimonic well-being refers to experiences related to personal growth and character development.

Much of the research shows that the brain centers responsible for hedonic well-being involve the VTA and the medial forebrain bundle. Stimulation of these regions activates pathways from the VTA that project to the NAc, the amygdala, the hippocampus, and the prefrontal cortex (i.e., the mesolimbic dopamine pathway) generating a surge of dopamine, which in turn induces positive hedonic well-being. Drugs of abuse and addictive behaviors produce their euphoric effects via the mesolimbic dopamine system. Endogenous and exogenous endorphins (opioids) modulate the reward system. Chronic excitation of the reward system (e.g., by a drug) generally results in a reduction in hedonic well-being, and at the same time, an increase in wanting the drug (resulting in compulsive drug-seeking behaviors). Furthermore, the research indicates that the reward system (the system that produces hedonia) is also involved in eudaimonic well-being, possibly as a motivating force underlying personal growth.

Stress hormones, such as cortisol, are heavily implicated in negative hedonic well-being. Not only does positive affect, and a more positive disposition, correlate with increased well-being, but also with decreased cortisol release. Reduced cortisol release is associated with higher levels of eudaimonic

well-being as well. Hedonic well-being has been found to be correlated with a poorer immune system response as measured by CTRA, whereas increased immune function is associated with higher scores on eudaimonia. Healthier profiles of diurnal cortisol are correlated with inventories measuring personal growth and purpose in life.

Hedonic and eudaimonic well-being appear to differ in their neural substrates. Hedonic well-being is more closely associated with the mesolimbic dopamine pathway, whereas eudaimonic well-being is more closely regulated by the prefrontal cortex; although both brain regions are clearly involved in both types of well-being. Individuals high on eudaimonia not only experience a higher pattern of activation in the left PFC but also are better in controlling their negative affect via PFC inhibition of amygdala response. Evidence suggests that the left PFC may be involved in approach-related, goal directed planning of actions, as well as positive affect, whereas the right PFC may be more involved in threat-related vigilance and negative affect. Individuals with high eudaimonia are also less susceptible to cognitive impairment than their low eudaimonic counterparts. Individuals who have a purpose in life, a major characteristic of eudaimonia, have an advantage in this regard as well. Importantly, a person's sense of purpose in life seems to increase resilience, buffer against mild cognitive impairments, and protect against relapse to substance use.

Much progress has been made in neuroscience research related to well-being, and much remains to be done. The hope is that this chapter will provide scholars interested in the neuroscience of well-being with a brief synopsis of this research and possibly inspire and motivate future research on this very important topic.

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ENDNOTE

[1] It should be noted that the current level of subjective well-being experienced by an individual is likely to moderate the effects of euphoric drugs, such as pain killers or psychostimulants, as well. This phenomenon is commonly known as the "Law of Initial Value" (Wilder, 1958). Wilder's law states that a change, such as that produced by a drug, cannot affect the person's mood or cognitive state beyond their capability for change. In addition, the effect of the drug depends on the user's initial state. If the person is close to their maximum state for the effect in question, then little change will occur; however, if they are quite distant then the greater the potential effect. For example, a person who is currently in a negative mood state (i.e., experiencing anxiety, pain, or melancholy) may experience euphoria when given small doses of morphine. In contrast, a similar dose of morphine given to a happy person may have little effect or even induce anxiety and fear (Wenk, 2009, p. 20).