Michael S. Ritsner *Editor*

Anhedonia: A Comprehensive Handbook Volume I

Conceptual Issues And Neurobiological Advances

Springer

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Volume I

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This book is dedicated, with love,
to my smart sons and best friends
Edward and Israel Ritsner
and their lovely families

About the Editor

Michael S. Ritsner, M.D., Ph.D.

Dr. Ritsner, MD, PhD is an Associate Professor of Psychiatry at the Rappaport Faculty of Medicine, Israel Institute of Technology (Technion) in Haifa. He also serves as Head of the Acute Department of the Sha'ar Menashe Mental Health Center. Dr. Ritsner received his *M.D.* in 1971 from the Khabarovsk State Medical University and *Ph.D.* in 1975 from the Siberian State Medical University of Tomsk (Russia). Dr. Ritsner is certified by the Israeli Board of Psychiatry. He has over 40 years of experience in psychiatry, medical genetics, education, and research, and has held administrative and teaching positions at numerous institutions.

Dr. Ritsner is internationally renowned for his research in schizophrenia spectrum disorders. Particular areas of interest include genetic epidemiology, molecular genetics and biomarkers, the role of neurosteroids, novel antipsychotic drugs and agents with neuroprotective properties (*DHEA, Pregnenolone, L-Theanine, and Bexarotene*), and cognitive impairments. He develops the *Distress/Protection Vulnerability Model* of quality of life deficit syndrome in schizophrenia spectrum disorders.

Dr. Ritsner has published over 160 articles, reviews, and book chapters and has lectured widely in national and international scientific forums. He has given more than 200 presentations including as invited speaker at scientific conferences and medical education events. His research work has been supported by grants from the Stanley Foundation (USA).

Dr. Ritsner is the co-author of two books on neuropsychiatry and editor of series follows 14 volumes, which provide a comprehensive up-to-date state of the art overview of the literature that addresses the challenges facing clinical and biological psychiatry:

1. Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders. New Perspectives on Research and Treatment. Ritsner, *Michael S.; Awad, A. George* (Eds.), Springer, Dordrecht. The Netherlands, 2007, 388 p.
2. Neuroactive Steroids in Brain Functions, and Mental Health. Novel Strategies for Research and Treatment. *Ritsner, Michael S.; Weizman A.* (Eds.), Springer Science + Business Media, B.V., 2008. 559 p.
3. The Handbook of Neuropsychiatric Biomarkers, Endophenotypes, and Genes. Volumes I–IV. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V., 2009.
   - *Volume I: Neuropsychological Endophenotypes and Biomarkers. 231 pp.*
   - *Volume II: Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers. 244 pp.*
   - *Volume III: Metabolic and Peripheral Biomarkers. 231 pp.*
   - *Volume IV: Molecular Genetic and Genomic Markers. 232 pp.*
4. Brain Protection in Schizophrenia, Mood and Cognitive Disorders. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2010. 663 p.
5. Handbook of Schizophrenia Spectrum Disorders. Volumes I–III. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2011.
   - *Volume I: Conceptual Issues and Neurobiological Advances. 494 pp.*
   - *Volume II: Phenotypic and Endophenotypic Presentations. 526 pp.*
   - *Volume III: Therapeutic Approaches, Comorbidity, and Outcomes. 461 pp.*
6. Polypharmacy in Psychiatric Practice. Volumes I–II. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2013.
   - *Volume I: Multiple Medication Use Strategies. 287 pp.*
   - *Volume II: Use of Polypharmacy in the "Real World". 321 pp.*
7. Anhedonia: A Comprehensive Handbook. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2014.
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Dr. Ritsner served as Associate Editor, Quality of Life Research (An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, Amsterdam, The Netherlands); Board Member, American Journal of Neuroprotection and Neuroregeneration (USA); CNS & Neurological Disorders-Drug Targets (Italy); member of the Scientific Committee, International Society for the Study of Neuroprotection and Neuroplasticity (Romania). Referee activity: CNS Drugs, Quality of Life Research, Psychiatry Research, Clinical Drug Investigation, Social Psychiatry and Psychiatric Epidemiology, Biological Psychiatry, etc.

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Preface

To the best of my knowledge, this might be the first comprehensive oriented two-volume collection on anhedonia across neuropsychiatric and physical disorders. Anhedonia played an important role in psychopathology theories at the beginning of the twentieth century. It frequently occurs in mood disorders, as a negative symptom in schizophrenia, and in substance use disorders, as well as in neurological and physical disorders. Anhedonia or hedonic capacity deficit is a condition in which the capacity of pleasure is totally or partially lost, and it refers to both a personality trait, and a state symptom in various disorders. Over the past three decades cognitive psychology and behavioral neuroscience have expanded our understanding of anhedonia and other reward-related processes. It has a putative neural substrate, originating in the dopaminergic mesolimbic and mesocortical reward circuit. The aim of this new collection is to highlight the contributions of eminent scientists in this field as well as to provide readers with comprehensive accounts of recent developments as perceived by the authors. It is expected that "Anhedonia" will be very well received in international circles because it presents important reviews of current interest in this "hot" area.

This monograph is divided *into five parts. Volume I* contains two parts (*Conceptual Issues and Neurobiological Advances*) including 14 chapters that serve as an introduction and overview of conceptual issues. Key topics include: the different components and facets of anhedonia, reward response, pleasure systems for food, sensory rewards in the human brain, anhedonia in children and adolescents, neurogenetics and neurobiology of dopamine in anhedonia, the endocrinology of anhedonia, electrophysiological signatures of reward processing, the role of perceived control, dopaminergic mechanisms for motivational deficits, musical anhedonia, stress-induced eating disorders, brain imaging correlates of anhedonia, mouse models and improving pleasure in patients with anhedonia.

Volume II contains three parts (*Anhedonia in Psychotic Disorders, Anhedonia in Mood and Personality Disorders, and Anhedonia in Neurological and Physical Disorders*) including 15 chapters that focus on the history and provide an overview of the construct, measuring anhedonia in schizophrenia spectrum disorders,

hedonic capacity and related factors in schizophrenia and schizoaffective disorder, anhedonia as an indicator of genetic liability for schizophrenia, and a trait marker for depression, the role of an anhedonia in trauma-related disorders, anorexia nervosa, schizotypal traits and risk of suicide. The authors discuss the relationships of anhedonia features with epilepsy, Parkinson's disease and other movement disorders, with heart and cerebrovascular disorders. *Since many of the* contributors to this collection are internationally known experts, they not only provide up-to-date state of the art overviews, but also clarify some of the ongoing controversies and future challenges and propose new insights for future research. I would like to thank to all contributors for their cooperation. Finally, for the support and patience of my family and friends I am truly thankful. I sincerely hope that this book will be of interest to a broad spectrum of readers including psychiatrists, psychologists, neurologists, neuroscientists, endocrinologists, pharmacologists, general practitioners, geriatricians, graduate students, and health care providers in the fields of mental health.

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Part I
Conceptual Issues

Chapter 1
The Different Facets of Anhedonia and Their Associations with Different Psychopathologies

Stewart A. Shankman, Andrea C. Katz, Alison A. DeLizza, Casey Sarapas, Stephanie M. Gorka, and Miranda L. Campbell

Abstract Over the last several decades, there has been increasing interest in the role that anhedonia plays in various psychopathologies, ranging from mood disorders, to eating disorders, to psychotic disorders. The term 'anhedonia' (which simply means, *without pleasure*) has been used to describe a wide range of constructs, affective experiences, and events. Given the breadth of the term, it is likely that different aspects of anhedonia may be related to different psychopathologies in various ways. This review discusses how the literature has parsed anhedonia and how the various components and facets of anhedonia may relate to various psychopathological constructs. In addition, this review takes concepts and theories from the broad affective science literature and identifies additional components of anhedonia that may be critical to the field's understanding of the construct. Given the importance that anhedonia plays in a multitude of psychopathological constructs, a careful analysis of the various components and facets of anhedonia may provide a conceptual framework for research in this area.

Keywords Anhedonia • Psychopathology • Affective experience • Anticipatory and consummatory positive affect

Abbreviations

AN	Anorexia nervosa
APA	Anticipatory positive affect
BED	Binge eating disorder
BN	Bulimia nervosa

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CPA	Consummatory positive affect
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
EEG	Electroencephalogram
HIV	Human immunodeficiency virus
HSDD	Hypoactive sexual desire disorder
MDD	Major depressive disorder
PTSD	Post-traumatic stress disorder
RDoC	Research Domain Criteria
SUD	Substance use disorder

1.1 Introduction

Anhedonia, which can broadly be defined as a diminished capacity to experience pleasure, is a construct associated with various psychiatric disorders. The importance of anhedonia in psychopathology (and hedonic capacity more generally) is further supported by its inclusion as a key domain in the Research Domain Criteria (RDoC), a new conceptual framework for psychopathology research recently launched by the United States' National Institute of Mental Health that focuses on transdiagnostic domains, rather than disorders.

Despite its importance, the scientific and clinical literature uses the term *anhedonia* in different ways and within different contexts to describe a broad range of emotional experiences. Given the breadth of the term, it is likely that various aspects of anhedonia relate to different psychopathologies differently.

The thesis of this review is therefore that the construct of anhedonia is more nuanced than what is often described in the literature, and divisible facets of it are often obscured. First, we will review different ways that anhedonia has been (or could be) parsed. Second, we will discuss how these separable facets relate to different psychopathologies. Of note is that in order to focus this review and to not overlap with other chapters in this volume, the present review will discuss hedonic experience and expression, rather than the cognitive aspects of hedonic capacity (e.g., evaluation of reward value, affective forecasting, reward learning, and reward prediction error).

1.2 A Review of the Various Facets of Anhedonia

1.2.1 Role of Anhedonia in the Time Course of Reward Processing

1.2.1.1 Anticipatory vs. Consummatory Positive Affect

Some researchers use *anhedonia* to refer to deficits in the affective response to a rewarding or pleasurable stimulus. However, there are two components to the

positive affect experienced in rewarding situations – anticipatory positive affect (APA) and consummatory positive affect (CPA). The difference between APA and CPA is temporal. APA is the excitement felt as the animal waits for the receipt of a reward, and CPA is the enjoyment felt after receipt of a reward. APA and CPA are also linked to different behavioral and motivational outcomes – with the former linked to motivation and goal-directed behavior and CPA linked to satiation at the attainment of a goal [1]. Berridge and Robinson [2] describe these constructs as 'wanting' and 'liking', respectively.

Although APA precedes CPA for a single rewarding stimulus, there is actually a bidirectional relationship between the two. On the one hand, animals experience APA as they await a reward and CPA after they receive it. On the other hand, animals only experience APA once they have experienced CPA in response to a novel stimulus and learned to associate positive affect with that stimulus [3–5]. That is, most of the time, an animal can only *want* something that it has previously *liked*. Additionally, studies have shown that the more one looks forward to a reward, the more one enjoys it when they get it [6, 7].

Neurobiological studies also support the distinction between anticipatory and consummatory positive affect. Animal models of reward processing have demonstrated that there are separable neural pathways associated with CPA and APA [2, 8]. Functional neuroimaging studies of humans have also supported this distinction. For example, Knutson et al. [9] observed activation in the nucleus accumbens while individuals anticipated reward, but this activation subsided during the delivery of rewards. On the other hand, the ventromedial frontal cortex appeared to be more involved during the experience of consummatory affect (see [10] for review).

Given the distinction between APA and CPA, it is important to consider that anhedonia may represent a deficit in anticipatory positive affect, consummatory positive affect, or both. That is, individuals with anhedonia may not anticipate that rewards will be pleasurable, not react with joy and/or satisfaction when they receive them, or both.

1.2.1.2 Distal vs. Proximal Reward

While deficits in APA and CPA are critical facets of the broad construct of anhedonia, there are other temporal demarcations that could be made within APA and CPA as well. First, it is possible that anhedonia may manifest as a deficit in anticipatory pleasure for more distal rewards (e.g., a reward occurring in several months), while anticipatory pleasure for proximal rewards (e.g., a reward occurring in several minutes) is relatively intact (see [11] for related work). For example, an individual may not look forward to receiving a university degree or work-related promotion, but still look forward to a movie that is about to start.

Second, after the reward is received (i.e., within the CPA phase), anhedonia may manifest as a more rapid decrease in consummatory pleasure. That is, the hedonic impact of a stimulus, and the amount of consummatory positive affect that it generates, might fade more quickly in certain individuals or in certain psychopathologies.

This deficit in the time course of the hedonic response may or may not also relate to the "peak" affective response experienced by the individual [12].

Thus, anhedonia can reflect the length of time a stimulus generates anticipatory processes, consummatory processes, or both. From this discussion, we see that it is also possible to describe anhedonia as a 'narrowing of the time window' during which APA and CPA are experienced surrounding the receipt of reward.

1.2.2 Loss of Interest vs. Loss of Pleasure

Anhedonia, along with persistent depressed mood, is one of the cardinal symptoms of major depressive disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [13]. However, even within the context of one disorder, there are two definitions of anhedonia. According to the DSM-5, an individual is experiencing anhedonia if he/she reports deriving less pleasure from daily activities than usual *or* if he/she reports feeling less interested in those daily activities. While "loss of interest" and "loss of pleasure" are considered anhedonia, it is not clear whether they are equivalent.

Animal models illustrate a behavioral distinction between loss of interest and loss of pleasure. In rats, 'loss of interest' is often operationalized as reduced exploratory behavior in novel environments such as the classic open field tests [14, 15]. This pattern of behavior is often conceptualized as a loss of incentive motivation [16]. On the other hand, 'loss of pleasure' is operationalized as a reduction in responsiveness to previously rewarding stimuli (e.g., decreased preference for and consumption of sucrose [17]).

In animal models of depression, both of these behaviors are conceptualized as anhedonia and, indeed, both are consequences to exposure to chronic stress [18] and improve with the administration of antidepressant medications [19]. However, a factor analysis of these putative animal indices of depression indicates that exploratory behavior and sucrose consumption load onto separate factors [20]. Given that separable behaviors are observed in animal models of depression, it is unclear whether the construct of "anhedonia" should apply to both loss of interest and loss of pleasure.

In humans, self-reports of loss of interest and loss of pleasure have been shown to be correlated but separable constructs [21]. This distinction is supported by epidemiological, neuroimaging and psychopharmacological data as well. For example, although the symptoms of loss of pleasure and loss of interest tend to cluster together in clinical populations, not every patient with major depression experiences both symptoms, and they correlate differently with other symptoms of depression [22]. Dysfunction in the mesocorticolimbic dopaminergic pathway has been linked to both symptoms, although different structures within the pathway have been implicated in loss of pleasure (nucleus accumbens; see [23] for review) and loss of interest (prefrontal cortex; [24]). Finally, pharmacological studies examining the effects of non-serotonergic antidepressants on treatment-resistant symptoms (among them loss of interest and

loss of pleasure) have found that different classes of noradrenergic and dopaminergic drugs are more effective at treating loss of interest and loss of pleasure [25].

1.2.3 Anhedonia as Flat Affect

Anhedonia has also been used to describe flattened affect across multiple emotions and valences. That is, rather than experiencing a diminished capacity to experience pleasure, some scientists and clinicians use the term anhedonia to mean reduced affect across numerous emotional dimensions (e.g., reduced happiness, reduced sadness, reduced anger, etc.) This phenomenon, also known as 'restricted range of affect' or 'emotional numbing', is associated with psychopathologies such as post-traumatic stress disorder (PTSD).

Supporting this definition, factor analytic research in traumatized populations has shown that loss of interest/pleasure and emotional numbing load onto the same latent factor [26–28]. As discussed below, it is possible that this association between symptoms might contribute to the high rates of comorbidity between post-traumatic stress disorder and major depressive disorder [29] – if the two symptoms are in fact part of the same construct rather than two separate ones.

1.2.4 Role of the Stimulus in Anhedonia

A final consideration in our discussion of anhedonia concerns the quality (or category) of the stimulus that elicits the anhedonia. Anhedonia can refer to decreased ability to experience pleasure to all (or at least multiple) positive stimuli, or it can refer to a specific stimulus. Thus, individuals can experience less pleasure in response to a particular stimulus, while responses to other stimuli remain intact. In the present review, we consider three types of stimuli – social stimuli, sensory stimuli, and drug/substances.

1.2.4.1 Social Anhedonia

Most individuals derive pleasure from their social interactions with others, such as conversing, sharing experiences, doing activities together, expressing their feelings, loving, and even competing with other people. Social anhedonia, therefore, involves deriving significantly less or even no pleasure from these social situations.

1.2.4.2 Sensory Anhedonia

Individuals also derive pleasure from various sensory or physical stimuli (i.e., stimuli affecting any of the five senses). Those who experience this type of anhedonia

(often labeled "physical anhedonia") [30] derive less pleasure from physical sensations than those who do not experience physical anhedonia. Although physical anhedonia refers to decreased pleasure for all sensory stimuli, such as smells, sounds, touch, movement, and temperature, two of the physical stimuli most commonly studied in the context of are sexual and gustatory stimuli. Sexual anhedonia, though often associated with major depression, has also been examined in the context of sexual dysfunction. As mentioned earlier, gustatory anhedonia is often used in animal models of anhedonia.

1.2.4.3 Anhedonia and Drug Use

Anhedonia can be associated with several aspects of drug use. Several hedonic theories of addiction posit that drugs act on the mesocorticolimbic dopamine systems, which mediate the intense feelings of pleasure when addictive drugs are administered and the anhedonia during withdrawal [31, 32]. Additionally, it is possible that physiological and psychological tolerance to addictive drugs are related to anhedonia – that is, when taken regularly, the same amount of a particular addictive drug induces less pleasure than it did when the individual first began taking the drug [33].

1.2.5 Summary

In the previous section, we outlined several instances in which the term anhedonia is used to describe a constellation of clinical symptoms including: deficits in the temporal experience of reward, restricted range of affect, loss of interest, loss of pleasure, and anhedonia across a wide range of pleasurable stimuli. This array of deficits may play different roles in various psychopathologies. In the next section, we review the role that these different facets of anhedonia may play in various psychopathological constructs. Of note is that many of the disorders reviewed in this chapter are discussed in more detail in other chapters in this volume. The present chapter therefore focuses on how the different components of and definitions of anhedonia relate to each disorder rather than being an exhaustive review of the role of anhedonia in those disorders.

1.3 Role of Anhedonia in Various Psychopathologies

1.3.1 Anhedonia and Major Depression

Although anhedonia is a feature of many clinical syndromes, major depression is perhaps its archetypal disorder. As mentioned earlier, loss of interest or pleasure is one of

the two symptoms required by the *DSM-5* for a diagnosis of MDD, and approximately 70 % of individuals with the disorder experience anhedonia [13, 34].

1.3.1.1 MDD and Deficits in Reward Processing

A large literature indicates that disturbed reward processing is a prominent, perhaps central, feature of depression [35]. Theoretical models dating back to Donald Klein's work have posited that deficits in *anticipatory* reward processing are most relevant to depression [1, 36] and behavioral, neurobiological, and physiological evidence generally supports this thesis. For instance, Sherdell, Waugh, and Gotlib [37] found that reduced anticipatory, but not consummatory, positive affect predicted lower motivation to expend effort to obtain reward among individuals with MDD. Many studies have implicated the mesolimbic dopamine system in depression (see [38] for a review), which is primarily involved in prediction of and motivation for future rewards. Several studies have also found that frontal electroencephalogram (EEG) asymmetry, a psychophysiological index of reward processing, is altered among depressed individuals during anticipation of monetary reward [39, 40], but not during reward consumption [41].

However, some depressed individuals – for instance, those with melancholic depression – may experience altered consummatory as well as anticipatory reward processing. Klein wrote that these individuals "enjoy nothing and their mood cannot be improved by positive rewards" [36, p. 4], and a DSM-5 criterion for melancholic depression is lack of mood reactivity to positive stimuli [13]. Consistent with this conceptualization, melancholic depressed individuals show an abnormal posterior EEG asymmetry during consummatory reward processing, whereas their non-melancholic counterparts do not [40]. Thus, deficits in anticipatory reward processing seems to be a feature common to most depressed individuals, and a smaller subset of these individuals also show deficits in consummatory reward processing.

As discussed above, another aspect of reward processing is the distinction between temporally proximal and distal rewards. Healthy individuals typically ascribe more value to immediately available rewards than to future rewards of equal or even greater value, a phenomenon labeled delay discounting. Lempert and Pizzagalli [42] reported that this temporal gradient was reduced among anhedonic individuals – that is, these individuals were more apt to choose future rewards of greater value than current rewards of lesser value. The authors speculate that this reflected a reduced responsiveness to immediate reward associated with anhedonia. Although preferring a future of greater value over a lesser current reward is technically more 'rational', it is notable that this pattern of reduced delay discounting is predictive of suicide attempt lethality among depressed individuals [43].

1.3.1.2 Affective Flattening and Major Depression

The diminished interest and pleasure observed in individuals with depression may merely be part of a broad pattern of affective blunting of which diminished interest/pleasure

are merely components. That is, depression may be associated with reduced affective responding for a broad array of emotions and not just positive. Studies examining this have been mixed. While some laboratory studies have found that MDD is characterized by blunted emotional responses to both pleasant and unpleasant events (a pattern referred to as emotion context insensitivity) [44, 45], other conflicting results have been reported. In one study, depressed participants reported less happiness than controls in response to positively-valenced pictures, but comparable levels of sadness in response to negative pictures, and greater sadness than controls in response to the positive pictures (inconsistent with affective flattening) [46]. Similarly, whereas affective blunting would predict low sensitivity to reward *and* punishment, depressed individuals actually show *enhanced* punishment sensitivity in several studies (reviewed in [35]). Another study directly addressed the relationship between anhedonia and blunted affect among depressed participants and found that anhedonia and affective flattening were orthogonal constructs [47]. Thus, while studies have consistently found that depression is associated with reduced responding to positive stimuli, it is unclear whether it is also associated with reduced to negative stimuli – a pattern possibly due to differences in methodology and paradigms [48].

1.3.1.3 The Role of the Stimulus in Depressive Anhedonia

A final question concerns whether anhedonia in depression is circumscribed to loss of pleasure in specific classes of stimuli, or whether anhedonic depressed individuals experience a broad loss of pleasure in most or all stimuli. An early study suggests that the latter is the case – Fawcett and colleagues [49] found that anhedonic depressed individuals reported loss of pleasure in all areas assessed, including food, sex, social interaction, and work. Consistent with this, depressed individuals experiencing anhedonia are more likely to experience both social withdrawal and appetite loss than depressed individuals without anhedonia, suggesting that anhedonia extends to both physical and social stimuli [34].

However, these findings are qualified by two points. First, although it does appear that depressed individuals *may* experience loss of pleasure in a variety of domains; this is not the same as saying that *all* anhedonic individuals lack pleasure in *all* domains. At the individual level, some may experience a generalized loss of pleasure; some may have diminished pleasure in some domains (e.g., physical stimuli) and intact pleasure in others (e.g., social contact); while others show the opposite pattern (e.g., diminished social pleasure with intact physical pleasure) [50, 51]. In other words, individual depressed persons may experience either broad or circumscribed anhedonia, but a given depressed individual is just as likely to lose pleasure in physical, social, or intellectual stimuli.

A second caveat is that while studies investigating specific aspects of anhedonia have generally agreed that both physical and social pleasure may be impaired during depressive episodes, their long-term course may be different. For instance, a 20-year longitudinal study found that physical anhedonia in depression is stable

and trait-like, associated with depression severity, and predictive of psychosocial functioning [52]. In contrast, another longitudinal study found that currently depressed individuals experienced higher levels of social anhedonia than healthy controls, but that social anhedonia declined over a 1-year follow-up period as participants recovered from depression [53].

1.3.1.4 Can Anhedonia Improve the Classification of Depression?

As we have seen, deconstructing the broad construct of anhedonia into more specific facets can yield greater insight into depression. The reverse may also be true. Depression is a heterogeneous disorder, and presence or absence of anhedonia is a factor that may help parse this heterogeneity. That is, depressed individuals with and without anhedonia differ on a number of clinical variables, suggesting that anhedonic and non-anhedonic depression may be separate syndromes. For instance, individuals with anhedonia are more likely to experience psychomotor retardation, diurnal variation in mood, and brooding (as well as social withdrawal and appetite loss, as mentioned above) [34, 54], and tend to have poorer long-term outcome [55, 56]. Interestingly, anhedonia is *not* associated with overall depression severity [57], and is associated with *lower* rates of other symptoms, such as suicidality [34]. This suggests that anhedonia is not merely a marker of more severe depression, but instead may be associated with a qualitatively different constellation of symptoms.

The idea that anhedonic and non-anhedonic depression are separable syndromes is further supported by their associations with dimensions of personality. Although both types are associated with high neuroticism as compared to healthy individuals, anhedonia is uniquely associated with lower extraversion than controls, as well as lower neuroticism than those with non-anhedonic depression [49, 58]. Indeed, evidence reviewed extensively by Clark and Watson [59] suggests that anhedonic depression is a syndrome or dimension separate from non-anhedonic depression, while the latter is *not* separable from the general distress seen in anxiety disorders. In other words, while anhedonic depression may be a valid syndrome, non-anhedonic depression may have more in common with traditional anxiety disorders than anhedonic depression.

The *DSM-5* "melancholic features" specifier is somewhat similar to the concept of anhedonic depression [13]. However, unlike anhedonic depression, depression with melancholic features is a polythetic construct, and anhedonia per se is not sufficient (and perhaps, not even necessary) for the specifier. As such, many non-melancholic depressed individuals also demonstrate anhedonia or deficits in reward processing [52]. Multivariate genetic evidence suggests that (perhaps in contrast to anhedonic depression), melancholia may simply be a quantitatively more severe form of depression, rather than a qualitatively distinct syndrome [60]. Finally, although there is some evidence for the validity of melancholia [50], others have questioned its validity (at least in its current form) [61]. Future research should examine whether an anhedonic subtype of depression has greater validity and utility than the melancholic subtype.

1.3.2 Anhedonia and Anxiety Disorders

Compared to the large literature investigating anhedonia in depressive disorders, relatively less is known about the role of anhedonia in the anxiety disorders. This is likely due to the widely held belief that although both depression and anxiety are characterized by increased negative affect, anhedonia is thought to be a symptom that distinguishes depression from anxiety [59, 62]. However, studies have examined hedonic deficits in social anxiety and post-traumatic stress disorder (PTSD), and some work has investigated the relationship between worry and reduced positive affect. With many of these studies, however, given the sizeable overlap between depression and anxiety [59], it is unclear whether the effects are due to comorbid depression or the anxiety disorder.

1.3.2.1 Anhedonia in Social Anxiety

In studies of social anxiety, anhedonia is most often characterized as a reduction in positive affect. Additionally, to our knowledge, studies of anhedonia in social phobia have not examined the specific facets/conceptualizations of anhedonia espoused in this chapter, but rather look at anhedonia as a unitary construct (although see [63] for a discussion of how loss of interest/curiosity is different from loss pleasure in social anxiety). Overall, the symptom profile of social anxiety is similar to that of depression as it is also associated with low levels of positive affect and high levels of negative affect [64]. However, depression is more strongly associated with low positive affect than social phobia [65]. Additionally, although socially anxious individuals generally exhibit more depressive symptoms than those who are not, the presence of anhedonia in this population is not completely attributable to depressive symptoms [66].

1.3.2.2 Anhedonia and Post-Traumatic Stress Disorder

The majority of studies examining anhedonia in post-traumatic stress disorder (PTSD) have focused on the presence of emotional numbing. Emotional numbing is characterized by reduced interest and/or pleasure in previously enjoyed activities, a restricted range of emotional expressiveness, and a detachment from others [13, 67]. The presence of emotional numbing in some individuals with PTSD may contribute to the high rate of comorbidity between PTSD and depression [29]. This symptom cluster, however, is broader than just reduced positive affective experience and reflects a reduction of affective experience across different emotions. Factor analytic studies have also shown that numbing and related symptoms are separable from other symptoms of PTSD and have separate correlates [26, 28]. Emotional numbing is further delineated from anhedonia as it is associated with an increased likelihood of a comorbid anxiety disorder (and to a lesser extent a psychotic disorder), whereas anhedonia has been associated with comorbid major depressive disorder [27].

1.3.2.3 Worry and Anhedonia

Worry (i.e., a repetitive thought or series of thoughts related to potential negative future outcomes) is a core symptom of nearly every anxiety disorder. Although the content of these thoughts generally varies by disorder and feared stimuli, worry is a pervasive pattern of thinking that is often associated with increased negative affect and negative mood states [68]. Repetitive thinking of any form (whether it is anticipatory worry or rumination on past events) is known to maximize cognitive resources, which could lead to a restricted range of expressed emotion and reduced ability to experience positive affect as well. Consistent with this hypothesis, studies have shown that both rumination *and* worry, independent of one another, have been associated with decreases in positive affect [69].

In sum, hedonic deficits have been found in social anxiety disorder and post-traumatic stress disorder (and worry more broadly), but much less is known about these deficits in other anxiety disorders, specifically, obsessive-compulsive disorder, panic disorder (although see [40]), and specific phobias. Future research examining distinctive and/or overlapping features of anhedonia that may be present in anxious disorders is needed in order to establish a more complete clinical picture of this class of disorders.

1.3.3 Anhedonia and Substance Use Disorders

Research indicates that anhedonia is a common feature in patients with substance use disorders (SUD) [70, 71]. Even when controlling for overall depressive symptoms, abstinent substance users display high levels of anhedonia during acute and chronic withdrawal periods [72, 73]. Moreover, recent evidence suggests that anhedonia may actually precede substance use initiation, as drug-naïve individuals with elevated levels of baseline anhedonia report greater subjective "highs" during acute intoxication. Baseline anhedonia may also be a risk factor for the development of SUDs, as anhedonic individuals are more vulnerable to SUD onset [74, 75]. However, similar to its presentation in other psychiatric disorders, there are important nuances to the presentation of anhedonia in those with SUDs.

1.3.3.1 APA and CPA Dysfunction in Substance Use

SUDs are characterized by dysfunctional APA (i.e., wanting) and CPA (i.e., liking). Regarding APA, one key feature of substance dependence is craving – a strong desire or urge to ingest drugs. Substance users display preoccupation with drug attainment and compulsive drug seeking behaviors (and given its importance, craving was recently added to the criteria for substance use disorder in DSM5 [13]). Although reward anticipation is often conceptualized as a positive affective experience (i.e., anticipatory *positive* affect), in individuals with SUDs, craving and wanting are marked by high levels of anxiety and distress, coupled with exacerbated

biological stress reactivity [76]. In sum, people with SUDs experience high levels of wanting *without* anticipatory pleasure.

Once the drug is obtained, substance-dependent individuals report diminished CPA, which underlies the phenomenon of "chasing the first high." A large body of research suggests that diminished CPA is a function of physical tolerance, such that chronic drug administration results in adaptive changes in the central nervous system, including altered dopaminergic and serotonergic neurotransmission, which modifies the drug's psychophysiological effects over time [77, 78]. It is likely that these neuroadaptive changes result in a dampened hedonic "peak" as well as a more rapid decrease in consummatory pleasure over time. Thus, in response to drug administration, the addicted individual experiences only a small spike of hedonic pleasure that quickly dissipates as compensatory processes become more efficient at returning the body to homeostasis [79]. There is also some evidence to suggest that compensatory processes may even undershoot baseline functioning, producing a state of dysphoria, which serves to re-elicit cravings and compulsive drug seeking behaviors.

1.3.3.2 Delayed Reward Discounting in SUDs

Similar to major depression, delayed reward discounting is an additional anhedonic feature of SUDs. However, unlike individuals with major depression, who show *reduced* delayed reward discounting, individuals with SUDs exhibit enhanced reward discounting. That is, they display a deficit in appropriately guiding goal-directed behavior towards distal, relative to proximal, rewards [80, 81]. Specifically, drug dependent individuals will often select the proximal reward of drug intoxication over a variety of adaptive behaviors that would lead to deferred rewards that are actually more beneficial to them in the long run. A common example is seen in injection drug users who share hypodermic needles to achieve immediate drug intoxication instead of postponing drug use until the needles can be cleaned or replaced. This more adaptive behavior, which would still allow them to get high but would of course reduce their risk for contracting blood-borne illnesses like Human Immunodeficiency Virus (HIV). Broadly speaking, the desire/anticipation for drug intoxication is heightened, and possibly prolonged, yet the interest in long-term legal, financial, and interpersonal rewards is significantly reduced.

1.3.3.3 Generalization of Anhedonia to Other Stimuli

Data also suggest that over time, substance users experience diminished sensitivity to natural rewards, including food and sexual activity [82, 83]. This broadening of stimuli is thought to be the result of dysregulated hedonic homeostatic balance or a "set-point shift" in hedonic thresholds [32]. As was previously mentioned, repeated and prolonged substance abuse has been shown to change the functioning of reward system neurocircuitry. These changes not only affect the way the body responds to acute drug administration, but also the way all rewards are processed. Over time, substance users require higher stimulation to reach previously achieved levels of

hedonic pleasure. In other words, it is as if individuals with SUDs develop tolerance to natural rewards, in addition to addictive drugs. Together, these separate, yet overlapping, aspects of anhedonia serve to maintain drug taking behaviors and significantly contribute to the pathophysiology of SUDs.

1.3.4 The Role of Anhedonia in Eating Disorders

Eating disorders (anorexia nervosa [AN], bulimia nervosa [BN] and binge eating disorder [BED]), are increasingly pervasive disorders with high rates of comorbid depression and anxiety [84]. Recently, the role of anhedonia in eating disorders has become a topic of growing interest. However, as with the other disorders reviewed thus far, there seems to be a difference in how anhedonia and hedonic responses manifest in different eating disorders [85].

1.3.4.1 Anhedonia and Anorexia Nervosa

Anhedonia in the context of AN is often described as both a lack of desire for food and as a lack of pleasure received from food (i.e., APA and CPA). Indeed, compared to controls, studies have shown that individuals with AN report less desire and pleasure for food when presented with food either visually or olfactorily [86] – an effect that remains, even after controlling for depressive symptoms [87]. Some studies have also suggested that the observed anhedonia towards food in anorexia actually reflects a fear of weight gain towards the food and not a reduced experience of pleasure from the food [88].

Pleasure from food, however, is different from fullness/satiety, as individuals with AN report higher fullness ratings compared to controls (even after a return to normal weight), a finding which may reflect a cognitive distortion or lack of interoceptive awareness [89, 90]. It is also noteworthy that these effects may be specific to food, as some studies have reported that AN individuals rate non-food, but positive stimuli comparable to controls [87].

Neurobiological studies also support APA and CPA deficits to food in individuals with AN. Several studies have reported that while anticipating and responding to food, AN individuals and individuals who have recovered from AN exhibit hypoactivation in neural structures involved in affective processing (e.g., amygdala, anterior insula) [91–93]. Interestingly, studies have also found that even after a meal, individuals with AN, exhibited hypoactivation in some of these structures, suggesting CPA deficits [92, 94].

1.3.4.2 Anhedonia in the Context of Binge Eating

The primary symptom of BN and BED is regular binge episodes (a time period during which an individual eats more than others would consider appropriate in a given amount of time [13]). On the surface, a binge may be thought of as a focal

source of pleasure during which individuals experience CPA [95]. However, a meta-analysis of ecological momentary assessment studies found that positive affect significantly decreases (not increases) after a binge. Of course, this does not rule out the possibility that heightened positive affect occurs *during* a binge episode [96]. Indeed, a significant number of eating disordered individuals report "euphoria" during binges, although the presence of this type of CPA is higher in those with BED than in BN [97].

Binge-eaters have also exhibited abnormal neural responses during food anticipation and intake, suggesting deficits in APA and CPA circuits [98, 99]. Interestingly, one recent study suggests that the neural response during anticipation and intake of pleasurable food may be moderated by the individual's negative mood state [100].

1.3.4.3 Physical Anhedonia and Eating Disorders

It should be noted that the anhedonia in the context of eating disorders is predominantly related to one specific stimulus: food. Although individuals with eating disorders may experience anhedonia in relation to other stimuli, food is the dominant stimulus, which may be due to the fact that food intake is the primary factor in maintaining a desired weight or shape. In contrast to food, Davis and Woodside [101] note that anorexic individuals may derive *more pleasure* from exercise because it helps them burn calories and maintain a low weight. Thus, people suffering from anorexia experience anhedonia in relation to one stimulus (food) but a more pronounced hedonic response to another (exercise).

Our understanding of eating disorders is relatively limited, especially compared with other disorders [102]. Consequently, research examining the role of anhedonia in eating disorders is still in its early phases. From the current evidence, it is clear the relationship between anhedonia and eating disorders is complex and differs across the various diagnoses. More research is necessary to further understand how the hedonic response contributes to the onset, maintenance and remission of eating disorders.

1.3.5 Anhedonia and Other Disorders

Two other disorders are worth mentioning in this chapter – sexual dysfunction and schizophrenia.

1.3.5.1 Sexual Dysfunction

Sexual anhedonia is one form of physical anhedonia that is receiving increased attention in the literature, particularly in its role in sexual dysfunction. Relevant to the present review, the functions of anticipatory and consummatory positive affect

can be illuminating for disorders such as hypoactive sexual desire disorder (HSDD). In Acquired HSDD (as opposed to Lifelong HSDD), individuals report a loss of sexual desire, even though they have previously experienced it. In other words, it is possible that individuals with acquired HSDD no longer experience pleasure during sex (i.e., reduced consummatory positive affect), and therefore lose their desire for sexual interaction (i.e., reduced anticipatory positive affect) [103]. Here, a distinction could also be made between loss of interest and loss of pleasure. Individuals suffering from Acquired HSDD may not lose interest in sexual actions until they experienced a loss of pleasure during sex.

1.3.5.2 Schizophrenia

The presence of anhedonia in schizophrenia is well documented and is one of the most widely studied negative symptoms of schizophrenia and relative to many other symptoms of the disorder, is fairly resistant to treatment [104]. We mention it here briefly, with the caveat that other chapters in this volume are devoted to a more in-depth analysis of the research in this area.

The scope of the anhedonia in schizophrenia literature is so vast, that anhedonia has been conceptualized in nearly all of the aspects presented earlier in this chapter. For example, regarding time course, several studies have reported that individuals with schizophrenia exhibited deficits in anticipatory positive affect but not consummatory positive affect [105, 106]. With regard to the role of stimuli, studies have shown that anhedonia towards social stimuli/situations have different correlates than anhedonia towards physical stimuli [107, 108]. Lastly, studies of anhedonia in schizophrenia have examined whether the disorder is associated with flat or restricted range of affect or specific to low positive emotions. Specifically, while Kraeplin's classic conceptualization of schizophrenia emphasized flat affect (i.e., reduced responding to both positive and negative stimuli), modern conceptualizations generally argue that the deficit in most schizophrenic individuals is specific to positive stimuli (and perhaps even heightened for negative stimuli; [109]). Taken together, these studies suggest that the different models of how anhedonia can be parsed espoused in this chapter are particularly critical for our standing of the neurobiology of schizophrenia.

1.4 Conclusions and Future Directions

Anhedonia, or the diminished capacity to experience pleasure/reward, is an important construct in various psychopathologies. Based on the present review, the role of anhedonia in psychopathology varies across disorders and, most importantly, depends upon the conceptualization or facet of anhedonia being examined. For example, Major Depressive Disorder and Schizophrenia appear to be characterized by deficits in anticipatory positive affect more than deficits in

consummatory positive affect [37, 106]. However, some depressed individuals, such as those with melancholic depression, also experience deficits in consummatory positive affect [41]. As a second example, response to distal vs. proximal rewards is a mechanism that plays a different role in depression vs. substance use disorders [42, 81].

The important lesson to be taken from this review is that anhedonia is a nuanced construct and its different components or facets are likely to have different correlates and underlying neurobiology. Moreover, as anhedonia is one of the hardest features to treat in various psychopathologies [55, 104], a more fine-grained conceptualization of anhedonia would likely identify different targets of treatment. This line of research would, hopefully, lead to improved efficacy rates across psychopathologies.

References

1. Klein DF. Depression and anhedonia. In: Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1987. p. 1–14.
2. Berridge KC, Robinson TE. Parsing reward. TINS. 2003;26:507–13.
3. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning or incentive salience? Brain Res Rev. 1998;28:306–69.
4. Smith KS, Berridge KC, Aldridge JW. Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. Proc Natl Acad Sci. 2011;108:E255–64.
5. Waelti P, Dickinson A, Schultz W. Dopamine responses comply with basic assumptions of formal learning theory. Nature. 2001;412:43–8.
6. Smith CA, Ellsworth PC. Patterns of cognitive appraisal in emotion. J Pers Soc Psychol. 1985;48:813–38.
7. Roseman I, Evdokas A. Appraisals cause experienced emotions: experimental evidence. Cogn Emot. 2004;18:1–28.
8. Tye KM, Janak PH. Amygdala neurons differentially encode motivation and reinforcement. J Neurosci. 2007;27:3937–45.
9. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci. 2001;21:RC159.
10. Burgdorf J, Panksepp J. The neurobiology of positive emotions. Neurosci Biobehav Rev. 2006;30:173–87.
11. Tanaka SC, Doya K, Okada G, Ueda K, Okamoto Y, Yamawaki S. Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. Nat Neurosci. 2004;7:887–93.
12. Davidson RJ. Anterior electrophysiological asymmetries, emotion, and depression: conceptual and methodological conundrums. Psychophysiology. 1998;35:607–14.
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). Arlington, VA: American Psychiatric Association; 2013.
14. Katz RJ, Roth K. Open field behavior after chronic self-stimulation. Int J Neurosci. 1979;9:17–9.
15. Katz RJ, Roth KA, Carroll BJ. Acute and chronic stress effects on open field activity in the rat: implications for a model of depression. Neurosci Biobehav Rev. 1981;5:247–51.
16. Rygula R, Abumaria N, Flügge G, et al. Anhedonia and motivational deficits in rats: impact of chronic social stress. Behav Brain Res. 2005;162:127–34.
17. Moreau JL. Validation of an animal model of anhedonia, a major symptom of depression. Encéphale. 1997;23:280.

18. Papp M, Willner P, Muscat R. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. Psychopharmacology (Berl). 1991;104:255–9.
19. Gambarana C, Scheggi S, Tagliamonte A, et al. Animal models for the study of antidepressant activity. Brain Res Protoc. 2001;7:11–20.
20. Brenes Sáenz JC, Villagra OR, Fornaguera Trías J. Factor analysis of forced swimming test, sucrose preference test and open field test on enriched, social and isolated reared rats. Behav Brain Res. 2006;169:57–65.
21. Storch EA, Roberti JW, Roth DA. Factor structure, concurrent validity, and internal consistency of the Beck Depression Inventory—Second Edition in a sample of college students. Depress Anxiety. 2004;19:187–9.
22. Steer RA. Self-reported inability to cry as a symptom of anhedonic depression in outpatients with a major depressive disorder. Psychol Rep. 2011;108:874–82.
23. Chau DT, Roth RM, Green AI. The neural circuitry of reward and its relevance to psychiatric disorders. Curr Psychiatry Rep. 2004;6:391–9.
24. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol. 2001;11:240–9.
25. Nutt D, Demyttenaere K, Janka Z, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. J Psychopharmacol. 2007;21:461–71.
26. Simms LJ, Watson D, Doebbelling BN. Confirmatory factor analyses of posttraumatic stress symptoms in deployed and nondeployed veterans of the Gulf War. J Abnorm Psychol. 2002;111:637.
27. Kashdan TB, Elhai JD, Frueh BC. Anhedonia and emotional numbing in combat veterans with PTSD. Behav Res Ther. 2006;44:457–67.
28. Gros DF, Simms LJ, Acierno R. Specificity of posttraumatic stress disorder symptoms: an investigation of comorbidity between posttraumatic stress disorder symptoms and depression in treatment-seeking veterans. J Nerv Ment Dis. 2010;198:885–90.
29. Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the national comorbidity survey. Arch Gen Psychiatry. 1995;52:1048–60.
30. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374.
31. Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Pappas N. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D-2 receptor levels. Am J Psychiatry. 1999;156:1440–3.
32. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 2001;24:97–129.
33. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci. 2002;22:3306–11.
34. Buckner JD, Joiner Jr TE, Pettit JW, Lewinsohn PM, Schmidt NB. Implications of the DSM's emphasis on sadness and anhedonia in major depressive disorder. Psychiatry Res. 2008;159:25–30. doi:10.1016/j.psychres.2007.05.010.
35. Eshel N, Roiser JP. Reward and punishment processing in depression. Biol Psychiatry. 2010;68:118–24. doi:10.1016/j.biopsych.2010.01.027.
36. Klein DF. Endogenomorphic depression. A conceptual and terminological revision. Arch Gen Psychiatry. 1974;31:447–54.
37. Sherdell L, Waugh CE, Gotlib IH. Anticipatory pleasure predicts motivation for reward in major depression. J Abnorm Psychol. 2012;121:51–60. doi:10.1037/a0024945.
38. Nestler EJ, Carlezon Jr WA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006;59:1151–9.
39. Shankman SA, Klein DN, Tenke CE, Bruder GE. Reward sensitivity in depression: a biobehavioral study. J Abnorm Psychol. 2007;116:95–104.
40. Shankman SA, Nelson BD, Sarapas C, et al. A psychophysiological investigation of threat and reward sensitivity in individuals with panic disorder and/or major depressive disorder. J Abnorm Psychol. 2013;122:322–38. doi:10.1037/a0030747.

41. Shankman SA, Sarapas C, Klein DN. The effect of pre- vs. post-reward attainment on EEG asymmetry in melancholic depression. Int J Psychophysiol. 2011;79:287–95. doi:10.1016/j.ijpsycho.2010.11.004.
42. Lempert KM, Pizzagalli DA. Delay discounting and future-directed thinking in anhedonic individuals. J Behav Ther Exp Psychiatry. 2010;41:258–64. doi:10.1016/j.jbtep.2010.02.003.
43. Dombrovski AY, Szanto K, Siegle GJ, et al. Lethal forethought: delayed reward discounting differentiates high- and low-lethality suicide attempts in old age. Biol Psychiatry. 2011;70:138–44. doi:10.1016/j.biopsych.2010.12.025.
44. Rottenberg J. Mood and emotion in major depression. Curr Dir Psychol Sci. 2005;14:167–70.
45. Bylsma LM, Morris BH, Rottenberg J. A meta-analysis of emotional reactivity in major depressive disorder. Clin Psychol Rev. 2008;28:676–91.
46. Dunn BD, Dalgleish T, Lawrence AD, Cusack R, Ogilvie AD. Categorical and dimensional reports of experienced affect to emotion-inducing pictures in depression. J Abnorm Psychol. 2004;113:654–60.
47. Loas G, Salinas E, Pierson A, Guelfi JD, Samuel-Lajeunesse B. Anhedonia and blunted affect in major depressive disorder. Compr Psychiatry. 1994;35:366–72.
48. Bylsma LM, Taylor-Clift A, Rottenberg J. Emotional reactivity to daily events in major and minor depression. J Abnorm Psychol. 2011;120:155–67.
49. Fawcett J, Clark DC, Scheftner WA, Hedeker D. Differences between anhedonic and normally hedonic depressive states. Am J Psychiatry. 1983;140:1027–30.
50. Leventhal AM, Rehm LP. The empirical status of melancholia: implications for psychology. Clin Psychol Rev. 2005;25:25–44. doi:10.1016/j.cpr.2004.09.001.
51. Snaith P. Anhedonia: a neglected symptom of psychopathology. Psychol Med. 1993;23:957–66.
52. Shankman SA, Nelson BD, Harrow M, Faull R. Does physical anhedonia play a role in depression? A 20-year longitudinal study. J Affect Disord. 2010;120:170–6. doi:10.1016/j.jad.2009.05.002.
53. Blanchard JL, Horan WP, Brown SA. Diagnostic differences in social anhedonia: a longitudinal study of schizophrenia and major depressive disorder. J Abnorm Psychol. 2001;110:363.
54. Lemke MR, Puhl P, Koethe N, Winkler T. Psychomotor retardation and anhedonia in depression. Acta Psychiatr Scand. 1999;99:252–6.
55. McMakin DL, Olino TM, Porta G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. J Am Acad Child Adolesc Psychiatry. 2012;51:404–11. doi:10.1016/j.jaac.2012.01.011.
56. Spijker J, Bijl RV, de Graaf R, Nolen WA. Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatr Scand. 2001;103:122–30.
57. Schrader GD. Does anhedonia correlate with depression severity in chronic depression? Compr Psychiatry. 1997;38:260–3.
58. Watson D, Gamez W, Simms LJ. Basic dimensions of temperament and their relation to anxiety and depression: a symptom-based perspective. J Res Pers. 2005;39:46–66. doi:10.1016/j.jrp.2004.09.006.
59. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol. 1991;100:316–36.
60. Kendler KS. The diagnostic validity of melancholic major depression in a population-based sample of female twins. Arch Gen Psychiatry. 1997;54:299–304.
61. Rasmussen KG. Attempts to validate melancholic depression: some observations on modern research methodology. Bull Menninger Clin. 2007;71:150–63. doi:10.1521/bumc.2007.71.2.150.
62. Watson D, Weber K, Assenheimer JS, et al. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol. 1995;104:3.
63. Kashdan TB. Social anxiety spectrum and reduced positive experiences: theoretical synthesis and meta-analysis. Clin Psychol Rev. 2007;27:348–65.

64. Brown TA, Chorpita BF, Barlow DH. Structured relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. J Abnorm Psychol. 1998;107:179–92.
65. Watson D, Naragon-Gainey K. On the specificity of positive emotional dysfunction in psychopathology: evidence from the mood and anxiety disorders and schizophrenia/schizotypy. Clin Psychol Rev. 2010;30:839–48.
66. Kashdan TB. The neglected relationship between social interaction anxiety and hedonic deficits: differentiation from depressive symptoms. J Anxiety Disord. 2002;18:719–30.
67. Litz BT. Emotional numbing in combat-related posttraumatic-stress-disorder – a critical-review and reformulation. Clin Psychol Rev. 1992;12:417–32. doi:10.1016/0272-7358(92)90125-R.
68. Segerstrom SC, Tsao JC, Alden LE, Craske MG. Worry and rumination: repetitive thought as a concomitant and predictor of negative mood. Cogn Ther Res. 2000;24:671–88.
69. McLaughlin KA, Borkovec TD, Sibrava NJ. The effects of worry and rumination on affect states and cognitive activity. Behav Ther. 2007;38:23–38.
70. Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. Am J Psychiatry. 2001;158:2033–7.
71. Martinotti G, DiNicola M, Reina D, et al. Alcohol protracted withdrawal syndrome: the role of anhedonia. Subst Use Misuse. 2008;43:271–84.
72. Gawin FH, Kleber HD. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers: clinical observations. Arch Gen Psychiatry. 1986;43:107–13.
73. Kalechstein AD, Newton TF, Leavengood AH. Apathy syndrome in cocaine dependence. Psychiatry Res. 2002;109:97–100.
74. Tremblay LK, Naranjo CA, Cardenas L, Herrmann N, Busto UE. Probing brain reward system function in major depressive disorder: altered response to dextroamphetamine. Arch Gen Psychiatry. 2002;59:409–16.
75. Tremblay LK, Naranjo CA, Graham SJ, et al. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. Arch Gen Psychiatry. 2005;62:1228–36.
76. Grüsser SM, Mörsen CP, Wölfling K, Flor H. The relationship of stress, coping, effect expectancies and craving. Eur Addict Res. 2007;13:31–8.
77. Koob GF. Alcoholism: allostasis and beyond. Alcohol Clin Exp Res. 2003;27:232–43.
78. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997;278:52–8.
79. Koob GF, Le Moal ML. Drug addiction and allostasis. New York: Cambridge University Press; 2004.
80. Bickel WK, Marsch LA. Toward a behavioral economic understanding of drug dependence: delay discounting processes. Addiction. 2001;96:73–86.
81. Reynolds B. A review of delay-discounting research with humans: relations to drug use and gambling. Behav Pharmacol. 2006;17:651–67.
82. Martin-Soelch C, Leenders KL, Chevalley AF, et al. Reward mechanisms in the brain and their role in dependence: evidence from neurophysiological and neuroimaging studies. Brain Res Rev. 2001;36:139–49.
83. Volkow ND, Fowler JS, Wang GJ, Goldstein RZ. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiol Learn Mem. 2002;78:610–24.
84. Fairburn C, Harrison P. Eating disorders. Lancet. 2003;361:407–16.
85. Berridge K. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol Behav. 2009;95:537–50.
86. Schreder T, Albrecht J, Kleemann AM, et al. Olfactory performance of patients with anorexia nervosa and healthy subjects in hunger and satiety. Rhinology. 2008;46:175–83.
87. Jiang T, Soussignan R, Rigaud D, Schaal B. Pleasure for visual and olfactory stimuli evoking energy-dense foods is decreased in anorexia nervosa. Psychiatry Res. 2010;180:42–7.
88. Keating C, Tilbrook AJ, Rossell SL, Enticott PG, Fitzgerald PB. Reward processing in anorexia nervosa. Neuropsychologia. 2012;50:567–75.

89. Halmi KA, Sunday SR. Temporal patterns of hunger and fullness ratings and related cognitions in anorexia and bulimia. Appetite. 1991;16:219–37.
90. Robinson PH. Perceptivity and paraceptivity during measurement of gastric emptying in anorexia and bulimia nervosa. Br J Psychiatry. 1989;154:400–5.
91. Keating C. Theoretical perspective on anorexia nervosa: the conflict of reward. Neurosci Biobehav Rev. 2010;34:73–9.
92. Holsen LM, Lawson EA, Blum J, et al. Food motivation circuitry hypoactivation related to hedonic and nonhedonic aspects of hunger and satiety in women with active anorexia nervosa and weight-restored women with anorexia nervosa. J Psychiatry Neurosci. 2012;37:322–32.
93. Wagner A, Aizenstein H, Venkatraman VK, et al. Altered reward processing in women recovered from anorexia nervosa. Am J Psychiatry. 2007;164:1842–9.
94. Santel S, Baving L, Krauel K, Münte TF, Rotte M. Hunger and satiety in anorexia nervosa: FMRI during cognitive processing of food pictures. Brain Res. 2006;1114:138–48.
95. Cassin SE, von Ranson K. Is binge eating experienced as a behavioral addiction? Appetite. 2007;49:687–90.
96. Haedt-Matt AA, Keel PK. Revisiting the affect regulation model of binge eating: a meta-analysis of studies using ecological momentary assessment. Psychol Bull. 2011;137:660–81.
97. Kjelsås E, Børsting I, Gudde CB. Antecedents and consequences of binge eating episodes in women with an eating disorder. Eat Weight Disord. 2004;9:7–15.
98. Bohon C, Stice E. Reward abnormalities among women with full and subthreshold bulimia nervosa. A functional magnetic resonance imaging study. Int J Eat Disord. 2011;44:585–95.
99. Frank GK, Wagner A, Achenbach S, et al. Altered brain activity in women recovered from bulimic-type eating disorders after a glucose challenge: a pilot study. Int J Eat Disord. 2006;39:76–9.
100. Bohon C, Stice E. Negative affect and neural response to palatable food intake in bulimia nervosa. Appetite. 2012;58:964–70.
101. Davis C, Woodside B. Sensitivity to the rewarding effects of food and exercise in the eating disorders. Compr Psychiatry. 2002;43:189–94.
102. Polivy J, Herman P. Causes of eating disorders. Annu Rev Psychol. 2002;53:187–213.
103. Brauer M, van Leeuwen M, Janssen E, Newhouse SK, Heiman JR, Laan E. Attentional and affective processing of sexual stimuli in women with hypoactive sexual desire disorder. Arch Sex Behav. 2012;41:891–905.
104. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32:259–73.
105. Chan RCK, Wang Y, Huang J, et al. Anticipatory and consummatory components of the experience of pleasure in schizophrenia: cross-cultural validation and extension. Psychiatry Res. 2010;175:181–3.
106. Gard DE, Kring AM, Gard MG, et al. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:253–60.
107. Blanchard JJ, Bellac AS, Mueser KT. Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. J Abnorm Psychol. 1994;103:719–28.
108. Burbridge JA, Barch DM. Anhedonia and the experience of emotion in individuals with schizophrenia. J Abnorm Psychol. 2007;116:30–42.
109. Suslow T, Roestela C, Ohrmanna P, Arot V. The experience of basic emotions in schizophrenia with and without affective negative symptoms. Compr Psychiatry. 2003;44:303–10.

Chapter 2
Understanding Anhedonia: The Role of Perceived Control

Rebecca K. MacAulay, Jessica E. McGovern, and Alex S. Cohen

Abstract Perceived control appears to play an important role in the manifestation of anhedonic symptoms, as it is integrally related to underlying neurobiological reward systems and motivated behaviors. Perceived control refers to the conscious process by which an event is determined to be manageable, or more simply put, it can be thought of as the extent to which an individual/organism believes that he/she has the resources and capability to manage an event. Consequentially, perceived control has a rich history in the depression literature (e.g., learned helplessness) and appears to be an important determinant in the manifestation of anhedonia. However, to this date, the link between perceived control and anhedonia remains unclear. In order to further elucidate this relationship, this chapter provides a model that seeks to explain perceived control's role in determining our psychological and behavioral responses to stress. To do so, we will discuss shared neurobiological mechanisms (i.e., the mesocorticolimbic system) in relation to how they pertains to perceived control and approach-avoidance motivation. Additionally, clinical implications will be discussed through the framework of perceived control's impact on specific coping strategies.

Keywords Perceived control • Emotion regulation • Positive affect • Negative affect • Mesocorticolimbic system • Individual differences • Anhedonia

Abbreviations

fMRI	Functional magnetic resonance imaging
HPA axis	Hypothalamic-pituitary-adrenal axis

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NAc	Nucleus accumbens
PFC	Prefrontal cortex
RN	Raphe nuclei

2.1 Introduction

Anhedonia can be defined as a profound diminished interest and/or loss of pleasure in activities, and while it is most notably found within depression and schizophrenia, it manifests in several other neuropsychiatric disorders. Perceived control appears to play an important role in the manifestation of anhedonic symptoms, as it is integrally related to underlying neurobiological systems that are involved in approach-avoidance motivation. Specifically, low perceived control appears to decrease approach-oriented behaviors and to increase behavioral avoidance. *Perceived control* refers to the conscious process by which an event is determined to be manageable, or more simply put, it can be thought of as the extent to which an individual/organism believes that they have the resources and capability to manage an event. From a neurological perspective, basic research suggests that motivated behaviors are significantly influenced by the controllability of the event through fluctuations of dopamine levels within the mesocorticolimbic system. These biological mechanisms are also associated with affective traits, in which positive affect is believed to facilitate approach behaviors while negative affect appears to promote behavioral avoidance, possibly through modulating levels of dopamine within the mesolimbic systems [1]. In order to elucidate the relationship between perceived control and anhedonia, this chapter provides a model that seeks to explain perceived control's role in determining our psychological and behavioral responses to stress. To do so, we first provide a brief history of perceived control, followed by a discussion of approach-avoidance motivation. Next, the mesocorticolimbic system functions are discussed in detail in order to provide a framework for our model. These findings are then integrated to highlight how individual differences in affective traits and approach-avoidance motivation impact perceptions of controllability. Subsequently, the relationship between mesocorticolimbic functioning and perceived control in relation to specific behavioral correlates that are endemic of anhedonia are discussed. To conclude, clinical implications are discussed through the framework of perceived control's influence on the use of specific coping strategies and approach-avoidance motivation.

This chapter has taken an interdisciplinary approach to examining the relationship between perceived control and anhedonia. In doing so, a broad amount of terminology for similar yet distinct phenomena was found across the different branches of psychology. Additionally, it is important to forewarn that some of the theory constructs discussed in this chapter, particularly in regards to emotional processing and motivational systems, overlap with one another and are not without controversy. Given these factors, for the sake of simplicity and coherency, we have attempted to organize these potentially confusing concepts into an integrated coherent model.

2.2 Perceived Control

Perceived control has a rich history in the depression literature, and as we will later discuss appears to play an important role in the manifestation of anhedonia. There is an overwhelming amount of interdisciplinary evidence that suggests that the extent to which an organism believes that their behavior is able to exert control over a stressor, has profound effects on their neuropsychological and physiological responses to stress. Early research, using animal paradigms, found that the process of learning (i.e., *expectancy*) that outcomes were uncontrollable via repeated exposure to non-contingent aversive stressors resulted in motivational (e.g., failure to escape), cognitive (e.g., failure to learn new contingency relationship), and emotional (e.g., aberrant physiological arousal) performance deficits (for reviews, see [2, 3]). This lead to the *learned helplessness hypothesis*, which posits that when organisms learn and come to expect that their behavior is independent of the stressor outcome (i.e., future expectancy of response-reinforcement independence), it produces aberrant motivational, cognitive, and emotional reactions [for review of the infrahuman literature, see 2]. While some initial support was found for the learned helplessness model in humans [4, 5], the original model could not account for *facilitation effects* (i.e., performance improvements that occurred following exposure to the uncontrollable condition) or individual differences in perceptions of controllability [6]. Thus, since that time the construct has evolved to acknowledge that the learned helplessness outcome is interdependent with global perception of events and individuals' causal attributions of lack of control (e.g., if participants believe that they have failed due to their general incompetence as opposed to non-personal aspects of the task itself will influence whether the behavioral correlates of learned helplessness occur) (for reviews, see [6, 7]).

Several factors appear to moderate whether an individual experiences "learned helplessness" in response to an uncontrollable stressor. Similar to animal models, in humans, the duration of the exposure (acute vs. chronic) and expectancies of personal control (i.e., organisms' expectations regarding their capability of controlling outcomes generally or in a particular instance) moderate the relationship between learned helplessness and controllability. Furthermore, the salience of the threat to self, meaning of the event, and attributions of causality moderate reactions to uncontrollable stressors [6, 7]. Within most, if not all, learned helplessness models, a necessary factor appears to be whether the non-contingency relationship of uncontrollability is learned. However, as we will discuss, recent developments in neuroscience have begun to challenge the notion that learning the non-contingency relationship is the basis of learned helplessness [8].

2.3 Motivation and Goal-Directed Behaviors

Motivation to perform goal-directed behaviors is integral to hedonic experience in that reduced motivation can manifest as reduced effort to obtain the goals one used to enjoy (i.e., no longer "wanting" to do a pleasurable activity). According to

Maslow, "man is a perpetually wanting animal" [9]. Maslow's theory of motivation stressed the importance of recognizing that "wanting" is influenced by prior situations and "prepotent needs" [9]. These prepotent needs or "goals" that predominate our motivational drives are pursued hierarchically. Basic needs (e.g., gratification of bodily needs) are the system's foundation. The next level entails the goal of safety from physical or psychological threat (which also entails cognitive components such as familiarity and manageability). Above this level, are goals that we can define as psychological needs or desires (e.g., love, affection, and acceptance), which is followed by the goal of self-esteem (e.g., self-confidence and the belief in one's capabilities). The pinnacle of the system's hierarchy is self-actualization (e.g., self-fulfillment, creative expression, and the fulfillment of one's potential and use of ones capacities). A critical component to this theory is that an individual's current level of need impacts his/her motivational goals. In this regard, individual differences that influence levels of need would be expected to substantially influence motivational goals. Using this model, we will later describe how individual differences in affective traits and approach-avoidance motivation can influence an individual's motivational goals (via level of need) through impacting perceptions of controllability.

Central to motivational theories of goal-directed behaviors are the concepts of approach and avoidance. Earlier "approach-withdrawal" motivation theories, operationally defined motivation by observable behaviors of an organism moving either towards (approach) or away from (withdrawal) a stimulus; however, such theories had important limitations and were unable to adequately address the complexity of human motivation systems [10]. Important to the understanding of human motivation is the concept of affective valence. *Affective valence* refers to the notion that stimuli have attractive (positive valence) and repellant (negative valence) properties that are connected with behavioral action tendencies to either approach or avoid the stimuli [10]. Other theories have built on this concept of affective valence to suggest that positively or negatively valenced stimuli may gain motivational properties (i.e., incentive motivation) through three processes that will be a focus of this chapter: (1) "liking" a stimulus triggers the positive affective state of pleasure or aversion to a stimulus triggers a negative affective state (e.g., fear or disgust), (2) associative learning processes connect the stimulus to its motivational properties, and (3) guided by associative learning processes, attributions regarding a stimulus' motivational value (its saliency and valence) are encoded through engagement of dopamine systems (i.e., "wanting") [11]. Central to this chapter is the knowledge that in the absence of this third process – the stimulus' motivational value attributions – associative learning processes and activation of hedonic systems do not appear to have the capacity to alone motivate goal-directed behavior in response to stimuli; rather, they only appear to be able to activate affective states [11]. In this regard, positive and negative affective stimuli are salient forces that attract or repulse individuals due to their positive or negative reinforcing properties, and through the three-step process described above are able to gain *affective value* that serves to motivate approach and/or avoidant behaviors.

Elliot posited that in approach motivation, behavior is guided by perceptions that a positive/desirable event may occur, whereas in avoidance motivation, behavior is guided by perceptions that a negative/undesirable event may occur [12]. Consistent with this view, there are several theories that, while not synonymous with each other, share the assumption that (1) the motivated behaviors of approach and avoidance are a function of valence, and which further specify that (2) there are specific underlying biological mechanisms that are the basis of approach and avoidant motivational processes [13–17]. Here, the distinction between *drive* as compared to approach-avoidance motivation theories is important to make: the original drive theories suggested that behaviors are largely driven by negative reinforcement in order for the organism to return to homeostasis (e.g., the action of obtaining food removes the negative emotional state of hunger) [18]. In contrast, approach-avoidance theories suggest that behavioral motivation is an adaptive process that, through affective value, is able to guide and shape future behaviors through positive reinforcement. For example, the experience of having a pleasant meal at a restaurant provides motivation to make plans to return to that restaurant for another meal. In this definition of motivation, the experience of enjoying the meal ("liking" it) has gained affective value, which will serve to motivate future behaviors (I "want" it again). It is important to note that these theories are not mutually exclusive in that basic needs or drives such as hunger can influence affective value (e.g., whether or not an individual is satiated will also impact the affective value of a meal).

The ability to take goal-directed action requires not only a coordinated motor response but also requires the ability to perceive the outcome of the event. Basic research has well established that the ability to perform complex goal-directed actions frequently involves associative learning processes [19, 20]. Two important ways by which associations are learned are the principles of contiguity and contingency. *Contiguity* refers to learning that events co-occur with each other and is determined by the temporal space between events (i.e., events that frequently occur in close proximity of one another will become associated with one another). *Contingency* refers to learning that an event occurs only if a specific condition(s) is met (e.g., a reward that only occurs if a tone is presented). According to Elsner and Hommel [21], it is through these associative learning processes that goal-directed behaviors become automatically primed by perceptions of previous event outcomes. Take for example, a student's study behaviors (i.e., the action) in relationship to whether they receive "good" or "bad" grades (i.e., the affective stimulus which is related to perceived outcomes). If the student consistently receives good grades on tests after the process of studying, and receives bad grades on tests when they do not the study, both the contiguity and contingency association between the process of studying and type of grade will be made (i.e., the type of grade received on a test depends on the study behavior). Furthermore, we can expect that the student will make distinct attributions about the outcome (success or failure) of receiving a good as compared to a bad grade on the test ("e.g., I succeeded because I studied"). In this example, studying behavior has acquired an affective value due to attributions made about the outcome; in turn, perceptions of this outcome will significantly influence subsequent events in that actions are controlled by the anticipation of their effects (i.e., "There will be a positive

outcome if I study"). Conversely, we can imagine if a student exerts effort towards a test ("studied hard") and still fails the test, then the relationship between action (studying behavior) and outcome will not be learned (i.e., approach-oriented behaviors are not related to a positive outcome). In this case, over time we would expect that perceptions of failure despite exerted effort would decrease approach motivation towards studying behaviors through priming memories of failure.

Altogether, motivated behaviors appear to be substantially shaped by an organism's knowledge about their environment and the likelihood of the possible effects of performing that action in a given situation. This acquired knowledge guides future behaviors in efforts to achieve future goals through allowing an individual to select a suitable/appropriate behavior-action repertoire that will serve to meet the desired goal (e.g., obtaining a reward or avoiding an aversive experience). Of additional importance, and in accord with Maslow's hierarchy, a stimulus' affective value is not static, and appears to fluctuate with an organism's needs. Thus, factors that have the capacity to influence perceptions of a stimulus' affective value would be able to impact motivational goals and the development of approach-avoidance behavioral repertoires.

This chapter acknowledges that there are differences in the various theories used to describe the distinction between approach and avoidant behaviors [10]. However, given the broad amount of terminology utilized in the field of motivation, for the sake of simplicity and coherency we will follow Elliot and Covington's [10] lead in using the label "approach–avoidance motivation" to describe the distinction between approach and avoidant behaviors within this chapter. Additionally, while there are also subtle differences behind the labels that are used to describe a stimulus' ability to motivate approach and avoidant behaviors (e.g., motivational value, incentive value, and affective value), in an effort to reduce the amount of terminology, we will heretofore refer to this stimulus property as *affective value*.

Given the importance of approach-avoidance motivation to adaptive human behavior, the following sections will highlight the role of the mesocorticolimbic dopaminergic system in connecting hedonic experience to the stimulus' affective value, and discuss the interdependency of reward processing functions and how fluctuations in dopamine release within this system influence approach-avoidance motivation. To do so, we will build on animal models that illustrate how individual differences in dopamine functioning may impact perceptions of stressor controllability and influence approach-avoidance motivation.

2.4 Approach-Avoidance Motivation and the Mesocorticolimbic Dopamine Pathway

Dopamine within the mesocorticolimbic system plays a large role in motivated behaviors and learning reinforcing properties (e.g., encoding the affective value); specifically, a role of the mesocorticolimbic systems appears to be to connect hedonic experience to the affective value, which serves to produce adaptive

behaviors (goal-directed actions) [22, 23]. The mesocorticolimbic dopamine pathway is often discussed in terms of two separate pathways, the mesolimbic and mesocortical pathways, which have feedback connections to each other. While both pathways originate in the ventral tegmental area (VTA) of the midbrain, the mesolimbic pathway dopaminergic neurons project to the limbic system (amygdala, nucleus accumbens [NAc], and hippocampus) while the mesocortical pathway dopaminergic neurons project to the prefrontal cortex (PFC) [24, 25]. Dopamine within the mesocorticolimbic pathway serves a number of functions. To begin, dopamine systems appear necessary for "wanting" the stimulus, which entails ascribing the affective value to the stimulus [for review, see 11]. A general modulatory role for phasic (i.e., bursts of neuronal activity) dopamine release in updating reward predictions in response to changing contingencies (i.e., the difference between expected and actual reward) has been found in both humans and animals [26]. Moreover, it is generally accepted that phasic dopamine release supports associative learning and is responsible for encoding reward value (i.e., affective value of the stimulus) [11]. For example, phasic dopamine is released in situations in which an unexpected or underestimated reward is received (for review, see [27]). Conversely, when an expected reward's value is overestimated or not received, there is a significant decrease in dopamine firing. Dopamine functioning within the NAc also appears to be necessary in order to sustain effort to obtain rewards. For instance, administration of dopamine antagonists in the NAc of rats decreases responses for large rewards that require higher effort, whereas responding for small rewards that require little effort is increased [22]. VTA dopaminergic neurons that synapse on the NAc (i.e., increasing levels of mesoaccumbens dopamine) appear to substantially influence the efficacy of reward learning during exposure to novel reward experiences [28] and are also involved in responses to stress (for review, see [29]). In humans, it has been shown that as anticipation of reward increases, dopaminergic neurons in the VTA and the NAc become more active to cues of reward (e.g., in response to monetary gain) [30], in which this activity and the subsequent goal-related behaviors may be directly influenced by innervations from the dorsolateral PFC [31]. Finally, as will later expand on, Depue and Collins [16] have provided a convincing argument that variations in mesolimbic dopamine functioning, which presumably involve genetic as well as environmental influences, provide the foundation by which individual differences in approach-avoidance motivation occurs. The following sections will begin to elaborate on the individual differences in mesocorticolimbic dopamine functioning, and how these individual differences in dopamine functioning are related to perceptions of control and approach-avoidance motivation.

2.5 Perceived Control and Approach-Avoidance Motivation

Of great interest is the impact that perceptions of uncontrollable stress have on the mesocorticolimbic dopamine pathway's functions and how this influences motivated behaviors. The motivated behaviors of approach and avoidance both appear to

be significantly influenced by fluctuations of dopamine levels within regions of the mesocoticolimbic dopamine pathway. Basic research suggests that the controllability of an event and the duration of the stressor also largely influence the functioning of dopaminergic neurons within this region. Specifically, it appears that dopamine release to stressors follows an inverted-U pattern that is influenced by both stressor duration and perceptions of controllability. Tonic NAc dopamine levels initially appear to be enhanced in response to acute controllable stress, while tonic NAc dopamine appears to be inhibited with prolonged exposure to uncontrollable stressors [for review, see 29]. These dopamine patterns in turn support behavioral changes, such that increased dopamine tone in the NAc appears to motivate active/approach-oriented coping strategies (e.g., learning necessary behaviors to escape from shock) in response to an acute controllable stressor, while decreased dopamine tone appears to support behavioral withdrawal from chronic uncontrollable stressors [29].

Importantly, evidence suggests that the ventromedial PFC is the mechanism that regulates responses to uncontrollable stressors. A series of studies by Christianson and colleagues [8] indicates that the ventromedial PFC may be the underlying mechanism that mediates the relationship between stressor controllability and subsequent anhedonic-like behaviors; more specifically, the ventromedial PFC appears to play an inhibitory role in stress response systems when behavioral control is present. These studies demonstrated that pharmacological inactivation (via the $GABA_A$ agonist muscimol) of the ventromedial PFC appears to prevent the protective effects of the presence of control (i.e., the ability to escape to from shock) and leads to less social exploration. In light of this and other evidence [32, 33], Christianson et al. suggested that the learned helplessness outcome may not be dependent on the individual learning the non-contingency relationship of uncontrollability; rather, it appears to be a function of ventromedial PFC emotion-regulatory processes (i.e., the presence of control activates the ventromedial PFC, which results in the attenuation of stress response systems). The next section will continue to discuss the implication of these findings in the context of how emotion-regulation processes appears to be responsible for underlying individual differences in perceptions of control.

2.6 Mesocorticolimbic Involvement in Emotion Regulation Processes

Importantly, emotions appear to influence appraisals that are made about stressful events. To build on this idea, we will first need to discuss how emotions are processed. According to LeDoux's model of emotional processing [19], emotions are thought to serve the important function of coordinating the mind and body. From a neurological perspective, the amygdala is critical in processing emotional information and is believed to play an important role in controlling behavioral, autonomic, and endocrine responses [20]. LeDoux proposed that emotional stimuli have a "low road" and a "high road" to the amygdala [19]. The low road of emotional processing

refers to the direct pathway from the thalamus to the amygdala. The thalmo-amygdala pathway detects danger and allows for immediate activation of arousal systems that motivate behaviors; however, the information that is sent is only a crude representation of the stimulus. The high road of emotional processing is not as direct; however, it benefits from cortical processing and is able to differentiate between stimuli. The high road of emotional processing involves emotional stimuli entering the thalamus via sensory pathways, the thalamus then projects this information to the cortex, and the cortex subsequently sends this information to the amygdala for further processing. Importantly, the cortico-amygdala pathway is bidirectional in that the amygdala provides the cortex with internal feedback about the stimulus via chemical signals, and the cortico-amygdala pathway can override the projections from the thalmo-amygala pathway. The benefit of having separate appraisal systems is that an emotional appraisal system allows for faster responding in the face of threat, while cognitive appraisal systems allow for more flexible responses that may be more adaptive to the situation [for review, see 20].

The animal literature has provided ample evidence that certain behavioral responses do not require learned cognitive responses and appear to be species engrained (e.g., species-specific defense reactions) [34]. These automatic behaviors are guided by emotions. For instance, negative emotions such as fear appear to reduce an organism's behavioral repertoire [19]. Specifically, the experience of fear creates a highly inflexible state that promotes avoidant behaviors such as freezing or fleeing in response to threats through activating stress response systems (e.g., the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system) as well as systems that promote behavioral disengagement (i.e, the periaqueductal gray) [19]. In the short term, these emotional reactions help provide the individual with the physiological resources necessary to cope with stress. However, there is a wide body of research that suggests that chronic activation of stress response systems can potentially impede an individual's ability to adapt to their environment through altering their physiological responses to stress via continued activation of stress response systems [35–37]. In this regard, the ability to effectively regulate emotions via cognitive appraisal systems in response to stress is critical to both mental and physical health.

A large body of research suggests that the mesocorticolimbic system plays an important role in emotion regulation. *Emotion regulation* refers to the ability to monitor and control the expression of emotional states via evoked thoughts and behaviors (i.e., cognitive appraisals) [38]. Emotion regulation is a dynamic process that engages several psychobiological processes in order to cope with sources of stress. It appears that both purposively increasing or decreasing negative emotions (i.e., intentional up- and down-regulation of negative emotion) via cognitive appraisals is dependent on regions of the PFC to modulate amygdala activity [39]; in turn, both of these structures directly and indirectly communicate with other stress response systems (e.g., the HPA axis which releases the stress hormone cortisol). Specifically, research indicates that PFC projections to the amygdala exert a top-down, inhibitory influence over negative affective states [39–41]. The top-down regulation of negative affect and the subsequent dampening of HPA axis stress responses via cognitive reappraisals appears to be a function of PFC efferent

projections (presumably via the ventromedial PFC) to the amygdala [41]. Upon receiving signals from the ventromedial PFC, amygdala activity is attenuated and its projections to the hypothalamus are inhibited, thereby reducing/halting further cortisol secretion from the HPA axis. Conversely, when levels of negative affect are intentionally increased through negative cognitive appraisals (e.g., "something terrible is going to happen to me"), there is an increase in amygdala activation [39], which in turn appears to elicit cortisol release, thereby prolonging activation of stress response systems [41].

Individual differences in the ability to down-regulate negative emotions appear to be a function of underlying differences in PFC activation. Functional magnetic resonance imaging (fMRI) studies of emotion regulation in non-clinical populations have found that intentionally increasing negative emotions appears to primarily recruit left PFC systems [39, 40], whereas intentionally decreasing negative emotion bilaterally recruits PFC [39]. Additionally, there appears to be a functional dissociation between limbic and cortex activation in the down-regulation of negative emotions, such that limbic activity (in particular, the NAc and amydala) has an inverse relationship with activation of the prefrontal cortices [40]. Conversely, greater self-reported intensity of negative affect positively associates with increased amygdala activity and decreased activation of the region of the brain responsible for conflict resolution (i.e., the dorsal anterior cingulate) [40]. Of clinical relevance, individual differences in observed fMRI patterns of neural activation in response to regulating negative affect have been found in individuals with a major depressive disorder as compared to a non-clinical control group, such that individuals with depression have been found to demonstrate greater bilateral PFC activation, while non-depressed individuals display left-lateralized PFC activation when down-regulating negative affect [42]. Furthermore, in a task designed to intentionally decrease negative emotions through reappraisal of negative emotional stimuli, non-depressed individuals demonstrated the predicted pattern of greater activation in the left ventrolateral PFC associating with decreased amygdala activity. However, this pattern of attenuated amygdala activity was not observed within depressed individuals; instead, there was positive association between ventromedial PFC and amygdala activity [42]. Further individual differences in hemispheric activation have been found in that increased avoidance motivation (as measured by a self-report, the Behavioral Inhibition System scale [43]) is associated with greater tonic electroencephalography activity in the right posterior dorsolateral PFC [44], and greater relative right to left prefrontal activation is positively associated with avoidance motivation and negative affect [45]. Conversely, greater left PFC activation is linked to increased levels of positive affect and decreased negative affect [46], as well as being associated with greater approach motivation and faster physiological recovery to negative events [15]. Altogether, there appears to be evidence of a biological basis for individual differences in the ability to regulate negative emotions that outwardly manifests in the trait characteristics of negative affect and positive affect. This is particularly important considering that failure to successfully regulate negative emotional responses is associated with increased avoidance motivation and dysregulation within the mesocorticolimbic system. Conversely, effective emotion regulation would be expected to allow the individual to more effectively use emotions to

successfully guide his or her behaviors and thoughts. In conclusion, affective traits appear to be important psychosocial factors that influence both physiological and psychological responses to stress. In this regard, as we will later discuss, differences in affective traits and their underlying proposed mechanisms, play an important role in perceived control.

2.7 Individual Differences in Approach-Avoidance Motivation

Importantly in human subjects, variability in baseline striatal dopamine functioning appears to be responsible for associative learning processes related to perceptions of reward and punishment. In this regard, individual differences in baseline dopamine functioning (e.g., having extremely high levels versus low levels of tonic dopamine) play an important role in anhedonia. Baseline dopamine functioning appears to be supported by a steady state concentration of dopamine neuron firing (i.e., tonic firing) [see 47]. Moreover, baseline striatal dopamine levels appear to be involved in the prediction error signal, which updates reward predictions in response to changing contingencies, and has been measured by performance on probabilistic reversal learning paradigms [48, 49]. In such paradigms, individuals initially learn to choose via trial and error with corrective feedback whether a highlighted stimulus leads to reward or punishment. Subsequent trials then reverse these learned stimulus-outcome associations, and participants must learn to switch (i.e., update) their responses to match the new unexpected reward or punishment contingencies. "On such tasks, those with higher baseline striatal D2 dopamine synthesis capacity showed better reversal learning performance from unexpected rewards than from unexpected punishments, whereas those with relatively lower baseline striatal D2 dopamine synthesis capacity performed better after unexpected punishments than after unexpected rewards." However, when these same individuals were given a single dose of bromocriptine (i.e., a D2 receptor agonist that increased dopamine levels), those low in baseline striatal dopamine improved their performance whereas those high in baseline striatal dopamine now had impaired performance (an "overdose" effect) [48]. In this sense, dopamine levels and reward-based reversal learning performance follow an inverted-U pattern; tonic dopamine levels create the set point from which additional dopamine synthesis capacity enhances or impairs reward-based reversal learning among other cognitive functions (e.g., working memory) [49]. Furthermore, unmedicated individuals with major depressive disorder show impaired reward, although not punishment, reversal accuracy as well as reduced striatal response to unexpected reward [50]. The authors suggested this mechanism may underlie the *negativity bias* seen in depression, wherein individuals are more sensitive to punishing stimuli and do not adapt as quickly to rewarding stimuli. In conclusion, punishing stimuli appear to hold more weight than rewarding stimuli and internal cost-benefit calculations do not accurately represent (i.e., update) the value of rewarding situations within depressed individuals.

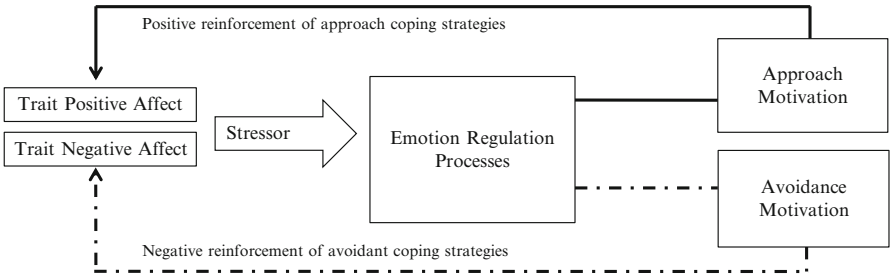

Fig. 2.1 *Bold line* represents the emotion regulation process of trait positive affect and the *dashed line* represents the process of trait negative affect

Greater self-reported approach motivation (as measured by the Achievement scale of the Multidimensional Personality Questionnaire [51]) is also correlated with higher left relative to the right hemisphere dopamine receptor availability in healthy subjects [52]. It has been proposed that genetic variation that influences the expression of dopamine D2 receptors differentially influences reward-seeking behaviors, such that individuals with the allele (A1+) associated with reduced dopamine receptor concentration may be more likely to seek out experiences that increase dopamine receptor stimulation, whereas individuals with higher levels of dopamine (A1- allele) would be more likely to avoid stimulus-seeking behaviors because of adverse effects on the brain [53]. D2 receptor availability is also associated with individual differences in hedonic experience, such that in healthy individuals, those with high D2 receptor availability find stimulating drugs to be less pleasant and experience greater negative emotional states (annoyance and distrust) than those with low D2 receptor availability [for review, see 54]. Thus, there is evidence to suggest that genetic differences in dopamine influence hedonic experience and tendencies toward approach- or avoidant-oriented behavior in ways that compensate for their relatively lower or higher dopamine levels, respectively. As we will describe in the following section, there is also evidence to suggest that dopamine plays a role in individual trait differences in the degree of approach as compared to avoidance motivation (Fig. 2.1).

2.8 Affective Traits Role in Motivated Behaviors in Response to Stress

Depue and Collins posited that individual differences in the functioning of VTA dopamine projections largely explain differences in approach motivation [16]. According to Depue and Collins, positive affective stimuli are salient forces that attract individuals due to their positive reinforcing properties. In this regard, active/approach-oriented behaviors are promoted by the anticipation of reward

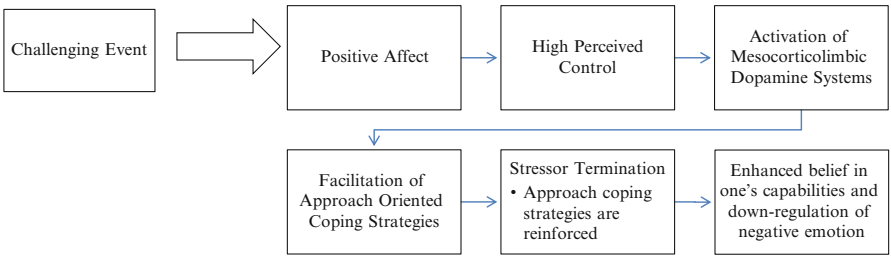

Fig. 2.2 Positive affect's role in motivated behavior

acquisition and enhanced VTA dopamine release into the NAc [16]. These dopamine-mediated differences in increased sensitivity to reward as compared to punishment are presumed to be reflected in predispositions towards the personality trait of extroversion, which is believed to be composed of several individual personality characteristics that facilitate approach behaviors (e.g., positive emotionality, sociability, and achievement) [16]. Other theorists have proposed similar underlying higher-order factors of personality traits, most notable is Watson and colleagues' [55] conceptualization of affective traits (positive and negative affect). Trait positive affect and trait negative affect are important individual difference variables that appear to play a key role in moderating individuals' response to stress. The neurobiological mechanisms of approach-avoidance motivation appear to be coupled to affective traits, such that dispositions towards positive approach emotions (e.g., interest and enthusiasm) are associated with greater activation of left frontal regions of the brain, whereas greater avoidant-related emotions (e.g., fear) are associated with selective activation of the right frontal region [14]. Affective traits also have a robust relationship with coping strategies, in which trait negative affect is associated with significantly greater use of avoidant coping strategies while positive affect is positively associated with greater use of approach oriented coping strategies [56]. Furthermore, the pattern of high negative/low positive affect has been repeatedly linked to both depression and schizophrenia [57–60]. Building on this, we provide two models (see Figs. 2.2 and 2.3) that elucidate how individual differences in affective traits and their hypothesized underlying neural mechanisms influence stressor outcomes.

Uncontrollable stress has been shown to reliably provoke large psychophysiological changes, particularly in HPA axis activity in both humans and animals (for reviews, see [35–37]). However, there are individual differences in the degree of susceptibility to it. It has been recognized that individuals often vary widely in their subjective responses to the same situations; thus, a useful indicator of experienced distress depends upon the individual's perceptions of the event and not the situation per se [37]. As we have discussed, stressor duration and perceptions of one's capability of controlling event outcomes moderate the relationship between learned helplessness and controllability. Further important factors that determine the reaction to the stressor are the salience of the threat to self, meaning of the

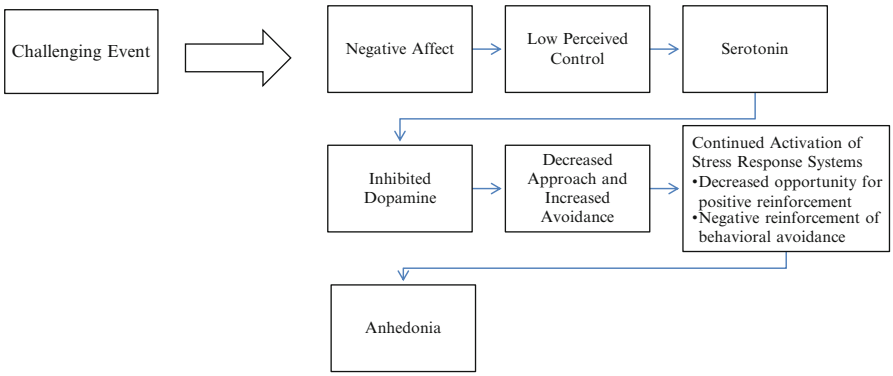

Fig. 2.3 Negative affect's role in motivated behaviors

event, and attributions of causality [6]. Of relevance, the process of learning to behaviorally control stressors appears to lead to improvements in executive functioning performance under stress, but only in individuals with a moderate level of self-reported response to stress and not in those with extreme subjective responses to stress [61]. All considered, individual differences in the ability to regulate emotional reactions to challenging events appear to be the basis of how perceived control exerts its effects. Importantly, individual differences in affective traits and their proposed underlying biological mechanisms appear to be related to differences in the ability to regulate negative emotion and approach-avoidance motivation. Because the capacity to successfully guide behaviors in the face of distress is critical to both psychological and physiological resilience, we will now build on these concepts in order to provide a model of how differences in trait positive affect as compared to trait negative affect and their respective underlying mechanisms have the capacity to alter perceptions of controllability by influencing appraisals of the stimulus' affective value.

Importantly, the experience of positive emotions appears to promote physiological states that serve to guide behavior that supports not only basic survival, but also overall states of well-being [62]. *Trait positive affect* is believed to represent the general tendency to experience positive emotional states, such as joy and enthusiasm, and is associated with the facilitation of rewarding experiences [55]. Trait positive affect is associated with greater amounts of approach behaviors, as well as lower autonomic arousal to negative stimuli [15]. Individuals who experience more positive affective states also have faster physiological recovery and generally lower cortisol output following stress [63–65]. Conversely, ecological momentary assessment ratings of low positive affect have been linked to a potential biomarker of neuroendocrine dysregulation (i.e., greater cortisol awakening response) [64].

Another potential mechanism by which the benefits of trait positive affect may occur is through the cognitive appraisals of the event. Importantly, "challenge" as compared to "threat" appraisals are dependent on the degree to which the

individual feels that they have the capacity to manage or control the event [66]. In this regard, approach motivation that is associated with trait positive affect, would also play an important role in one's personal expectancies (e.g., "It may be difficult but I can manage it"). Thus, it may be that individuals that are high in positive affect and approach motivation experience stressors as being challenging, rather than threatening, because they perceive that they are capable of managing the problem. In turn, these appraisals of challenge, as compared to threat, promote adaptive problem-solving skills that produce positive outcomes [66]. In turn, through associative learning processes, a positive cycle is created such that this acquired knowledge of successfully handling the problem by one's actions serves to guide future adaptive behaviors through priming perceptions of this successful outcome. Consistent with this notion, the experience of positive emotional states is thought to broaden individuals' behavioral repertoires, such that positive emotions appear to promote active exploration of the environment, which in turn allows individuals to accrue positive reinforcing experiences that presumably foster a sense of well-being and mastery of their environment (i.e., a sense of personal control; see Fredrickson's Broaden and Build Theory [67]). Furthermore, stressors that are appraised as being a "challenge" rather than a "threat" are characterized by the experience of positive emotions [66, 68]. Lastly, individuals high in positive affect also appear to be more effective at ascribing a positive meaning to a negative event that has occurred (e.g., "I really grew as a person from this experience") [66]. Altogether, positive affect appears to positively reinforce approach-oriented coping strategies and increase environmental interactions that serve to foster self-esteem and beliefs in one's own competencies.

According to the dopaminergic theory of positive affect, the experience of mild positive affect is accompanied by increased dopamine release primarily within the mesocorticolimbic system; more specifically, positive affect in conjunction with heightened dopamine levels within the mesocorticolimbic system appears to increase cognitive flexibility via executive attention systems [for review, see 69]. This improved cognitive flexibility is believed to be responsible for the enhancement in creative problem-solving skills.

Sustaining high levels of positive affect in the face of adversity has been proposed to be the mechanism by which resiliency to stress occurs [14, 15]. In this view, it is not that individuals high in trait positive affect do not experience adverse events along with negative emotions, but rather such individuals appear to be more effective at attenuating negative emotions, and thus recover faster both psychologically and physiologically.

As Fig. 2.2 illustrates, we suggest that individuals high in trait positive affect tend to appraise stressful events as challenges rather than as uncontrollable threats. In turn, high perceived control activates regions of the PFC that inhibit further physiological responses to stress and promotes adaptive mesocorticolimbic functioning by inhibiting stress responses and freeing cognitive resources in order to successfully cope with the demand. Approach-oriented coping strategies are facilitated by concomitant elevations in positive affect (e.g., hope) and dopamine within the mesocorticolimbic system. Through the use of approach-oriented coping

strategies (e.g., problem solving), which is mediated by frontal cortex inputs, the individual may begin to work on resolving their conflict, which will continue to attenuate the experience of distress through the down-regulation of stress response systems (e.g., dampening amygdala activity and HPA-axis responses). In this regard, approach-oriented coping strategies would be positively reinforced. The final outcome becomes somewhat of a self-fulfilling prophecy in that high perceived control leads to an enhanced belief in one's own self-efficacy that serves to guide future adaptive behaviors and personal expectancies of control. In this respect, trait positive affect promotes a cycle of behaviors that impact future motivational goals and allows the development of approach behavioral repertoires that may lend psychological resilience to stress.

Trait negative affect reflects the general tendency to experience negative emotional states (e.g., fear, shame and anger) [55]. In contrast to positive affective states, dysfunction in the mesolimbic dopamine-mediated reward system is related to increased negative affective states (e.g., anxiety and depression) [70]. Negative affective states are also associated with heightened physiological reactivity to stress and slower physiological recovery following stress [63–65]. Individuals who are high in trait negative affect appear to be prone to heightened emotional reactivity to stress and engage in greater amounts of behavioral avoidance in response to stress [71–73]. Additionally, eliciting negative emotions (anger and shame) as compared to a positive emotion (pride) has been found to differentially associate with stressor attributions, physiological reactivity, and task performance in an uncontrollable social evaluation performance task. Specifically, in contrast to those in whom a positive emotion (pride) was elicited, participants in whom a negative emotion was elicited appraised the same performance task as threatening and difficult, displayed significantly higher cardiovascular reactivity to the task, and demonstrated an impaired performance with an increased level of avoidant coping strategies [74]. Additionally, ecological momentary assessment techniques have found that individuals within a broad age range (18–89 years old) report higher negative affect on days in which they felt less in control [75]. Furthermore, negative affect is associated with an increased expectancy of uncontrollable negative events and decreased feelings of self-efficacy [76]. Lastly, as previously discussed, individuals that are high in trait negative affect appear to be less effective at down-regulating negative emotional reactions to stress. Overall, negative affect appears to have a clear relationship with heightened reactions to stress and perceptions of uncontrollability.

Of clinical relevance, the continued experience of negative emotions appears to prolong states of physiological and psychological distress through engagement of the amygdala and its connections with stress response systems. This heightened sensitivity to threat would promote the motivational goal of safety from perceived threats. In this regard, individuals who are high in negative affect developmentally may have less opportunity to accrue experiences that foster resiliency to stress, as their motivational goal of safety would be less frequently met, and thus cognitive resources would be spent on monitoring potential environmental threats. As Fig. 2.3 outlines, we suggest that this heightened sensitivity to stress in individuals high in trait negative affect decreases perceptions of

controllability. As perceptions of control decrease, avoidance motivation increases and negative emotions are up-regulated (presumably mediated by fluctuations of dopamine and activation of stress response systems). Additionally, as the next section will discuss, low perceived control appears to activate serotoninergic neurons within the raphe nuclei, thereby creating a cascade of psychological and physiological effects within the mesocorticolimbic system that heralds the decreased use of approach-oriented coping strategies and increased use of avoidant coping strategies. In turn, because avoidant coping strategies can temporarily reduce exposure to the aversive situation, they have the capacity to blunt physiological responses to stress. In this regard, avoidant coping strategies are negatively reinforced due to their capacity to initially attenuate distress. In the long-term, avoidant coping strategies would impede an individual's ability to adapt to their environment through altering their physiological responses to stress and decreasing opportunities for positive reinforcement and, thus, reinforce a cycle that reduces perceptions of control and increases behavioral avoidance.

2.9 Understanding the Relationship Between Perceived Control and Anhedonia: Functional Interaction Between Serotonin and Dopamine Systems

Serotonin neurons play a large role in regulating dopamine function within the mesocorticolimbic dopamine system and appear to be particularly sensitive to stressors that are perceived to be uncontrollable [23, 77]. The raphe nuclei host serotonin-containing cell bodies that send their projections to dopaminergic cells within the mesocorticolimbic systems (namely, VTA, NAc, and PFC), as well as to the substantia nigra and its terminals in the striatum [23]. Serotonin plays both an inhibitory as well as excitatory role in dopamine functioning, and although we will not go into detail, it is important to note that serotonin serves diverse functions that appear to be mediated by the wide variety of serotonin receptor types [23]. For our purposes, it is important to note that the role serotonin plays in the mesocorticolimbic dopamine system is largely inhibitory. For example, it appears that activation of serotonin receptors via pharmacological agonists decrease VTA activation and dopamine release within the NAc, while serotonin antagonists enhance mesocorticolimbic dopamine function (for review, see [78]). Uncontrollable stressors (e.g., inescapable shock) as compared to controllable stressors have been shown to significantly increase extracelluar serotonin levels [8, 79]. Moreover, activation of serotonin neurons appears to play a causal role in the observable changes in motivated behaviors and increased negative affect that are produced by uncontrollable stress: stimulation of serotonin neurons in the dorsal raphe nuclei (1) inhibits defensive behaviors (fight or flight) via projections to a region of the midbrain that induces freezing behavior (dorsal periaqueductal gray), as well as (2) sends excitatory projections to the amygdala [79]. Furthermore, differential effects of serotonin

have been found such that serotonin microinjected into the rat amygdala enhances resistance of conditioned fear to extinction, whereas serotonin antagonists in the same region appear to block conditioned responses to punishment; and serotonin microinjected into the periaqueductal gray inhibits unconditioned fear responses (i.e., biologically innate fear from a predator) [80]. Similar effects have also been found in humans via pharmacological manipulation of serotonin [for review, see 81]. In sum, serotonin has a modulatory effect on dopamine in the mesocorticolimbic system which influences stress related responses and impacts motivated behaviors.

Given serotonin's role in inhibiting dopamine within the mesocorticolimbic system and its differential role in emotional responses to uncontrollable stress, it would appear that the functional interaction between serotonin and dopamine along with perceived control's ability to elicit serotonin play a crucial role in the behavioral correlates of anhedonia. Consistent with this notion, disinhibition of the mesocorticolimbic dopamine system has been posited to be the mechanism of action within several antidepressant drugs [77]. For example, the antidepressants amitriptyline and mianserin, which have a high affinity for serotonin receptors found within the mesolimbic system, appear to enhance dopamine release in the rat NAc potentially through the blockade of these receptors [78]. Administration of amitriptyline and mianserin have also proven to be effective at reversing uncontrollable stress-induced anhedonic behaviors (i.e. decreased consumption of sucrose) in rats, and these beneficial effects were reversed when selective dopamine antagonists were administered to the rats [82]. It is also important to note that although the exact mechanisms of action remain unclear, certain atypical antipsychotics that have had some success with attenuating negative as well as positive symptoms of schizophrenia appear to act on both serotonin and dopamine systems [83]. These observed beneficial effects of atypical antipsychotics appear to be mediated by a preferential increase of dopamine release in the medial PFC [for review, see 84]. There is also evidence that individual differences in perceived control influence responses to reward. For instance, predispositions for learned helpless in rats (i.e., congenital learned helplessness) appear to interact with uncontrollable stress to trigger reductions in consumptive behaviors to preferred liquids and decreased pleasure-attenuated startle response [85]. In humans, the degree to which participants report low perceived control over present life stressors is associated with a reduced hedonic capacity in objective laboratory measures that test reward responsiveness [86]. In conclusion, there is evidence to suggest that perceptions of uncontrollable stress induce anhedonic-like behavior in animals and humans.

Importantly, as we have outlined, perceptions of control influence reward expectancies, modulate psychophysiological responses to stress, and are involved in dysregulation of the mesocorticolimbic dopamine system. In all, the experience of uncontrollable stress appears to reduce hedonic capacity and to alter functioning of the neural circuitry involved in approach-avoidance motivation.

2.10 Mesocorticolimbic System and the Behavioral Correlates of Anhedonia

We have defined anhedonia as a profound diminished interest and/or loss of pleasure in activities; however, behavior that outwardly manifests as anhedonia has numerous independent and inter-dependent reward-related neural mechanisms that complicate theoretical explanations of this symptom. Of further complication, the term "consummatory behavior," which is often used to describe hedonic capacity, actually reflects a number of behaviors that are not a united category of responses [e.g., 11]. More recent evidence has shown that "wanting" and "liking" neural pathways are only two potential areas of reward-related dysfunction among a milieu of other mechanisms, with separate yet inter-related neural correlates, which may each or in some combination manifest outwardly as behavior that has been considered exemplary of "anhedonia." Along with deficits in experiential pleasure received in-the-moment for obtaining a reward or outcome (i.e., liking or consummatory pleasure), it is recognized that deficits in (1) the ability to predict or anticipate whether a reward will occur (i.e., wanting or anticipatory pleasure), (2) updating stimulus value (i.e., computing the cost vs. reward in relation to how much the stimulus was previously liked), (3) the ability to accurately calculate the amount of effort necessary to acquire reward, (4) conducting a cost-benefit analysis of potential behavioral actions (e.g., Is the amount of effort required worth it?), and (5) having sufficient motivation to perform the necessary behaviors in order to obtain reward, may be governed by different neural mechanisms and may all lead to behaviors that outwardly manifest as anhedonic symptoms [22]. However, these reward processing deficits do not necessarily reflect deficits in the ability to experience pleasure. For example, deficits in the ability to accurately predict a reward's value (e.g., predicting how enjoyable a party will be) does not equate to one not actually enjoying the activity (e.g., having fun at the party). In this regard, "wanting to go to the party" and "liking the party" represent distinct processes with different underlying neurological mechanisms that serve them.

Numerous theories of motivation have been studied over the decades but understanding the underlying mechanisms involved in "wanting" as compared to "liking" has proven to be a formidable task. Given the multiple roles that the mesolimbic pathway plays in the processing of both rewards and stressors, determining factors that alter functioning within this region has garnered a large amount of interdisciplinary interest. The actual experience of pleasure appears to be mediated by activation of cannabinoid and opioid receptors in the NAc regions of the mesolimbic pathway. In this regard, animal research has been useful in identifying discrete biological underpinnings (e.g., cannabinoid and opioid receptors in the nucleus accumbens) that are specifically associated with hedonic capacity [22]. In some respects, better delineating these respective features of reward processing has begun to increase our understanding of the underlying mechanisms involved in

anhedonia. However, as we have discussed, the systems involved in hedonic experience are substantially influenced by mesocorticolimbic dopamine functioning. Moreover, this task is complicated in that whether these factors are reducible to their respective functions remain to be determined, as there is a significant amount of interaction between these processes. Furthermore, many of these processes (particularly, associative learning processes) appear to have the capacity to alter hedonic properties (e.g., the stimulus' affective value). Thus, while fine-grained distinctions between the various underlying neurological mechanisms and their respective functions may be made, it is important to note the interdependency of these systems in relation to how individual differences in these underlying processes impact motivation as a whole. While preclinical models of anhedonia may be useful for clarifying the discrete neural correlates for specific reward deficits, these models are limited in the generalizability to human clinical models of anhedonia due to the complex interdependence of these mechanisms as well as certain aspects of clinical anhedonia that are not easily operationalized in preclinical models (e.g., subjective ratings of perceived control and perceived benefit of executing a specific action in anticipation of pleasure). All considered, clinical anhedonia appears to reflect a sequelae of psychobiological events that alter reward processing functions.

2.11 Clinical Implications of Mesocorticolimbic Dopamine Functioning

Motivation to perform goal-directed behaviors is integral to hedonic experience. Research suggests that impairments in the ability to adjust behaviors as a function of prior reinforcements may be the basis of diminished hedonic capacity in depression [87]. Deficits in motivated behavior have also been linked to impairments in reinforcement reward learning in individuals with a major depressive disorder (MDD), in individuals high in trait anhedonia, upon stress exposure, and with pharmacological manipulation of dopamine tonicity [22, 88]. As with major depression [89], individuals with schizophrenia also do not show the same increase in effort to obtain higher rewards compared to healthy individuals [90]. Moreover, this decreased willingness to expend effort for higher rewards is correlated with higher negative symptoms in individual with schizophrenia [90]. In addition, the belief that behavioral responses and reinforcement are independent of one another appears to play an important role in situational depression [91]. All considered, alterations in dopamine functioning would be expected to play a large role in the manifestation of schizophrenia and depression. Indeed, there is evidence that dysfunction in mesolimbic dopamine functioning is involved in the pathophysiology of both of these disorders [84]. Furthermore, dysfunction within prefrontal dopamine functioning, which plays a regulatory role in mesolimbic dopamine functioning, has been linked to decreased motivation in both depression and schizophrenia [for review, see 84]. Lastly, abnormalities in mesocorticolimbic activation (i.e., heightened activation in the amygdala and decreased activation in both the dorsolateral prefrontal cortex

and anterior cingulate cortex) in response to criticism has been associated with a vulnerability towards depression [92]. Thus, in both depression and schizophrenia, mesocorticolimbic dysfunction has been related to deficits in motivation and connecting positive affective value to pleasurable events; these deficiencies appear to outwardly manifest as a reduced ability to anticipate and evaluate potentially pleasurable or rewarding events.

In schizophrenia, in addition to the posited low tonic levels of dopamine within the frontal cortex (hypoactive mesocortical pathway) and consequent mesolimbic hyperactivity, Grace posits that this imbalance leads to homeostatic compensations that dysregulate phasic dopamine release [47]. Grace suggested that mesolimbic dopamine tone appears to be mediated by prefrontal regions of the cortex and that tonic dopamine levels set the boundaries for phasic dopamine release; that is, the amount of extracellular dopamine already present affects the magnitude of the effect of phasic dopamine release [47]. Of clinical relevance, in patients with schizophrenia, normal reward processing appears to be disrupted by abnormalities in phasic dopamine release [93] which is believed to contribute to increased behavioral avoidance learning and negative symptoms [94]. Similarly, phasic levels of dopamine are associated with anhedonic-like behavioral changes in response to uncontrollable psychosocial stress in mice. Optogenetic induction of phasic activation of VTA dopamine neurons that project to the NAc (mesolimbic pathway), but not PFC projections (mesocortical pathway), have been found to mediate the relationship between anhedonic-like behaviors (social avoidance and decreased sucrose intake) and psychosocial stress to a social defeat paradigm [95]. Conversely, the authors found that optogenetic inhibition of the VTA–NAc projection induced resilience to the psychosocial stressor. Furthermore, the VTA-NAc pathway's heightened sensitivity to uncontrollable psychosocial stress has been linked to increased social avoidance in mice, which is reversible with chronic antidepressant treatment [96]. In summary, it has been recognized that consequences to dysregulation of dopamine systems result in disruptions to normal reward encoding processes that are likely due to complex compensatory mechanisms that attempt to restore the organism to homeostasis [47], and the coordination between affective stimulus value and approach motivation appears to be disrupted.

2.12 Clinical Implications, Conclusions, and Future Directions

There is a growing body of research that suggests that the clinical symptom of anhedonia observed in patients with depression and schizophrenia is associated with aberrant motivational, cognitive, and emotional reactions to stress that are related to mesocorticolimbic dopamine functioning. Of importance, ineffective emotion regulation processes, reflected in individuals coping strategies, appear to substantially mediate these effects.

Coping with stress involves both the anticipation of future stressful events and the recovery from distress [97]. In this view, coping is a dynamic process, in which individuals make adjustments (via thoughts and behaviors) in attempts to reduce the negative impact of stress. There is substantial evidence to suggest that the development of dynamic behavior-action repertoires in response to emotional distress are shaped significantly by both affective and cognitive appraisal processes. We have proposed a model in which affective traits and their proposed underlying biological mechanisms interact with emotion regulation processes to guide behavioral responses to stress. In this model, individual differences in affective traits, which are presumed to have biological underpinnings, substantially influence approach-avoidance motivation and impact perceptions of controllability. In turn, high and low perceived control differentially activate a biological cascade that helps the individual cope with the source of stress: whereas low perceived control activates systems that promote avoidant copings strategies, high perceived control activates systems that facilitate approach-oriented coping strategies.

Over time, when an individual learns that his or her behavior is an unreliable predictor of outcomes in their environment (i.e., low perceived control), approach motivation decreases and motivational goals are adjusted. This acquired knowledge guides future behaviors in efforts to achieve goals through allowing an individual to select a suitable/appropriate behavior-action repertoire that will serve to meet the desired goal (e.g., avoiding an aversive experience). In this regard, cognitive resources are directed at avoiding unpleasant experiences, rather than attempting to improve the outcome. In contrast, positive affect enhances personal expectancies of control and promotes adaptive coping strategies that are directed at managing the stressor. In this regard, trait positive affect appears to promote a cycle of behaviors that lead to psychological resilience to stress, while trait negative affect in conjunction with low perceived control decreases an individual's capacity to adapt behaviors to shape future motivational goals (through priming perceptions of past negative event outcomes). In conclusion, motivated behaviors are substantially shaped by an organism's knowledge about their environment and the likelihood of the possible effects of performing that action in a given situation (i.e., cost-benefit analysis). In this regard, the same event can have disparate affective value for different individuals that substantially effects motivated behaviors.

It is important to note that there are several relevant considerations in the relationship between anhedonia and mesocorticolimbic functioning that were outside the scope of this chapter that are important for future work. First, we believe that memory encoding processes play a large role in relationships between anhedonia and approach-avoidance motivation. For example, research suggests that anticipatory activation of this mesolimbic circuit is involved in translating motivation into memory [30] and memory encoding processes appear to be affected by uncontrollable stress (e.g., disruption of synaptic plasticity in the hippocampus [for review, see 98]). Additionally, while we focused on the interaction between dopamine and serotonin systems, several other neuromodulators and neurotransmitters play a role in "wanting" behaviors (e.g., dopamine's interaction with glutamate [99]). Moreover, while we discussed the dynamic relationship between tonic and phasic levels of

dopamine, it also bears mention that individual differences in serotonin functioning play an important role in the relationship between stress and anhedonia. Specifically, a functional polymorphism in a serotonin transporter gene (short vs. long allele) appears to moderate the relationship between depression and stress reactivity [100, 101]; furthermore, this polymorphism is associated with a decreased capacity for problem-solving strategies in the face of stress [102]. In this regard, future work should aim to clarify the precise neural mechanisms underlying specific aspects of motivated behavior as well as the forces driving the functional interactions between them. Moreover, these functional interactions should be studied longitudinally over the course of depression and schizophrenia as well as other neuropsychiatric disorders with anhedonic symptoms (e.g., Parkinson's disease, substance dependence and withdrawal) to explore the causal role that positive/negative affect and perceived control play in the development of these symptoms. Lastly, it is of great import to consider that cognitive therapy may be less efficacious in those individuals who are less effective at down-regulating negative emotional states. Indeed, research has demonstrated that behavioral activation for depression (i.e., a psychosocial therapy that focuses on behavioral changes) is as effective as therapies that incorporate cognitive restructuring (i.e., cognitive therapy) [103]. In this regard, developing empirically supported psychological interventions that incorporate active coping strategies (i.e., behavioral activation) with emotion regulation strategies may be the front line intervention for those individuals who are high in trait negative affect/low trait positive affect.

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References

1. Everitt BJ, Parkinson JA, Olmstead MC, et al. Associative processes in addiction and reward: the role of amygdala- ventral striatal subsystems. Ann N Y Acad Sci. 1999;877:412–38.
2. Maier SF, Seligman MEP. Learned helplessness: theory and evidence. J Exp Psychol Gen. 1976;105:3–46.
3. Miller WR, Seligman ME. Depression and learned helplessness in man. J Abnorm Psychol. 1975;84:228–38.
4. Hiroto DS. Locus of control and learned helplessness. J Exp Psychol. 1974;102:187–93.
5. Hiroto DS, Seligman MEP. Generality of learned helplessness in man. J Pers Soc Psychol. 1975;31:311–27.
6. Roth S. A revised model of learned helplessness in humans. J Pers. 1980;48:103–33.
7. Abramson LY, Seligman MEP, Teasdale JD. Learned helplessness in humans: critique and reformulation. J Abnorm Psychol. 1978;87:49–74.
8. Christianson JP, Thompson BM, Watkins LR, et al. Medial prefrontal cortical activation modulates the impact of controllable and uncontrollable stressor exposure on a social exploration test of anxiety in the rat. Stress. 2009;12:445–50.
9. Maslow AH. A theory of human motivation. Psychol Rev. 1943;50:370–96.
10. Elliot AJ, Covington MV. Approach and avoidance motivation. Educ Psychol Rev. 2001;13:73–92.

11. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev. 1998;28:309–69.
12. Elliot A. Approach and avoidance motivation and achievement goals. Educ Psychol. 1999;34:169–89.
13. Davidson RJ, Ekman P, Saron CD, et al. Approach-withdrawal and cerebral asymmetry: emotional expression and brain physiology: I. J Pers Soc Psychol. 1990;58:330–41.
14. Davidson RJ. Affective style and affective disorders: perspectives from affective neuroscience. Cogn Emot. 1998;12:307–30.
15. Davidson RJ. Well-being and affective style: neural substrates and biobehavioural correlates. Philos Trans R Soc Lond B Biol Sci. 2004;359:1395–411.
16. Depue RA, Collins PF. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav Brain Sci. 1999;22:491–517.
17. Gray JA. The neuropsychology of anxiety: an enquiry into the functions of the septo-hippocampal system. 1st ed. New York: Oxford University Press; 1982.
18. Hull C. Principles of behavior. New York: Appleton-Century-Crofts; 1943.
19. LeDoux JE. The emotional brain. New York: Simon and Schuster; 1996.
20. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155–84.
21. Elsner B, Hommel B. Effect anticipation and action control. J Exp Psychol Hum Percept Perform. 2001;27:229–40.
22. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35:68–77.
23. Di Giovanni G, Esposito E, Di Matteo V. Role of serotonin in central dopamine dysfunction. CNS Neurosci Ther. 2010;16:179–94.
24. Carlson NR. Psychopharmacology. In: Physiology of behavior. 11th ed. Boston: Pearson Education, Inc.; 2013;99–129
25. Le Moal M, Simon H. Mesocorticolimbic dopaminergic network: functional and regulatory roles. Physiol Rev. 1991;71:155–234.
26. Corlett PR, Honey GD, Krystal JH, et al. Glutamatergic model psychoses: prediction error, learning, and inference. Neuropsychopharmacology. 2011;36:294–315.
27. Schultz W. Multiple reward signals in the brain. Nat Rev Neurosci. 2000;1:199–207.
28. Luciana M, Wahlstrom D, Porter JN, et al. Dopaminergic modulation of incentive motivation in adolescence: age-related changes in signaling, individual differences, and implications for the development of self-regulation. Dev Psychol. 2012;48:844–61.
29. Cabib S, Puglisi-Allegra S. The mesoaccumbens dopamine in coping with stress. Neurosci Biobehav Rev. 2012;36:79–89.
30. Adcock RA, Thangavel A, Whitfield-Gabrieli S, et al. Reward-motivated learning: mesolimbic activation precedes memory formation. Neuron. 2006;50:507–17.
31. Ballard IC, Murty VP, Carter RM, et al. Dorsolateral prefrontal cortex drives mesolimbic dopaminergic regions to initiate motivated behavior. J Neurosci. 2011;31:10340–6.
32. Amat J, Baratta MV, Paul E, et al. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat Neurosci. 2005;8:365–71.
33. Baratta MV, Christianson JP, Gomez DM, et al. Controllable versus uncontrollable stressors bi-directionally modulate conditioned but not innate fear. Neuroscience. 2007;146:1495–503.
34. Bolles RC. Species-specific defense reactions and avoidance learning. Psychol Rev. 1970;71:32–48.
35. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull. 2004;130:355–91.
36. Sapolsky RM. In: Freeman WH, editor. Why zebras don't get ulcers: an updated guide to stress, stress related diseases, and coping. 2nd ed. New York: Henry Holt and Company; 1998.
37. Taylor SE. Health psychology. In: Baumeister RF, Finkel EJ, editors. Advanced social psychology: the state of the science. New York: Oxford University Press; 2010. p. 697–731.
38. Richards JM, Gross JJ. Emotion regulation and memory: the cognitive costs of keeping one's cool. J Pers Soc Psychol. 2000;79:410–24.

39. Ochsner KN, Ray RD, Cooper JC, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage. 2004;23:483–99.
40. Phan KL, Fitzgerald DA, Nathan PJ, et al. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry. 2005;57:210–9.
41. Urry HL, Van Reekum CM, Johnstone T, et al. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J Neurosci. 2006;26:4415–25.
42. Johnstone T, van Reekum CM, Urry HL, et al. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J Neurosci. 2007;27:8877–84.
43. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS Scales. J Pers Soc Psychol. 1994;67:319–33.
44. Shackman AJ, McMenamin BW, Maxwell JS, et al. Right dorsolateral prefrontal cortical activity and behavioral inhibition. Psychol Sci. 2009;20:1500–6.
45. Davidson RJ. Cerebral asymmetry, emotion and affective style. In: Davidson RJ, Hugdahl K, editors. Brain asymmetry. Cambridge, MA: MIT Press; 1995. p. 361–87.
46. Tomarken AJ, Davidson RJ, Wheeler RD, et al. Individual differences in anterior brain asymmetry and fundamental dimensions of emotion. J Pers Soc Psychol. 1992;62:676–87.
47. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience. 1991;41(1):1–24.
48. Cools R, Frank MJ, Gibbs SE, et al. Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. J Neurosci. 2009;29:1538–43.
49. Cools R, Robins TW. Chemistry of the adaptive mind. Philos Trans A Math Phys Eng Sci. 2004;362:2871–88.
50. Robinson OJ, Cools R, Carlisi CO, et al. Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. Am J Psychiatry. 2012;169:152–9.
51. Tellegen A, Waller NG. Exploring personality through test construction: development of the multidimensional personality questionnaire. In: Boyle GJ, Matthews G, Saklofske DH, editors. The SAGE handbook of personality theory and assessment, vol. 2. Thousand Oaks: Sage; 2008. p. 261–92.
52. Tomer R, Goldstein RZ, Wang GJ, et al. Incentive motivation is associated with striatal dopamine asymmetry. Biol Psychol. 2008;77:98–101.
53. Cohen MX, Krohn-Grimberghe A, Elger CE, et al. Dopamine gene predicts the brain's response to dopaminergic drug. Eur J Neurosci. 2007;26:3652–60.
54. Volkow ND, Fowler JS, Wang GJ, et al. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiol Learn Mem. 2002;78:610–24.
55. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988;54:1063–70.
56. Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. J Pers Soc Psychol. 1989;56:267–83.
57. Berenbaum H, Fujita F. Schizophrenia and personality: exploring the boundaries and connections between vulnerability and outcome. J Abnorm Psychol. 1994;103:148–58.
58. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol. 1991;100:316–36.
59. Horan WP, Blanchard JJ. Emotional responses to psychosocial stress in schizophrenia: the role of individual differences in affective traits and coping. Schizophr Res. 2003;60:271–83.
60. Watson D, Clark LA, Stasik S. Emotions and the emotional disorders: a quantitative hierarchical perspective. Int J Clin Health Psychol. 2011;11:429–42.
61. Henderson RK, Snyder HR, Gupta T, et al. When does stress help or harm? The effects of stress controllability and subjective stress response on stroop performance. Front Psychol. 2012;3:179.

62. Damasio AR. Emotions and feelings: a neurobiological perspective. In: Manstead ASR, Frijda N, Fischer A, editors. Feelings and emotions: the Amsterdam symposium, Studies in emotion and social interaction. New York: Cambridge University Press; 2004. p. 49–57.
63. Polk DE, Cohen S, Doyle WJ, et al. State and trait affect as predictors of salivary cortisol in healthy adults. Psychoneuroendocrinology. 2005;30:261–72.
64. Steptoe A, Gibson EL, Hamer M, et al. Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire. Psychoneuroendocrinology. 2007;32:56–64.
65. Tugade MM, Fredrickson BL. Resilient individuals use positive emotions to bounce back from negative emotional experiences. J Pers Soc Psychol. 2004;86:320–33.
66. Folkman S. Personal control and stress and coping processes: a theoretical analysis. J Pers Soc Psychol. 1984;46:839–52.
67. Fredrickson BL. The role of positive emotions in positive psychology. The broaden-and-build theory of positive emotions. Am Psychol. 2001;56:218–26.
68. Folkman S, Moskowitz JT. Stress, positive emotion, and coping. Curr Dir Psychol Sci. 2000;9:115–8.
69. Ashby GF, Valentin VV, Turken AU. The effects of positive affect and arousal and working memory and executive attention: neurobiology and computational models. In: Moore SC, Oaksford M, editors. Emotional cognition: from brain to behaviour. Amsterdam: John Benjamins Publishing Company; 2002. p. 245–87.
70. Spanagel R, Weiss F. The dopamine hypothesis of reward: past and current status. Trends Neurosci. 1999;22:521–7.
71. Bartels JM. Dispositional positive and negative affect and approach-avoidance achievement motivation. Individ Differ Res. 2007;5:246–59.
72. Brenner SL, Beauchaine TP, Sylvers PD. A comparison of psychophysiological and self-report measures of BAS and BIS activation. Psychophysiology. 2005;42:108–15.
73. Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. J Abnorm Psychol. 1994;103:103–16.
74. Herald MM, Tomaka J. Patterns of emotion-specific appraisal, coping, and cardiovascular reactivity during an ongoing emotional episode. J Pers Soc Psychol. 2002;83:434–50.
75. Diehl M, Hay EL. Risk and resilience factors in coping with daily stress in adulthood: the role of age, self-concept incoherence, and personal control. Dev Psychol. 2010;46:1132–46.
76. Bandura A. Self-efficacy: the exercise of control. New York: W. H. Freeman; 1997.
77. Di Giovanni G, Di Matteo V, Pierucci M, et al. Serotonin-dopamine interaction: electrophysiological evidence. Prog Brain Res. 2008;172:45–71.
78. Di Matteo V, Cacchio M, Di Giulio C, et al. Role of serotonin(2C) receptors in the control of brain dopaminergic function. Pharmacol Biochem Behav. 2002;71:727–34.
79. Maier SF, Watkins LR. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. Neurosci Biobehav Rev. 2005;29:829–41.
80. Graeff FG, Silveira MCL, Nogueira RL, et al. Role of the amygdala and periaqueductal gray in anxiety and panic. Behav Brain Res. 1993;58:123–31.
81. Graeff FG, Guimarães FS, De Andrade TG, et al. Role of 5-HT in stress, anxiety, and depression. Pharmacol Biochem Behav. 1996;54:129–41.
82. Sampson D, Willner P, Muscat R. Reversal of antidepressant action by dopamine antagonists in an animal model of depression. Psychopharmacology (Berl). 1991;104:491–5.
83. Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol. 2011;11:59–67.
84. Di Matteo V, Di Giovanni G, Pierucci M, et al. Serotonin control of central dopaminergic function: focus on in vivo microdialysis studies. Prog Brain Res. 2008;172:7–44.
85. Enkel T, Spanagel R, Vollmayr B, et al. Stress triggers anhedonia in rats bred for learned helplessness. Behav Brain Res. 2010;209:183–6.

86. Pizzagalli DA, Bogdan R, Ratner KG, et al. Increased perceived stress is associated with blunted hedonic capacity: potential implications for depression research. Behav Res Ther. 2007;45:2742–53.
87. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol Psychiatry. 2005;57:319–27.
88. Treadway MT, Zald DH. Parsing anhedonia: translational models of reward-processing deficits in psychopathology. Curr Dir Psychol Sci. 2013;22:244–9.
89. Treadway MT, Bossaller NA, Shelton RC, et al. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J Abnorm Psychol. 2012;121:553–8.
90. Gold JM, Strauss GP, Waltz JA, et al. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. Biol Psychiatry. 2013;74:130–6.
91. Miller WR, Seligman MEP. Depression and the perception of reinforcement. J Abnorm Psychol. 1973;82:62–73.
92. Hooley JM, Gruber SA, Parker HA, et al. Cortico-limbic response to personally challenging emotional stimuli after complete recovery from depression. Psychiatry Res. 2009;172:83–91.
93. Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. Schizophr Bull. 2010;36:472–85.
94. Strauss GP, Frank MJ, Waltz JA, et al. Deficits in positive reinforcement learning and uncertainty-driven exploration are associated with distinct aspects of negative symptoms in schizophrenia. Biol Psychiatry. 2011;169:424–31.
95. Chaudhury D, Walsh JJ, Friedman AK, et al. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature. 2013;493:532–6.
96. Berton O, McClung CA, DiLeone RJ, et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science. 2006;311:864–8.
97. Roth S, Cohen LJ. Approach, avoidance, and coping with stress. Am Psychol. 1986;41:813–9.
98. Kim JJ, Diamond DM. The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci. 2002;3:453–62.
99. Faure A, Reynolds SM, Richard JM, et al. Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens. J Neurosci. 2008;28:7184–92.
100. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301(5631):386–9.
101. Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. Science. 2002;297(5580):400–3.
102. Wilhelm K, Siegel JE, Finch AW, et al. The long and the short of it: associations between 5-HTT genotypes and coping with stress. Psychosom Med. 2007;69:614–20.
103. Dimidjian S, Martell CR, Addis ME, et al. Behavioral activation for depression. In: Barlow DH, editor. Clinical handbook of psychological disorders. A step-by-step treatment manual. 4th ed. New York: Guilford Press; 2008. p. 328–64.

Chapter 3
Circadian Fluctuation of Reward Response and Synchronization to Reward

Bruno Jacson Martynhak and Roberto Andreatini

Abstract Several physiological processes common to almost all living beings show fluctuations within the 24 h that compose the Earth's light/dark cycle. Some examples of this in humans are the rise of cortisol levels early in the morning, the secretion on melatonin during the night and the core body temperature maxima and minima occurring during the late afternoon and late at night, respectively. Disruption of the circadian system can be one of the factors leading to depression and anhedonia. Alterations in circadian rhythms found in depressive patients include reduced amplitude of circadian rhythms, elevated temperature at night and early cortisol secretion. One feature of depression is diurnal variation in mood, which is generally worse during the morning and improves throughout the day. Moreover, the hedonic value of reward changes throughout the day and reward can synchronize circadian rhythms, as daily injections of methamphetamine can induce anticipation behavior. In this chapter, we will address the neurobiology of circadian rhythms, diurnal mood variation, fluctuating properties of reward over the 24 h cycle and, finally, the ability to synchronize circadian rhythms to reward regardless of the imposed light/dark cycle.

Keywords Anhedonia • Depression • Circadian rhythms • Diurnal mood variation • Reward • Food-entrainable oscillator

Abbreviations

5-HIAA	5-Hydroxyindoleacetic acid main metabolite of serotonin
5-HT	5-Hydroxytryptophan or serotonin
CMS	Chronic mild stress

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CT	Circadian time. CT0 is the onset of the activity
DA	Dopamine
DD	Dark:dark cycle or constant darkness
DMV	Diurnal mood variation
DOPAC	3,4-Dihydroxyphenylacetic acid a dopamine metabolite
DAT	Dopamine transporter
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
HVA	Homovanillic acid a dopamine metabolite
ICD	International Classification of Diseases
FAA	Food anticipatory activity
FEO	Food entrainable oscillator
GABA	γ-Aminobutyric acid
LD	Light:dark cycle
MASCO	Methamphetamine-sensitive circadian oscillator
Nac	*Nucleus accumbens*
REM	Rapid eye movement
SCN	Suprachiasmatic nucleus
SCNx	Lesion in the suprachiasmatic nucleus
SSRI	Selective serotonin reuptake inhibitors
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TH	Tyrosine hydroxylase
VTA	Ventral tegmental area
ZT	Zeitgeber time. ZT0 is the lights on time

3.1 Overview of the Neurobiology of the Circadian Rhythms

Nearly all organisms on the planet show 24 h rhythmicity across multiple levels of their biology, from gene expression to behavior. This rhythmicity persists even in the absence of time cues. In this case, the organism is said to be free-running, displaying an endogenous circadian period. This period is close to the 24 h cycle of the Earth, and it is synchronized every day from exposure to the light/dark cycle. In mammals, light stimulates a photopigment called melanopsin, localized in the ganglion cells of the retina. Light information flows through the retino-hypothalamic tract to a tiny structure called the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN is responsible for generating both endogenous circadian rhythms and for entraining this rhythm to light information from the environment. The SCN sends projections to many areas of the brain including the paraventricular nucleus and the pineal gland.

Inside every single nucleated cell lies a set of genes that are not only expressed in a circadian manner but also drive the expression of other genes, orchestrating a molecular clock. The molecular clock is composed of core clock genes and clock-controlled genes. Given that each nucleated cell has its own clock, the role of the

SCN is to synchronize rhythms within different cells and different tissues. Therefore, the SCN is also known as the master clock or the central pacemaker. The core clock genes show both positive and negative feedback loops of expression. The basic feedback loop is composed of the heterodimer *Clock:Bmal1* that promotes the expression of members of the *Per* and *Cry* gene families, which in turn also form heterodimers. These dimers enter the nucleus and inhibit the action of *Clock:Bmal1*, therefore inhibiting their own expression. The dimers are then degraded, restarting the cycle.

Because the circadian timing system influences a vast array of behavioral and molecular responses, it is not surprising that the properties of the reward system are also influenced by the phase of these rhythms. Additionally, circadian rhythm disruption may be involved in a series of disorders, including depression, which will be a particular focus of this chapter. This chapter will address (i) the diurnal mood variation in both depressed and healthy subjects, (ii) the diurnal variation of the reward system in animal models, and (iii) the synchronization of the circadian system to the availability of reward.

3.2 Circadian Alterations in Depression

Major depressive disorder and bipolar disorder have long been associated with circadian rhythm disruption. As far back as the sixteenth century, there have been descriptions of sleep-wake cycle disturbances and its effects on mood [1].

Symptoms related to circadian rhythm disruption in major depression include elevated nocturnal body temperature, advanced or delayed and increased cortisol secretion, as well as advanced or delayed and reduced melatonin secretion. Reduced amplitude of circadian rhythms is also common in depressive patients. Flatter diurnal cortisol curves were more likely to occur in participants with severe depression than in those with mild to moderate levels of depression [2], including healthy adolescents that have been through one episode of major depression [3]. Temperature rhythms have been shown to have reduced amplitude [4] or are even absent in some depressed patients [5].

The internal synchronization of different rhythms might also be compromised in severely depressed patients. The onset of melatonin secretion and minimum core body temperature is desynchronized in severely depressed patients [6]. Moreover, the extent of this misalignment is correlated with the severity of the anhedonic state, measured by the BDI-anhedonia score.

Changes in sleep architecture are also observed in depressed patients, including shortened latency to rapid eye movement (REM) sleep and increased overall duration and reduction in slow-wave sleep, all of which contribute to earlier wake from sleep in patients [7]. Bipolar patients in the mania phase have reduced need for sleep [8] and show increased melatonin levels [9]. Interestingly, one night of sleep deprivation can promote temporary antidepressant effects in depressed patients or manic shift in some bipolar patients [10]. Sleep deprivation is also effective when the

subject is sleep-deprived only for the second-half of the night when REM sleep is more concentrated in healthy individuals.

It is important to note that remitted patients who fail to restore normal rhythms have increased risk of major depression early relapse [11]. Moreover, most of current treatments for mood disorders shift or stabilize circadian rhythm [12]. In particular, selective serotonin reuptake inhibitors (SSRI) advance the phase of circadian rhythms [13].

Animal models have successfully provided further information regarding the relationship between circadian rhythmicity and depression. Some models have attempted to study seasonal depressive disorder in either diurnal [14] or in nocturnal rodents [15]. In these studies, reduction of the photoperiod led to depressive-like behavior, such as increased mobility during the forced swimming test and reduction in sucrose preference. Interestingly, melatonin administration during the light phase of the cycle also promoted depressive-like behavior in nocturnal rodents [14]. This finding can be interpreted as a reduction of the photoperiod or a conflict between melatonin signaling and information from the light. Other models do not have clear correlations to human life, such as the induction of depressive-like behavior in nocturnal mice after exposure to a photoperiod of 22 h of light and 2 h of dark [16]. Even more drastic changes in the photoperiod were analyzed in animal models. Animals exposed to 6 weeks of constant darkness (DD) displayed an increase in immobility during the forced swimming test and showed damage to monoaminergic neurons [17]. On the other hand, constant light (LL), which is known to lead to arrhythmicity, also induced depressive-like behavior [18, 19].

In summary, it is clear that changes in the light/dark cycle can lead to depressive-like behavior, including anhedonia, and that depressed patients show circadian rhythm disruption. Additionally, restoring rhythmicity is associated with better treatment outcomes, and the prevention of rhythm disruption can avert the development of depressive-like behavior.

3.3 Diurnal Variation of Mood in Depressed Patients

Most of the studies described in this session focus on mood in a general sense, not specifically in states of anhedonia. However, as anhedonia is a core symptom of depression, the diurnal variation in mood might be correlated with diurnal variation in the ability to experience pleasure.

Diurnal mood variation (DMV) with early morning worsening is considered a classic symptom of melancholic features in The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) as well as the 10th International Classification of Diseases (ICD) criteria for somatic major depressive disorder (MDD) [20]. Depression patients exhibit the worst depressive mood during the morning, gradually improving throughout the day. However, patterns of DMV were analyzed in a large cohort of patients composed of individuals in the STAR*D (Sequenced Treatment Alternatives to Relieve Depression). DMV was reported in 22.4 % of

cases; 31.9 % reported morning, 19.5 % afternoon and 48.6 % evening worsening [21]. Melancholic symptom features were associated with DMV, regardless of timing. Therefore, melancholic depression is in fact not limited to having a worse mood in the morning, but instead to any type of diurnal mood variation.

Diurnal mood variation has also been hypothesized to influence treatment outcome. In a large study comprising 2,875 major depressive patients in a 14-week clinical trial of the selective serotonin reuptake inhibitor (SSRI) citalopram, participants were divided into three groups: those with early morning worsening DMV, those with any form of DMV, and those with no DMV. Though the group with the classic morning worsening DMV had slightly increased responses compared to the no DMV group, remission rates were not different between groups [22]. Another study compared three groups of depressed patients: morning worsening DMV, evening worsening DMV and no DMV. Among patients between 18 and 24 years old, those with no DMV and those with morning worsening DMV responded better to fluoxetine (SSRI) than to nortriptyline (tryciclic antidepressant that inhibits noradrenaline re-uptake), whereas patients with worse mood during the evening did not. On the other hand, patients older than 24 years demonstrated the opposite results: patients with evening worsening responded better to nortriptyline, whereas the other groups did not show any difference between treatments [23]. Additionally, patients with classic morning worsening DMV responded better to the acute antidepressant effects of total sleep deprivation in comparison to those with evening worsening DMV or no DMV [24].

In an attempt to unravel the neurobiology of diurnal variation in mood, depressed subjects with a worse mood in the morning had their neuronal activity measured and compared to healthy subjects, both in the morning and in the evening [25]. Positron emission tomography (PET) scans of the regional cerebral metabolic rate of glucose revealed a hypometabolism in frontal cortical areas and hypermetabolism in subcortical and limbic-paralimbic areas in depressed subjects regardless of the time of day. However, evening improvement in mood was associated with greater increases in both parietal and temporal cortical glucose metabolism. Though the increases were greater compared to healthy subjects, these areas were still hypometabolic. Despite the fact that causal relations are hard to establish, one could say that there is at least a common factor underlying both mood expression and glucose metabolism in specific brain areas. Of note, in this study [25], the healthy subjects also showed DMV, but instead of the classic morning worsening, the healthy subjects showed evening worsening DMV.

One important difference between DMV in healthy and depressed patients is that melancholic patients experience spontaneous mood variations outside of their control, suggestive of helplessness, whereas healthy controls consider mood variation almost exclusively related to their own activities and/or external circumstances [26]. Naturally, healthy individuals can show some non-clinical depressive features. A group of healthy individuals were divided into two groups for low and high depression according to their score in a depression scale evaluated by the Centre for Epidemiological Studies-Depression Scale (CES-D). The participants had their positive affect evaluated throughout the day using an abbreviated version of the well

Positive and Negative Affect Scales (PANAS). It was observed that both low and high depression groups had the same low scores of positive affect during the morning, with both groups improving in the evening [27]. However, the evening peak was lower in the high depression group [27], reinforcing the idea that amplitude reduction/rhythm ablation may be underlying the development of depression.

A very interesting study identified individual-level diurnal and seasonal mood rhythms in cultures across the globe, using data from millions of public Twitter messages [28]. The authors found that mood deteriorates as the day progresses. Not surprisingly, they also found that people had increased positive affect on weekends, with the morning peak in mood delayed by 2 h.

One bias to consider in the study of mood variation throughout the day is the influence of the circadian phase, the time spent awake or both. A protocol termed forced desynchronization was developed to separate the effect of circadian phase and sleep. Using this protocol (a sleep schedule of 30 h, instead of 24 h), the moods of healthy volunteers were evaluated using two visual analog scales administered regularly during waking periods. Analysis indicated an effect of the circadian phase but not of the time spent wake on mood [29]. Interestingly, a significant interaction was found between the circadian phase and time awake: depending on the circadian phase, mood improved, worsened or did not change according to the duration of prior wakefulness.

3.4 Diurnal Variation of Reward in Animal Models

Early studies demonstrated that rewarding self-stimulation of the brain varies across the day, peaking during the mid to late dark period (see [30] for review). This rhythm has been shown to persist under constant darkness conditions, suggesting circadian modulation. Other studies that used drugs of abuse as a reward also detected circadian fluctuations in drug intake, where the peak usually correlated with the more active phase within the light/dark cycle [31, 32].

However, intake itself might be increased during the dark phase simply due the use of nocturnal animals, which are more active at night, instead of being related to an intrinsic rhythmicity property of the reward system. Further experiments were performed to address this issue. One study compared consecutive sucrose preference tests in the light and dark phases [33]. Importantly, the sucrose preference is calculated as the percentage of sucrose intake over the total liquid intake, controlling for factors that might influence locomotor activity. The authors observed increased preference in subjects for glucose during the dark phase. However, in subsequent tests, sucrose preference during the light phase increased to the same levels as the dark phase [33]. Another study evaluated the influence of the time of day on intravenous self-administration of cocaine in Sprague-Dawley rats [31]. Four selected times of day were chosen for training: ZT01, ZT07, ZT13, and ZT19. ZT refers to *zeitgeber time*, and ZT0 is the time when lights are turned on. Groups that were trained at ZT07 and ZT19 (around the middle of light and dark phase,

respectively) appeared to exhibit enhanced sensitivity to the reinforcing properties of low-dose cocaine relative to other groups, independent of locomotor activity and cocaine pharmacokinetics [31].

Daily rhythms have also been reported for psychomotor stimulant-induced behavioral sensitization and conditioned place preference in mice. Cocaine sensitization and conditioned place preference were shown to be more evident when performed at ZT4 (light phase) than at ZT12 (the onset of dark phase) [34]. Similarly, in another study, conditioned place preference was more evident at ZT5 than at ZT20. Furthermore, pinealectomy prevented this reduction in conditioned place preference at ZT20, demonstrating a possible protective role for melatonin during the night [35]. In other words, pinealectomy rendered the animals more sensitive to the rewarding effects of cocaine administered at night. Such a conclusion may sound exquisite given that melatonin would be reducing reward, whereas reward has an active role in the normal and adaptive behavior. The answer might lie in the difference between how natural and drug-associated reward are processed throughout the day.

Natural and drug-based rewards were evaluated at different times of the day using the conditioned place preference paradigm. The chosen natural reward was mating, and amphetamine was used as a drug reward. Diurnal rhythms were observed for both mating and amphetamine-reward. The peak of the mating-based reward occurred in the middle of the dark phase (ZT17), and the peak for the low-dose amphetamine reward occurred between the end of the dark phase (ZT23) and the middle of the light phase (ZT05). Moreover, this rhythm persisted in constant conditions, reaching its peak at CT17 [36], where CT refers to circadian time, and CT0 is the onset of activity in free-running animals. Interestingly, the peak for mating reward showed the opposite results as those observed for drugs of abuse, in which subjects were less likely to develop place preference during the dark phase [34, 35]. In fact, as aforementioned, the increased intake of drugs of abuse is usually during the active phase, but the mentioned studies found it easier to induce place preference in the less active phase. Therefore, there seems to be a difference between the absolute intake of reward, association between intake and reward and, finally, the type of reward. One could hypothesize that an organism is ready to receive small rewards during the active phase (natural rewards) but would be more sensitive to excessive activation of the reward system during the inactive phase.

Given the central role of the dopaminergic system in reward, many studies have looked at the circadian fluctuation of dopamine and its metabolites in the mesolimbic reward system [30]. Most of the components of the dopaminergic system have been shown to express some degree of diurnal variation.

Using microdialysis, the extracellular concentrations of dopamine (DA) and the metabolites DOPAC and HVA were evaluated both in the striatum and nucleus accumbens in Wistar rats over a 30 h period [37]. Additionally, glutamate, gamma-aminobutyric acid (GABA), serotonin (5-HT) and its metabolite 5-HIAA were also measured. When animals were exposed to a regular light/dark schedule (12:12), the authors observed a clear circadian rhythm for DOPAC, HVA as well as glutamate and GABA in both the striatum and nucleus accumbens (NAc). Though dopamine

was also reported to follow a circadian rhythm, the peak occurred only during the first measurements of the 30 h experiment and was not observed 24 h later. Therefore, the dopamine peak was most likely only due to arousal. However, when animals were exposed to constant light during sample collection, the rhythm of dopamine concentration was more evident in both the VTA and NAc [37]. Additionally, dopamine clearance has been shown to vary diurnally in the NAc and medial prefrontal cortex [38]. Using rotating disk electrode voltammetry and adding a fixed concentration of dopamine, the authors observed the highest clearance at ZT4 [38].

The dopamine transporter (DAT) protein levels and the rate-limiting enzyme in DA synthesis, tyrosine hydroxylase (TH) is also expressed with diurnal variation [39]. Western blots analysis was performed at ZT4 and ZT20 in the NAc and caudate, both in sham-operated and SCN-lesioned (SCNx) rats [39]. In the NAc, both DAT and TH expression were higher at ZT20 than at ZT4. However, SCNx blunted the difference in DAT expression and increased the peak of TH. Caudate TH expression was slightly elevated at ZT20 in sham-operated but not in SCNx rats. These results indicate that most of the diurnal variation in the dopaminergic system is dependent on the activity in the master clock located in the SCN.

A population of neurons in the VTA was found to rhythmically fire selectively during the active phase of the rat and that the SCN indirectly projects to VTA via the medial preoptic nucleus [40]. Additionally, rhythmic expression of cFos was observed in the nucleus accumbens (NAc) core and shell in the medial prefrontal cortex and in TH-IR and non-TH-IR cells in the ventral tegmental area (VTA), with peak expression during the late night and nadirs during the late day [41].

Circadian fluctuation in anhedonia has also been described. The chronic mild stress protocol (CMS) was developed by Paul Willner's group as an animal model of depression with face, predictive and construct validity [42]. The CMS is comprised of a series of unpredictable mild stressors that within weeks leads animals to anhedonic-like behavior, observed by reduction of intake or preference for sucrose solution, which is rescued with chronic antidepressant treatment. However, despite successful use of the model in other laboratories, Paul Willner's group experienced difficulties in replicating their own results. One of the differences they noticed was that in most of the studies from other groups, sucrose preference occurred during the end of the light phase, instead of the beginning of the light phase [43]. Therefore, it was tested whether animals submitted to the CMS would show anhedonia only when tested close to the dark phase. The animals tested at the beginning of dark phase displayed reduced sucrose intake and consumption, while those tested at the light phase did not [43], suggesting a diurnal variation in sucrose reward in an animal model of depression.

In addition to decreasing responsiveness to reward, CMS also causes the appearance of many other symptoms of major depressive disorder. Behavioral changes in animals exposed to CMS include decreases in sexual and aggressive behaviors [44]. These phenotypes were observed during the dark phase of the light-dark cycle, which is the active period for the rat [45]. EEG measurement of active waking is also decreased during the dark phase [46], and a variety of sleep disorders characteristic of depression, including decreased REM sleep latency, an increased number of REM sleep episodes, and more fragmented sleep patterns were also observed [46].

3.5 Synchronization to Reward

Not only does the response to reward vary throughout the 24 h cycle, but the availability of reward can also set the internal time. When food is available during a restricted and predictable time of the day, mammals exhibit food-anticipatory activity (FAA), an increase in locomotor activity preceding the presentation of food. If food is presented during the light phase, animals shift their activity phase to the time of food availability, despite the phases of the light/dark cycle. Although the participation of the dopaminergic system may not be enough to explain this behavior, it is becoming clear that dopamine plays a central role in the FAA.

When mice received either a D1 or D2 dopaminergic receptor antagonist, the expression of FAA was significantly reduced [47]. Interestingly, the co-administration of high doses of antagonists for both receptors showed a synergic effect, promoting a more robust reduction of the FAA [47] and suggesting that the D1 and D2 receptors contribute in different ways to the expression of FAA. Consistently, the levels of dopamine and its metabolites in the striatum and midbrain were significantly increased during FAA [47], which is in agreement with the phasic release of dopamine after exposure to a conditioned stimulus associated with reward. In this case, an internal oscillator would function as the conditioned stimulus, a neutral time point that has been now associated with reward. This theoretical oscillator has been termed the food-entrainable oscillator (FEO), and its discrete localization is not clear yet. Studies point to the dorsomedial nucleus of the hypothalamus; although the SCN may not be necessary, it plays a role in the FAA.

FAA can occur when meals are provided at different intervals other than every 24 h. The availability of food 2 or 4 times a day, every 12 h or 8 h, is able to induce FAA [48]. When food is provided in intervals of 30 min, mice can anticipate up to six meal times. Interestingly, to a lesser extent, mice can anticipate food availability given every 18 h [48].

Considering that the protocol to promote FAA requires food restriction, one could assume that metabolic pathways might be more important than reward to this anticipatory activity. Notwithstanding, it has been shown that palatable daily meals can also promote FAA in rats fed ad-libitum [49]. Mistlberger & Rusak also showed that to promote FAA in free-fed animals, the palatable food needs to nutrient-rich and to have significant size, as 4 g of palatable food was insufficient, yet 2 h of free availability promoted FAA [49]. However, a daily 5 g dose of a chocolate bar is sufficient to induce FAA in rats [50]. Moreover, the palatable food also shifts the phase within the SCN, specially the dorsal area, observed by cFos expression. Additionally, cFos expression is also induced in the NAc [51], reinforcing the role of the reward system in FAA and FEO.

This anticipatory activity is not restricted to food, as drugs of abuse can also promote anticipatory activity. Animals can anticipate the administration of drugs such as cocaine [52], nicotine [53], methamphetamine [54] and fentanyl [55]. Administration of cocaine for 7 days can induce anticipatory increases of temperature ranging from 2 to 10 days following withdrawal [56]. Additionally, this

anticipatory activity remains intact in SNCx rats, reinforcing the idea that the core of this oscillator involves areas other than the SCN. These data pose the question whether the FEO is also responsible for entrainment to drugs of abuse. To answer this question, rats were placed on a 3-h daily restricted feeding regimen (every 24 h) followed by daily cocaine injections (every 25 h). Though both procedures lead to increases in temperature and activity, the 24 h rhythm induced by restricted feeding predominated over the cocaine rhythm. During free-running and drug withdrawal, the authors detected two free-running periods, one close to the feeding period and other close to the cocaine administration period. One could speculate that FEO and the drug-related oscillator are comprised of two different oscillators [56]. However, in the same way that the SCN can be uncoupled in aberrant light/dark cycles, [57], the FEO oscillator could also be uncoupled to mediate different rewards given at different times or periods.

As mentioned above, daily methamphetamine can also trigger anticipatory activity in rodents [54]. However, the most intriguing aspect involving circadian rhythms related to methamphetamine is its ability to generate a substantial increase in the free-running period when administered via drinking water. As the methamphetamine anticipatory activity seems very distinguish from the FAA, it has been theorized as being controlled by the methamphetamine-sensitive circadian oscillator (MASCO). The hyperlocomotor effect promoted by administration of psychostimulants such as methamphetamine or methylphenidate can be used to model manic-like behavior in rodents [58]. Lithium is a well-known mood stabilizer, and it is able to prevent psychostimulant-induced hyperlocomotion [59]. Curiously, lithium also lengthens the circadian period and the combination of lithium and methamphetamine leads to a dramatic increase in the circadian period [60]. The MASCO is mostly likely located extra-SCN. Arrhythmic SNCx mice show restored intrinsic rhythm after treatment with methamphetamine in drinking water [61]. Whether this reward system comprises the MASCO is not known; however, understanding it could prove helpful in the treatment of addiction.

3.6 Conclusions and Future Directions

Anhedonia is a core symptom of depression. In this chapter, we reviewed how mood varies throughout the day in both healthy and depressed individuals. Anhedonia varies according to the circadian time in animal models of depression, and the reinforcing effects of reward are also influenced by circadian rhythms. Mood variation in depressed patients can be viewed as a general reduction in amplitude of the circadian rhythms. The lower peak of mood and ability to feel pleasure could explain very complex disorders, such as severe depression and bipolar disorder.

The differential sensitivity to reward, along with the difference between natural rewards and drugs of abuse, could be involved in the initial steps leading to addiction. Moreover, the synchronization to reward could explain increased cravings for the drug at specific times. It is known that environmental cues can lead to craving.

Therefore, it is not surprising that time cues can also be involved in facilitating drug craving. Strengthening entrainment to the light/dark cycle over periods of drug abuse could be an additional tool to improve drug addiction treatment.

References

1. Lemmer B. Discoveries of rhythms in human biological functions: a historical review. Chronobiol Int. 2009;26:1019–68.
2. Hsiao FH, Yang TT, Ho RT, et al. The self-perceived symptom distress and health-related conditions associated with morning to evening diurnal cortisol patterns in outpatients with major depressive disorder. Psychoneuroendocrinology. 2010;35:503–15.
3. Doane LD, Mineka S, Zinbarg RE, et al. Are flatter diurnal cortisol rhythms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion. Dev Psychopathol. 2013;25:629–42.
4. Suzuki K, Miyamoto T, Miyamoto M, et al. Circadian variation of core body temperature in Parkinson disease patients with depression: a potential biological marker for depression in Parkinson disease. Neuropsychobiology. 2007;56:172–9.
5. van Londen L, Goekoop JG, Kerkhof GA, et al. Weak 24-h periodicity of body temperature and increased plasma vasopressin in melancholic depression. Eur Neuropsychopharmacol. 2001;11:7–14.
6. Hasler BP, Buysse DJ, Kupfer DJ, et al. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. Psychiatry Res. 2010;178:205–7.
7. Monteleone P, Maj M. The circadian basis of mood disorders: recent developments and treatment implications. Eur Neuropsychopharmacol. 2008;18:701–11.
8. Mitchell PB, Goodwin GM, Johnson GF, et al. Diagnostic guidelines for bipolar depression: a probabilistic approach. Bipolar Disord. 2008;10:144–52.
9. Kennedy SH, Tighe S, McVey G, et al. Melatonin and cortisol "switches" during mania, depression, and euthymia in a drug-free bipolar patient. J Nerv Ment Dis. 1989;177:300–3.
10. Benedetti F. Antidepressant chronotherapeutics for bipolar depression. Dialogues Clin Neurosci. 2012;14:401–11.
11. Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry. 1996;39:411–8.
12. McClung CA. How might circadian rhythms control mood? Let me count the ways. Biol Psychiatry. 2013;74:242–9.
13. Sprouse J, Braselton J, Reynolds L. Fluoxetine modulates the circadian biological clock via phase advances of suprachiasmatic nucleus neuronal firing. Biol Psychiatry. 2006;60:896–9.
14. Ashkenazy T, Einat H, Kronfeld-Schor N. We are in the dark here: induction of depression- and anxiety-like behaviours in the diurnal fat sand rat, by short daylight or melatonin injections. Int J Neuropsychopharmacol. 2009;12:83–93.
15. Prendergast BJ, Nelson RJ. Affective responses to changes in day length in Siberian hamsters (*Phodopus sungorus*). Psychoneuroendocrinology. 2005;30:438–52.
16. Becker A, Bilkei-Gorzo A, Michel K, et al. Exposure of mice to long-light: a new animal model to study depression. Eur Neuropsychopharmacol. 2010;20:802–12.
17. Gonzalez MM, Aston-Jones G. Light deprivation damages monoamine neurons and produces a depressive behavioral phenotype in rats. Proc Natl Acad Sci U S A. 2008;105:4898–903.
18. Fonken LK, Finy MS, Walton JC, et al. Influence of light at night on murine anxiety- and depressive-like responses. Behav Brain Res. 2009;205:349–54.
19. Martynhak BJ, Correia D, Morais LH, et al. Neonatal exposure to constant light prevents anhedonia-like behavior induced by constant light exposure in adulthood. Behav Brain Res. 2011;222:10–4.

20. Wirz-Justice A. Diurnal variation of depressive symptoms. Dialogues Clin Neurosci. 2008;10:337–43.
21. Morris DW, Rush AJ, Jain S, et al. Diurnal mood variation in outpatients with major depressive disorder: implications for DSM-V from an analysis of the Sequenced Treatment Alternatives to Relieve Depression Study data. J Clin Psychiatry. 2007;68:1339–47.
22. Morris DW, Trivedi MH, Fava M, et al. Diurnal mood variation in outpatients with major depressive disorder. Depress Anxiety. 2009;26:851–63.
23. Joyce PR, Porter RJ, Mulder RT, et al. Reversed diurnal variation in depression: associations with a differential antidepressant response, tryptophan: large neutral amino acid ratio and serotonin transporter polymorphisms. Psychol Med. 2005;35:511–7.
24. Reinink E, Bouhuys N, Wirz-Justice A, et al. Prediction of the antidepressant response to total sleep deprivation by diurnal variation of mood. Psychiatry Res. 1990;32:113–24.
25. Germain A, Nofzinger EA, Meltzer CC, et al. Diurnal variation in regional brain glucose metabolism in depression. Biol Psychiatry. 2007;62:438–45.
26. Wefelmeyer T, Kuhs H. Diurnal mood variation in melancholic patients and healthy controls. Psychopathology. 1996;29:184–92.
27. Murray G. Diurnal mood variation in depression: a signal of disturbed circadian function? J Affect Disord. 2007;102:47–53.
28. Golder SA, Macy MW. Diurnal and seasonal mood vary with work, sleep, and daylength across diverse cultures. Science. 2011;333:1878–81.
29. Boivin DB, Czeisler CA, Dijk DJ, et al. Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. Arch Gen Psychiatry. 1997;54:145–52.
30. Webb IC, Baltazar RM, Lehman MN, et al. Bidirectional interactions between the circadian and reward systems: is restricted food access a unique zeitgeber? Eur J Neurosci. 2009;30:1739–48.
31. Baird TJ, Gauvin D. Characterization of cocaine self-administration and pharmacokinetics as a function of time of day in the rat. Pharmacol Biochem Behav. 2000;65:289–99.
32. Roberts DC, Brebner K, Vincler M, et al. Patterns of cocaine self-administration in rats produced by various access conditions under a discrete trials procedure. Drug Alcohol Depend. 2002;67:291–9.
33. Tonissaar M, Herm L, Rinken A, et al. Individual differences in sucrose intake and preference in the rat: circadian variation and association with dopamine D2 receptor function in striatum and nucleus accumbens. Neurosci Lett. 2006;403:119–24.
34. Abarca C, Albrecht U, Spanagel R. Cocaine sensitization and reward are under the influence of circadian genes and rhythm. Proc Natl Acad Sci U S A. 2002;99:9026–30.
35. Kurtuncu M, Arslan AD, Akhisaroglu M, et al. Involvement of the pineal gland in diurnal cocaine reward in mice. Eur J Pharmacol. 2004;489:203–5.
36. Webb IC, Baltazar RM, Wang X, et al. Diurnal variations in natural and drug reward, mesolimbic tyrosine hydroxylase, and clock gene expression in the male rat. J Biol Rhythms. 2009;24:465–76.
37. Castaneda TR, de Prado BM, Prieto D, et al. Circadian rhythms of dopamine, glutamate and GABA in the striatum and nucleus accumbens of the awake rat: modulation by light. J Pineal Res. 2004;36:177–85.
38. Sleipness EP, Jansen HT, Schenk JO, et al. Time-of-day differences in dopamine clearance in the rat medial prefrontal cortex and nucleus accumbens. Synapse. 2008;62:877–85.
39. Sleipness EP, Sorg BA, Jansen HT. Diurnal differences in dopamine transporter and tyrosine hydroxylase levels in rat brain: dependence on the suprachiasmatic nucleus. Brain Res. 2007;1129:34–42.
40. Luo AH, Aston-Jones G. Circuit projection from suprachiasmatic nucleus to ventral tegmental area: a novel circadian output pathway. Eur J Neurosci. 2009;29:748–60.
41. Baltazar RM, Coolen LM, Webb IC. Diurnal rhythms in neural activation in the mesolimbic reward system: critical role of the medial prefrontal cortex. Eur J Neurosci. 2013;38(2): 2319–27.

42. Willner P, Towell A, Sampson D, et al. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology (Berl). 1987;93:358–64.
43. D'Aquila PS, Newton J, Willner P. Diurnal variation in the effect of chronic mild stress on sucrose intake and preference. Physiol Behav. 1997;62:421–6.
44. D'Aquila PS, Brain P, Willner P. Effects of chronic mild stress on performance in behavioural tests relevant to anxiety and depression. Physiol Behav. 1994;56:861–7.
45. Gorka Z, Moryl E, Papp M. Effect of chronic mild stress on circadian rhythms in the locomotor activity in rats. Pharmacol Biochem Behav. 1996;54:229–34.
46. Cheeta S, Ruigt G, van Proosdij J, et al. Changes in sleep architecture following chronic mild stress. Biol Psychiatry. 1997;41:419–27.
47. Liu YY, Liu TY, Qu WM, et al. Dopamine is involved in food-anticipatory activity in mice. J Biol Rhythms. 2012;27:398–409.
48. Luby MD, Hsu CT, Shuster SA, et al. Food anticipatory activity behavior of mice across a wide range of circadian and non-circadian intervals. PLoS One. 2012;7:e37992.
49. Mistlberger R, Rusak B. Palatable daily meals entrain anticipatory activity rhythms in free-feeding rats: dependence on meal size and nutrient content. Physiol Behav. 1987;41:219–26.
50. Mendoza J, Angeles-Castellanos M, Escobar C. A daily palatable meal without food deprivation entrains the suprachiasmatic nucleus of rats. Eur J Neurosci. 2005;22:2855–62.
51. Mendoza J, Angeles-Castellanos M, Escobar C. Entrainment by a palatable meal induces food-anticipatory activity and c-Fos expression in reward-related areas of the brain. Neuroscience. 2005;133:293–303.
52. White W, Feldon J, Heidbreder CA, et al. Effects of administering cocaine at the same versus varying times of day on circadian activity patterns and sensitization in rats. Behav Neurosci. 2000;114:972–82.
53. Gillman AG, Kosobud AE, Timberlake W. Pre- and post-nicotine circadian activity rhythms can be differentiated by a paired environmental cue. Physiol Behav. 2008;93:337–50.
54. Kosobud AE, Pecoraro NC, Rebec GV, et al. Circadian activity precedes daily methamphetamine injections in the rat. Neurosci Lett. 1998;250:99–102.
55. Gillman AG, Leffel 2nd JK, Kosobud AE, et al. Fentanyl, but not haloperidol, entrains persisting circadian activity episodes when administered at 24- and 31-h intervals. Behav Brain Res. 2009;205:102–14.
56. Jansen HT, Sergeeva A, Stark G, et al. Circadian discrimination of reward: evidence for simultaneous yet separable food- and drug-entrained rhythms in the rat. Chronobiol Int. 2012;29:454–68.
57. de la Iglesia HO, Cambras T, Schwartz WJ, et al. Forced desynchronization of dual circadian oscillators within the rat suprachiasmatic nucleus. Curr Biol. 2004;14:796–800.
58. Pereira M, Martynhak BJ, Baretta IP, et al. Antimanic-like effect of tamoxifen is not reproduced by acute or chronic administration of medroxyprogesterone or clomiphene. Neurosci Lett. 2011;500:95–8.
59. Sabioni P, Baretta IP, Ninomiya EM, et al. The antimanic-like effect of tamoxifen: behavioural comparison with other PKC-inhibiting and antiestrogenic drugs. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1927–31.
60. Mohawk JA, Miranda-Anaya M, Tataroglu O, et al. Lithium and genetic inhibition of GSK3beta enhance the effect of methamphetamine on circadian rhythms in the mouse. Behav Pharmacol. 2009;20:174–83.
61. Tataroglu O, Davidson AJ, Benvenuto LJ, et al. The methamphetamine-sensitive circadian oscillator (MASCO) in mice. J Biol Rhythms. 2006;21:185–94.

Chapter 4
Anhedonia in Children and Adolescents

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Abstract This chapter is intended to be a review of the multiple aspects of anhedona in children and adolescents. While anhedonia occurs not only in depression but also in schizophrenia and substance use disorders in this review we will focus on anhedonia in depressed youth. Anhedonia, a decreased ability to experience pleasure, is of major public health and clinical importance. It causes a sense of disengagement from the surrounding world and increases the risk of suicide. The prevalence of anhedonia is higher than the prevalence of depression and anhedonia is often underrecognized in youth. This review will address contributing factors in the development of anhedonia in children and adolescents. It will review the relationship between anhedonia and the severity and subtypes of depression in children and adolescents. The stability of anhedonia in relation to the severity of depressive episodes and outcomes of the episodes will be explored. As part of the chapter, the author will provide his own data from original research demonstrating that, at least in some depressed adolescents, anhedonia is a trait rather than a state. The literature on the neural substrate of anhedonia in children and adolescents at different developmental stages will be reviewed. The literature on anhedonia in treatment resistant depression will be explored separately. Finally, the author will review the literature on the somatic treatment approaches to treating anhedonia.

Keywords Anhedonia • Adolescents • Children • Dopamine • Ventral tegmental area • Nucleus accumbens • Mesocortical • Mesolimbal

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Abbreviations

DA	Dopamine
DBS	Deep brain stimulation
ECT	Electroconvulsive therapy
MDD	Major Depressive Disorder
NAcc	Nucleus accumbens
PFC	Prefrontal cortex
TARDIA	Treatment of SSRI-resistant depression in adolescents study
TRD	Treatment resistant depression
VmPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area

4.1 Introduction

Anhedonia, the diminished capacity to experience pleasure, is of special interest in relation to major depression because diminished pleasure is a core manifestation of the disorder [1] and is associated with higher suicidal risk [2]. Anhedonia is associated with very severe human suffering for multiple reasons. It is a major obstacle to well-being [3, 4]. It creates feeling of detachment from surrounding world [5]. Anhedonia is common among young people: almost 20 % of adolescents from the general population experience episodes characterized by marked loss of interest in things they usually enjoy. It is even more of concern because depression in young people is often underrecognized [6] and those who predominantly suffer from anhedonia rather than sadness may be particularly prone to be overlooked Moreover, the very nature of anhedonia interferes with strategies to improve mood, making it a topic of considerable clinical importance. Perhaps difficulties in recognition are related to the fact that depressed mood can be visible even in the absence of positive self-report (sad facial appearance, tearfulness, slopped posture) while anhedonia is not visible in the absence of positive self-report. Losing the ability to experience pleasure has particularly negative consequences in adolescence and young adulthood, when life course decisions are made on the basis of what is satisfying.

Anhedonia is a complex phenomenon which can be dichotomized into simple (food, sex) and higher order pleasures (e.g. esthetic pleasure) [7]. It also can be divided into anticipatory or motivational or appetitive pleasure (“wanting”) and consummatory pleasure (“liking”: when pleasurable things happen without effort) [8]. Anticipatory pleasure can be affected in demoralized but not depressed individuals while consummatory pleasure is affected in depressed individuals [9]. Anhedonia also includes hedonic awareness (i.e. cognitive awareness about receiving pleasure). For the purposes of this review we understand anhedonia as lack of both appetitive and consummatory pleasure, impairment in ability to experience both simple and higher order pleasures. All hedonic pleasures appear to involve the same brain circuits and neurotransmitters [10–12].

Core liking and wanting reactions have been found to be produced by so called hedonic hotspots in, for instance, the ventral pallidum and nucleus accumbens [8, 13]. Reduced activity in ventral striatal brain regions in response to positive stimuli has been reported so consistently [14–16] that it is considered a candidate biomarker for anhedonia [17]. It is of note that there is increasing evidence that DA is primarily linked to motivational aspects of anhedonia and not directly to the experience of pleasure [8].

4.2 Anhedonia in Adolescents

As mentioned, anhedonia is a major contributing factor to suicidal risk in adults and adolescents alike. We suggest that it is important to understand some underlying mechanisms of this association in order to develop targeted interventions. In particular we suggest the following possible explanations. Firstly, as mentioned above anhedonia is associated with feeling of detachment from surrounding world. Conversely, sense of belonging has been shown to be a protective factor from suicide in adult literature [18, 19]. Other adult studies demonstrated that "thwarted belongingness" is one of the few major risk factors for completed suicide [20]. Sense of belonging is known to be especially important during adolescence hence its relevance to suicide in anhedonic youth.

The second possible mechanism is related to decision making. Bridge et al. [21] investigated impaired decision making in adolescent suicide attempters. One of the factors contributing to suicidal behavior is poor problem-solving [22, 23]. One of the components of problem solving is decision making, the process of forming preferences, selecting and executing actions, and evaluating outcomes [24]. Bridge et al. [21] refer to the "Somatic Marker Hypothesis" that was proposed to provide a neural and cognitive framework for decision making and the influence on it by emotion [24]. Briefly, the Somatic Marker Hypothesis posits that affective signals of reward and punishment play a crucial role in decision making [25]. From a neurocognitive perspective, decision making is associated with activation of the ventromedial prefrontal cortex (VmPFC), which includes the orbitofrontal sector of the prefrontal cortex (PFC) [24, 26]. Individuals with damage to the VmPFC tend to make highly impaired decisions in real life and exhibit decision-making deficits on laboratory tasks, such as the Iowa Gambling Task (IGT), and other betting tasks [27], that simulate real-life decision making under conditions of uncertainty [25, 28]. Bridge et al. [21] investigated impaired decision making in 40 adolescent suicide attempters, 13–18 years old, and 40 never-suicidal, demographically matched psychiatric comparison subjects using the IGT [27]. Suicide attempters made more overall disadvantageous choices on the IGT relative to never-suicidal psychiatric comparison subjects. Neural bases of the construct of anhedonia that reflects deficits in hedonic capacity are also closely linked to other constructs in particular decision-making [29]. Those neural circuits include the ventral striatum, PFC regions, and afferent and efferent projections.

Thus we suggest that anhedonia is associated with suicidal risk in particular through lack of sense of belonging and through impairments in reward-based decision-making processes. We suggest that specific interventions helping anhedonic adolescents to engage into social networks as well as interventions aimed to enhance problem-solving skills may be helpful in reducing suicidal risk in this population.

4.2.1 Anhedonia and Clinical Course of Major Depressive Disorder in Adolescents

In an editorial paper [30] Rubin reviews different aspects of anhedonia and its neural substrate as it is relevant to the course of MDD in adolescents. He provides a definition of anhedonia that reflects recent advances in neurobiology: ventrtal striatum [16] contains the dopaminergic mesolimbic structures that mediate the conversion of emotional motivation into the motor behaviors of action. "Top-down" processes, such as cognitions of futility, and "bottom-up" processes, such as inflammatory and hormonal changes, work together to create the broad impact of anhedonia on living. The net result of these interwoven processes is a severe, protracted lack of reactivity to routine pleasurable experiences from which no behavior is immune. Anhedonia in this context is a hallmark symptom of depression and perhaps a "super-symptom" [30]. Later in the chapter we will discuss the role of dopamiergic mesocortical structures.

Further, in his editorial paper [30] Rubin reviews the article by McMakin et al. [31] who used the data provided by the Treatment of Selective Serotonin Reuptake Inhibitor-Resistant Depression in Adolescents (TORDIA) study [32, 33]. Based on the results of TORDIA study McMakin et al. [31] analyzed the ability of five dimensions of the Children Depression Rating Scale (CDRS)—reported depressed mood, anhedonia, somatic symptoms, morbid thoughts, and observed depression—to predict the time of remission and depression-free days over the following 6 months. Only one dimension, anhedonia, was able to predict a longer and more severe course of depression. Thus anhedonia, a key symptom in major depression, presages a poorer outcome even in the face of well-delivered, empirically based treatments. Just like psychosis or suicidality or inability to function, anhedonia precludes a conceptualization of depression as mild to moderate; its presence should compel the designation of a depression as severe [30]. Single-modality treatment, justifiable in only mild to moderate cases of depression by the current evidence base, probably has no place in the treatment of the anhedonic individual. Anhedonia may be a direct function of chronicity and may account for its critical role in poor outcomes. One other contribution from work of McMakin et al. may be to restore our understanding of the importance of anhedonia to depression and the role of anhedonia in discriminating clinical depression from normal human sadness and demoralization. As Klein et al. [9] pointed out demoralized patients often refuse to admit any form of enjoyment in response to direct inquiry but can experience pleasure passively when they are not called on to initiate or pursue pleasurable activities.

In our own study [34] we have also found chronic trait-like nature of anhedonia in hospitalized depressed adolescent and its resistance to inpatient treatment compared to such crucial symptom of depression as pessimism/demoralization which showed significant improvement during hospital stay. We examined 51 hospitalized depressed adolescents upon admission and upon discharge. We examined the change in severity of depression as measured by Beck Depression Inventory (BDI) [35], pessimism as measured by Attributional Style Questionnaire (ASQ) [36] and anhedonia as measured Pleasure Scale for Children [37] (adopted for adolescents). While in those with improvement on depression pessimism significantly improved reflecting more optimistic outlook based on scores on ASQ anhedonia showed very minimal improvement in the group as a whole and even in those adolescents who showed most marked overall improvement. This finding stayed even after adjustment for BDI scores. The finding that anhedonia is trait-like characteristic of depression is consistent with other literature [3, 38, 39].

The important question is what is underlying neurobiology that contributes to the vulnerability to anhedonia during adolescence? In a conceptual paper Davey et al. [40] described how developmentally determined changes during adolescence cause increase of vulnerability to anhedonia and how the significance of particular contributing factors changes from childhood. Davey points out that compared to preburtal depression that is more likely to be associated with an adverse family environment [41] adolescent depression is more likely to be familial [42]. Depression is usefully conceptualized as a reduction in reward sensitivity, and adolescence is a period where affective experiences become intensified and motivationally enhanced, especially in social contexts. Rather than portray depression as a failure of regulation; however, Davey et al. [40] suggest that vulnerability to depression is increased by the adolescent's enhanced capacity to anticipate different types of rewards to those that dominate childhood: rewards that are more abstract, tenuous and temporally distant, and, therefore, more easily frustrated. Thus depression in adolescence is associated with the maturation of PFC. Rejection by peers also has significant salience for adolescent depression [43–45]. It is social defeat that leads to both Depressive Disorder and anhedonia. The major underlying neural substrate of reward is the dopaminergic system, which at its core consists of the nucleus accumbens and dopaminergic projections to this area from the ventral tegmental area [46, 47]. It is the release of dopamine into the nucleus accumbens that is the principal event for the translation of motivation into action, and for driving of behaviors that seek to attain goals [48]. Adolescence sees substantial development of the dopaminergic system. As mentioned above DA is primarily linked to motivational aspects of anhedonia as opposed to consummatory pleasure [8] and thus more linked to depression than demoralized state or normal sadness [9]. The functional significance of the dopaminergic system more extensive integration with the PFC, where it has a role in shaping, is that the nature of the rewards that can be represented becomes more sophisticated, and thus an adolescent is able to be motivated by, and to respond to, rewards that are more distal and complex. Such rewards are frequently encountered in the increasingly complicated social milieu that emerges during

adolescence. Indeed, it may be part of the evolved design of the human brain that the capacity to be increasingly motivated and engaged by distal and abstract rewards emerges during a phase of life when the successful negotiation of such rewards, particularly in the context of success in peer and romantic relationships, is a critical determinant of inclusive fitness [49]. Relative shift to meso*cortical* dominance in adolescence compared to meso*limbic* dominance in pre-adolescence and increased projection of dopaminergic fibers from VTA is connected to ability and need of adolescents to pursue more distant and more complex rewards (peer status, romantic relationships) that are however tenuous and more readily frustrated compared to immediate rewards and may lead to the state of social defeat and anhedonia. The hypothetical clinical vignette presented in the paper [3] illustrates case of adolescent who is distressed over lack of friends and not being popular. He develops a plan how to improve his situation by being invited to the party by his only friend. At the party he is ignored and experiences social defeat. As a result he develops anhedonia and then full blown depression. This well familiar clinical scenario illustrates association of anhedonia with social defeat resulting from frustration of particular distant goal. We suggest that also it illustrates significance of anhedonia as a possible gateway to depression among adolescents. The fact that anhedonia is often prodromal to Major Depressive Disorder is supported by other literature [50].

The role of social isolation in developing anhedonia is supported by animal studies which can create social isolation and follow prospectively the development of anhedonia. Niwa et al. [51] showed that that maintaining mice in individual cages for 5 weeks during postnatal brain maturation, which may mimic separation from parents and family members and social isolation in humans [52], critically affects their adult behavioral patterns relative to those of mice raised in normal group housing [53]. The mice most susceptible to the negative effect of social isolation compared to other groups had genetically predetermined significantly decreased total and extracellular levels of dopamine in the Frontal Cortex while no alterations in levels of norepinephrine and serotonin were observed. This dopaminergic change may be more specific to the projections originating from the VTA, because there was no change in the total levels of dopamine in the caudate putamen.

Niwa et al. investigated the role of glucocortocoids [51] in developing anhedonia. She described an underlying mechanism in which glucocorticoids link adolescent stressors to epigenetic controls in neurons. In a mouse model of this phenomenon, a mild isolation stressor affects the mesocortical projection of dopaminergic neurons in which DNA hypermethylation of the tyrosine hydroxylase gene is elicited, but only when combined with a relevant genetic risk for neuropsychiatric disorders. These molecular changes are associated with several neurochemical and behavioral deficits that occur in this mouse model, all of which are blocked by a glucocorticoid receptor antagonist. The biology and phenotypes of the mouse models resemble those of psychotic depression. In preclinical model administering the glucocorticoid receptor (GR) antagonist prevents development of psychotic depression. These interesting experimental findings are intuitive and

demonstrate that pathogenic factors leading to development of anhedonia can be lessened by overall reduction of stress.

Evidence that depression and altered hedonic capacity is associated with altered reward functioning has emerged from other experimental paradigms in adult studies. Electroencephalographic studies have shown that activity in the left dorsolateral prefrontal cortex is correlated with stronger bias in responding to reward-related cues [54]. Trembley et al. [55] showed that the dopaminergic reward system is altered in anhedonic depressed individuals by demonstrating that amphetamines have enhanced rewarding effects in depressed subjects, correlated with the severity of *anhedonia.* This is perhaps a surprising result that may reflect disinhibition of dopaminergic neurons that are hypoactive at baseline.

4.3 Anhedonia in Children

Studies provide controversial results with regard to prevalence of anhedonia in children compared to adolescents. Childhood anhedonia has been characterized differently than adolescent anhedonia. Children have been said to present with other developmentally relevant symptoms of depression such as e.g. separation anxiety, somatic complaints etc. [56, 57] rather than anhedonia. However it does not mean that children do not experience anhedonia. For example in the study of Sorensen et al. [58] 199 consecutive child psychiatric patients were interviewed using a semi-structured diagnostic interview such as Schedule for Affective Disorders and Schizophrenia for Children- Present Lifetime version (K-SADS-PL) [59]. Comorbidity and symptoms were compared across age and gender. The subjects were first-ever admitted children, aged 8–13 years consecutively admitted to the Psychiatric Hospital for Children and Adolescents, Risskov, Denmark in the study period of 1 1/2 year. Twelve children were inpatients, 187 were outpatients. A total of 52 girls and 147 boys were interviewed. Forty-two (21 %) children, 23 boys and 19 girls, had current MDD. The data were analyzed separately for younger group of age 8 to 11 and for older group age 12–13. While there was a significant difference in anhedonia between those two groups, ten children in the younger group (43.5 % of those with MDD) exhibited anhedonia. It is of note that in the age group 12–13 i.e. young adolescents the proportion of subjects exhibiting anhedonia was as high as 73.7 %. In our opinion the significance of these data is that younger children with MDD do experience anhedonia and prevalence of anhedonia in *young* adolescents is high. Fu-I and Wang [60] studied 58 patients of age 5–17 meeting DSM-IV criteria for Major Depressive Disorder as determined via CDRS-Revised Version. The prevalence of anhedonia in the whole sample was 72.4 % (very close to 73.7 % in young adolescents of 12–13 years of age in Sorensen et al. study). Patients were divided into two age groups: 5–9 and 10–17. In Fu-I and Wang study the prevalence of anhedonia did not statistically differ between two age groups and 5–9 year-old children with MDD showed high prevalence of anhedonia.

4.3.1 Neurobiology of Anhedonia in Children

There is a relative paucity of neurobiological research on childhood anhedonia compared to adolescent depression. A study by Miller [61] stands out in this regard as it is concerned with both children and adolescents. Miller states that one of the most consistent observations among factor analytic studies of depression is that substantial unique variance in symptomatology is accounted for by a decreased hedonic capacity factor, characterized by items such as sad mood, anhedonia, loss of interest, lack of pleasure and enjoyment, decreased energy, fatigability, daytime sleepiness, psychomotor retardation, and walking or talking slower. A hedonic capacity construct has biological significance due to relationships with brain reward systems and adaptive processes. A large body of basic research has examined the brain reward system at multiple levels of analysis. The current adaptive systems framework suggests that early-onset depression may be characterized by deficits in hedonic capacity and dysregulation of the brain reward system. This hypothesis would be supported by neurobiological evidence that youth with early onset mood disorders have prefrontal and limbic abnormalities marked by disrupted brain development. This hypothesis also relates to molecular genetic evidence implicating neurotrophin gene variants in childhood-onset mood disorders. Such genetic polymorphisms may fundamentally alter brain development and adaptive processes. In addition, the mechanisms of reward-related prefrontal neurotransmitter and neurotrophic processes have implications for understanding the efficacy of antidepressant drugs and how such processes may change during development. Furthermore, promoting healthy mastery and reward-related behaviors, such as regular aerobic exercise, may be an important component of treating and preventing depression.

4.3.2 Clinical, Social and Biological Correlates of Anhedonia in Children

One direction of research that is relevant to childhood anhedonia is related to sleep. Liu et al. [62] studied sleep disturbances in childhood depression. Across sleep-disturbed children, those with both insomnia and hypersomnia had a longer history of illness, were more severely depressed, and were more likely to have anhedonia, weight loss, psychomotor retardation, and fatigue than were those with either insomnia or hypersomnia.

The concept of low positive emotionality [PE] is closely related to anhedonia. Shankman et al. [63] studied low PE in children. Low positive emotionality (PE; e.g., listlessness, anhedonia, and lack of enthusiasm) has been hypothesized to be a temperamental precursor or risk factor for depression. The study sought to evaluate the validity of this hypothesis by testing whether low PE children have similar external correlates of EEG asymmetry as individuals with depression. Children classified as having low PE at age 3 exhibited an overall asymmetry at age 5–6 with

less relative activity in the right hemisphere. This asymmetry appeared to be largely due to a difference in the posterior region because children with low PE exhibited decreased right posterior activity whereas high PE children exhibited no posterior asymmetry. These findings support the construct validity of the hypothesis that low PE may be a temperamental precursor or risk factor for depression.

Luby et al. [64] provided evidence of the melancholic subtype of depression in depressed preschoolers. This study investigated whether a melancholic subtype similar to that established in depressed adults can be identified in depressed preschool children. A final group total of 156 preschool children between the ages of 3.0 and 5.6 years and their caregivers underwent a comprehensive psychiatric assessment that included a structured psychiatric interview modified for young children. The clinical characteristics of four study groups (N = 156) were compared: depressed preschoolers with anhedonia, depressed preschoolers without anhedonia ("hedonic"), a psychiatric comparison group with DSM-IV attention deficit hyperactivity disorder and/or oppositional defiant disorder, and a healthy comparison group. Fifty-four depressed preschoolers were identified, and 57 % of this depressed group was anhedonic, a symptom deemed to be highly developmentally and clinically significant when arising in the preschool period. The anhedonic depressed subgroup identified was characterized by greater depression severity, alterations in stress cortisol reactivity, increased family history of major depressive disorder, and increased frequency of psychomotor retardation as well as other melancholic symptoms, such as a lack of brightening in response to joyful events.

Hecht et al. [43] demonstrated the role of peer status in depression across a wide range of ages. Participants were 1,687 students in fourth, sixth, seventh, eighth, ninth, and eleventh grades from a midsized Midwestern city. Based on previous studies, it was hypothesized that rejected and neglected youths would report greater depressive symptomatology than other peers. In addition, aggressive-rejected youth were predicted to report more interpersonal problems while submissive-rejected youths were expected to report more anhedonia. There were no sociometric group differences on global scores of depression as measured by the Children's Depression Inventory. However, there were specific findings distinguishing aggressive- and submissive-rejected youths. Aggressive-rejected youths reported more interpersonal problems and feelings of ineffectiveness, while the neglected and submissive-rejected youths reported more anhedonia. Taken together, such differences provide support for differentiating among types of rejected students and suggest that different interventions may be necessary to address the needs of these youths.

Measurement of anhedonia in prepubertal children presents a challenge. In prepubertal children motor activity is related to anhedonia. In a study by Aronen et al. [65] studied locomotor activity was quantified in 27 consecutively selected hospitalized prepubertal children. Activity was measured in 5-min epochs over a period of 72 h using belt-worn monitors. Activity measures correlated with clinical ratings of sadness, low self-esteem, anhedonia, and physical complaints, and to a lesser degree with ratings of hypoactivity, fatigue, and slow speech. Anhedonia was conceptualized as loss of interest and low capacity for fun.

Ability to enjoy and appreciate humor is a vital part of human well being and normal development and is related to hedonic state. Neuroimaging studies conducted with adults indicate that humor activates specific brain regions, including the temporo-occipito-parietal junction (TOPJ), involved in incongruity resolution [66], and mesolimbic regions including NAcc, involved in reward processing [67]. In a study by Neely et al. [68] 15 typically developing children (ages 6–12 years) were invited to watch and respond to video clips while neural activity was imaged with a 3 T GE Discovery MR750 scanner. Before presentation during functional imaging, the clips were evaluated by age-matched controls and were representative of three categories: Funny, Positive (enjoyable but not funny), and Neutral. The authors found TOPJ and mesolimbic activation in children's response to humor, suggesting these regions may form a humor-essential neural network already present in childhood. The authors observed greater activation in the inferior frontal gyrus and NAcc in younger participants, indicating humor activation intensity changes during development. It is of note that nucleus accumbens played a major role thus showing that same brain structure is involved into hedonic activity in young children and adolescents.

A major aspect of anhedonia in children is decreased interest in play. Trezza et al. [69] note that like human children, most young mammals devote a significant amount of time and energy playing together, and social play is fun. Although social play is very pleasurable, it is more than just a frivolous activity: it is crucial for the development of behavioral flexibility, the acquisition of social and cognitive competence, and the maintenance of group cohesion. Social play is a natural reinforcer, and the neurotransmitter systems intimately implicated in the motivational, pleasurable and cognitive aspects of natural and drug rewards such as opioids, endocannabinoids, dopamine and norepinephrine, play an important modulatory role in the performance of social play.

4.4 Treatment Approaches to Anhedonia

It has been demonstrated above that as Rubin [30] put it "Joy returns last" i.e. anhedonia is last symptom of Major Depressive Disorder to go which contributes to treatment resistance and chronicity of Major Depressive Disorder in adolescents. Hence exploring more specific approaches to treatment of the cases with significant anhedonia is crucial. We were not able to find any literature on specific treatments of anhedonia in adolescents or children. Therefore in this section we will review specific or novel approaches for treating anhedonia in adults as they potentially may be applied to treating anhedonic adolescents and children in the future.

DSM-5 like DSM-IV retained the specifier of depression "with melancholic features," and retains in the criterion A that either unreactive mood or pervasive anhedonia, but not both are necessary. Rush and Weissenburger [70] state in their study of adult depressed patients that melancholic symptom features are predictive

of a positive response to ECT and to tricyclic antidepressants in the severely ill. Key features include psychomotor retardation, unreactive mood, pervasive anhedonia, and distinct quality of mood.

One example of specific treatment of anhedonia based on its neurological underpinnings is described by Bewrnick et al. [71] for adult patients with very severe TRD. Deep brain stimulation (DBS) allows modulation of brain regions that are dysfunctional in depression. Since anhedonia is a feature of depression and there is evidence of dysfunction of the reward system, DBS to the nucleus accumbens (NAcc) might be promising. The NAcc was selected because of its central role in reward circuitry [72, 73] and its dysfunction regarding rewarding stimuli in patients with major depression [16, 55]. In the Bewrnick et al. study [71] ten adult patients suffering from very resistant forms of depression, not responding to pharmacotherapy, psychotherapy, or ECT, were implanted with bilateral DBS electrodes in the NAcc. Twelve months following initiation of DBS treatment, five patients reached 50 % reduction of the Hamilton Depression Rating Scale (responders, HDRS = 15.4 [± 2.8]). The number of hedonic activities increased significantly. Ratings of anxiety (Hamilton Anxiety Scale) were reduced in the whole group but more pronounced in the responders. The [18 F]-2-fluoro-2-deoxy-D-glucose positron emission tomography data revealed that NAcc-DBS decreased metabolism in the subgenual cingulate and in prefrontal regions including orbital prefrontal cortex. A volume of interest analysis comparing responders and nonresponders identified metabolic decreases in the amygdala. Thus in this pioneer study authors demonstrated antidepressant and antianhedonic effects of DBS to NAcc in patients suffering from TRD. In contrast to other DBS depression studies, there was also an antianxiety effect. These effects are correlated with localized metabolic changes.

Shelton and Tomarken [74] present a therapeutic heuristic that derives, in part, from a body of research that suggests that symptoms of mood disorders can be separated into three distinct components: somatic anxiety, which is most prominent in anxiety disorders, such as panic; anhedonia or low positive affect, which is most specific to depression; and general distress, which is present with both anxiety and depressive disorders. They state that positive affect, the dimension of reward-oriented motivation and enjoyment, appears to be most dependent on dopamine and, indirectly, norepinephrine. They further state that serotonergic agents would be chosen for monotherapy or augmentation for symptoms of distress. Alternatively, catecholaminergic drugs would be the first choice for anhedonia and decreased motivation.

4.5 Conclusion and Future Directions

There are multiple aspects of anhedonia that make it a unique symptom in depressed youth. It tends to be chronic and has trait-like characteristics in depressed adolescents. It is the last symptom to resolve in Major Depressive

Disorder, especially in treatment resistant depression in adolescents. It is related to social defeat and may be a prodromal symptom of depression. Animal experiments confirm the role of social isolation in anhedonia and demonstrate the moderating role of glucocorticoids. Anhedonia is related to increased suicidal risk in adolescents. Anhedonia leads to a sense of detachment from the surrounding world. A sense of not belonging as well as impaired decision making based on reward processes are probably two of the underlying mechanisms related to increased suicidal risk in adolescents due to anhedonia. While depression is highly prevalent in adolescents, anhedonia is even more prevalent; and yet it is often unrecognized, especially in those who suffer predominantly from anhedonia rather than from sadness. Anhedonia helps make a distinction between normal sadness and demoralization as opposed to Major Depressive Disorder. Adolescents experience a shift from mesolimbic to mesocortical connections alongside maturation of the prefrontal lobes. This process enhances the capacity to pursue more distal and more abstract goals, but those goals are tenuous and easily frustrated; this contributes to increased vulnerability to anhedonia in adolescents. Different dimensions of anhedonia—namely lack of enjoyment of lower and higher order pleasures, as well as motivational and consummatory pleasure—are mediated through the same neurotransmitters and neural substrates. Dopamine plays a crucial role in anhedonia, especially in motivational anhedonia. Neural substrates include ventral striatal brain regions and nucleus accumbens (NAcc). The release of dopamine to NAcc is a crucial event in the translation of motivation into behavior. Anhedonia is most common in the melancholic type of depression—a definition that is retained in DSM-5.

Very little studies are available on anhedonia in children. Like in adolescents, it is associated mostly with the melancholic type of Major Depressive Disorder. The neural reward circuitry in children with anhedonia includes prefrontal and limbic regions in a manner similar to adolescents. Lack of social play and sleep disturbances are associated with anhedonia in children. Childhood anhedonia is less familial than anhedonia in adolescents, and is associated more with problems in the family environment. Promising new treatments, in particular DBS of NAcc as well as established treatments such as ECT, have demonstrated effectiveness in anhedonic adults.

Future direction of research should include replication investigations of mentioned above promising treatments in older adolescents, and then in possibly younger age groups. Longitudinal studies of anhedonia in depressed adolescents and children are needed to further learn about trait-like vs. state-like characteristics of anhedonia. Significant research is necessary to learn more about childhood anhedonia—its nature, its clinical characteristics, and its response to treatment.

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References

1. Klein DF. Depression and anhedonia. In: Clark DC, Fawsett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1987. p. 1–14.
2. Fawcett J, Scheftener WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry. 1990;147:1189–94.
3. Hasler G, Drevets WC, Manji HK, et al. Discovering endophenotypes for major depression. Neuropsychopharmacology. 2004;29(10):1765–81.
4. Kringelbach ML, Berridge KC. The neuroscience of happiness and pleasure. Soc Res. 2010;77:659–78.
5. Brown LH, Silvia PJ, Myin-Germeys I, et al. When the need to belong goes wrong: the expression of social anhedonia and social anxiety in daily life. Psychol Sci. 2007;18:778–82.
6. Zuckerbrot RA, Jensen PS. Improving recognition of adolescent depression in primary care. Arch Pediatr Adolesc Med. 2006;160:694–704.
7. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374–82.
8. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55.
9. Klein DF, Gittelman R, Quitkin F, et al. Diagnosis and drug treatment of psychiatric disorders: adults and children. Baltimore: Williams & Wilkins; 1980.
10. Kringelbach ML, Berridge KC. Towards a functional neuroanatomy of pleasure and happiness. Trends Cogn Sci. 2009;13:479–87.
11. Kringelbach ML. The hedonic brain: a functional neuroanatomy of human pleasure. In: Kringelbach ML, Berridge KC, editors. Pleasures of the brain. New York: Oxford University Press; 2010.
12. Pecina S, Smith KS, Berridge KC. Hedonic hot spots in the brain. Neuroscientist. 2006;12:500–11.
13. Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci. 2007;27:1594–605.
14. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. NeuroImage. 2009;46:327–37.
15. Forbes EE, Hariri AR, Martin SL, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry. 2009;166:64–73.
16. Epstein J, Pan H, Kocsis JH, et al. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. Am J Psychiatry. 2006;163(10):1784–90.
17. Dichter GS. Anhedonia in unipolar depressive disorder: a review. Open Psychiatry J. 2010;4:1–9.
18. McLaren S, Challis C. Resilience among men farmers: the protective roles of social support and sense of belonging in the depression-suicidal ideation relation. Death Stud. 2009;33(3):262–76.
19. Hill DL. Relationship between sense of belonging as connectedness and suicide in American Indians. Arch Psychiatr Nurs. 2009;23(1):65–74.
20. Van Orden KA, Witte TK, Gordon KH, et al. Suicidal desire and the capability for suicide: tests of the interpersonal-psychological theory of suicidal behavior among adults. J Consult Clin Psychol. 2008;76(1):72–83.
21. Bridge JA, McBee-Strayer SM, Cannon EA, et al. Impaired decision making in adolescent suicide attempters. J Am Acad Child Adolesc Psychiatry. 2012;51(4):394–403.
22. Arie M, Apter A, Orbach I, et al. Autobiographical memory, interpersonal problem solving, and suicidal behavior in adolescent inpatients. Compr Psychiatry. 2008;49(1):22–9.
23. Wilson KG, Stelzer J, Bergman JN, et al. Problem solving, stress, and coping in adolescent suicide attempts. Suicide Life Threat Behav. 1995;25(2):241–2.

24. Ernst M, Paulus MP. Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. Biol Psychiatry. 2005;58:597–604.
25. Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. Cereb Cortex. 2000;10(3):295–307.
26. Rudebeck PH, Bannerman DM, Rushworth MF. The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behavior, and decision making. Cogn Affect Behav Neurosci. 2008;8(4):485–97.
27. Rogers RD, Owen AM, Middleton HC, et al. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. J Neurosci. 1999;19(20):9029–38.
28. Bechara A, Damasio AR, Damasio H, et al. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994;50(1–3):7–15.
29. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35(1):68–77.
30. Rubin DH. Joy returns last: anhedonia and treatment resistance in depressed adolescents. J Am Acad Child Adolesc Psychiatry. 2012;51(4):353–5.
31. McMakin DL, Olino TM, Porta G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. J Am Acad Child Adolesc Psychiatry. 2012;51(4):404–11.
32. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA. 2008;299:901–13.
33. Asarnow JR, Emslie G, Clarke G, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. J Am Acad Child Adolesc Psychiatry. 2009;48:330–9.
34. Gutkovich Z, Morrissey RF, Espaillat RK, et al. Anhedonia and pessimism in depressed hospitalized adolescents. Depression research and treatment. Special issue "multidisciplinary approach to child and adolescent depression." 2011;2011:Article ID 795173.
35. Beck AT, Beamesderfer A. Assessment of depression. The depression inventory. Mod Probl Pharmacopsychiatry. 1974;7:151–69.
36. Kaslow NJ, Nolen-Hoeksema S. Children's attributional style questionnaire – revised. Unpublished manuscript, Atlanta, Emory University; 1991.
37. Kazdin AE. Evaluation of the pleasure scale in the assessment of anhedonia in children. J Am Acad Child Adolesc Psychiatry. 1989;28:364–72.
38. Farmer A, Mahmood A, Redman K, et al. A sib-pair study of the temperament and character inventory scales in major depression. Arch Gen Psychiatry. 2003;60(5):490–6.
39. Oquendo MA, Barrera A, Ellis SP, et al. Instability of symptoms in recurrent major depression: a prospective study. Am J Psychiatry. 2004;161(2):255–61.
40. Davey CG, Yucel M, Allen NB. The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. Neurosci Biobehav Rev. 2008;32(1):1–19.
41. Harrington R, Rutter M, Fombonne E. Developmental pathways in depression: multiple meanings, antecedents, and endpoints. Dev Psychopathol. 1996;8(4):601–16.
42. Silberg J, Rutter M, Neale M, et al. Genetic moderation of environmental risk for depression and anxiety in adolescent girls. Br J Psychiatry. 2001;179:116–21.
43. Hecht DB, Inderbitzen HM, Bukowski AL. The relationship between peer status and depressive symptoms in children and adolescents. J Abnorm Child Psychol. 1998;26(2):153–60.
44. Prinstein MJ, Aikins JW. Cognitive moderators of the longitudinal association between peer rejection and adolescent depressive symptoms. J Abnorm Child Psychol. 2004;32(2):147–58.
45. Vernberg EM. Psychological adjustment and experiences with peers during early adolescence: reciprocal, incidental, or unidirectional relationships? J Abnorm Child Psychol. 1990;18(2):187–98.
46. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry. 2003;160(6):1041–52.

47. Nestler EJ, Carlezon WA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006;59(12):1151–9.
48. Panksepp J. Affective neuroscience: the foundations of human and animal emotions. New York: Oxford University Press; 1998.
49. Weisfeld GE, Janisse C. Some functional aspects of human adolescence. In: Ellis BJ, Bjorklund DF, editors. Origins of the social mind: evolutionary psychology and child development. New York: Guilford Press; 2004. p. 189–218.
50. Dryman A, Eaton WW. Affective symptoms associated with the onset of major depression in the community: findings from the US National Institute of Mental Health Epidemiologic Catchment Area Program. Acta Psychiatr Scand. 1991;84(1):1–5.
51. Niwa M, Jaaro-Peled H, Tankou S, et al. Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. Science. 2013;339(6117):335–9.
52. Morgan C, Charalambides M, Hutchinson G, et al. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. Schizophr Bull. 2010;36:655–64.
53. Niwa M, Matsumoto Y, Mouri A, et al. Vulnerability in early life to changes in the rearing environment plays a crucial role in the aetiopathology of psychiatric disorders. Int J Neuropsychopharmacol. 2011;14(4):459–77.
54. Pizzagalli DA, Sherwood RJ, Henriques JB, et al. Frontal brain asymmetry and reward responsiveness: a source-localization study. Psychol Sci. 2005;16(10):805–13.
55. Tremblay LK, Naranjo CA, Graham SJ, et al. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. Arch Gen Psychiatry. 2005;62(11):1228–36.
56. Ryan ND, Puig-Antich J, Ambrosini P, et al. The clinical picture of major depression in children and adolescents. Arch Gen Psychiatry. 1987;44(10):854–61.
57. Carlson GA, Kashani JH. Phenomenology of major depression from childhood through adulthood: analysis of three studies. Am J Psychiatry. 1988;145(10):1222–5.
58. Sorensen MJ, Nissen JB, Mors O, et al. Age and gender differences in depressive symptomatology and comorbidity: an incident sample of psychiatrically admitted children. J Affect Disord. 2005;84(1):85–91.
59. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36(7):980–8.
60. Fu-I L, Wang YP. Comparison of demographic and clinical characteristics between children and adolescents with major depressive disorder. Rev Bras Psiquiatr. 2008;30(2):124–31.
61. Miller A. Social neuroscience of child and adolescent depression. Brain Cogn. 2007;65(1):47–68.
62. Liu X, Buysse DJ, Gentzler AL, et al. Insomnia and hypersomnia associated with depressive phenomenology and comorbidity in childhood depression. Sleep. 2007;30(1):83–90.
63. Shankman SA, Tenke CE, Bruder GE, et al. Low positive emotionality in young children: association with EEG asymmetry. Dev Psychopathol. 2005;17(1):85–98.
64. Luby JL, Mrakotsky C, Heffelfinger A, et al. Characteristics of depressed preschoolers with and without anhedonia: evidence for a melancholic depressive subtype in young children. Am J Psychiatry. 2004;161(11):1998–2004.
65. Aronen ET, Teicher MH, Geenens D, et al. Motor activity and severity of depression in hospitalized prepubertal children. J Am Acad Child Adolesc Psychiatry. 1996;35(6):752–63.
66. Samson AC, Hempelmann CF, Huber O, et al. Neural substrates of incongruity-resolution and nonsense humor. Neuropsychologia. 2009;47:1023–33.
67. Mobbs D, Greicius MD, Abdel-Azim E, et al. Humor modulates the mesolimbic reward centers. Neuron. 2003;40:1041–8.
68. Neely MN, Walter E, Black JM, et al. Neural correlates of humor detection and appreciation in children. J Neurosci. 2012;32(5):1784–90.
69. Trezza V, Baarendse PJ, Vanderschuren LJ, et al. The pleasures of play: pharmacological insights into social reward mechanisms. Trends Pharmacol Sci. 2010;31(10):463–9.

70. Rush AJ, Weissenburger JE. Melancholic symptom features and DSM-IV. Am J Psychiatry. 1994;151(4):489–98.
71. Bewernick BH, Hurlemann R, Matusch A, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry. 2010;67(2):110–16.
72. Schlaepfer TE, Cohen MX, Frick C, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology. 2008;33(2):368–77.
73. Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci. 2008;10(3):291–9.
74. Shelton RC, Tomarken AJ. Can recovery from depression be achieved? Psychiatr Serv. 2001;52:1469–78.

Chapter 5
Musical Anhedonia and Visual Hypoemotionality: Selective Loss of Emotional Experience in Music and Vision

Masayuki Satoh

Abstract Anhedonia can occur selectively in a single modality, and the investigation of such symptoms has been carried out through case studies of brain-damaged patients. In this article, I present the main principles and methodologies of neuropsychology. The neural bases of emotion, including the limbic system and reward circuitry, are then described. Finally, based on the reported literature, rare cases exhibiting a selective loss of emotional experience in a single sensory modality, visual hypoemotionality and musical anhedonia (esthetic amusia), are described. The findings suggest that emotion perception and emotional experience have independent neural bases in the brain, at least partially. Neuropsychological approaches will continue to be useful to clarify the mental processing of emotion and open the door to approach the neural mechanisms of beauty appreciation.

Keywords Anhedonia • Emotion • Visual hypoemotionality • Musical anhedonia • Esthetic amusia

Abbreviations

AVM	Arterio-venous malformation
BLA	Basolateral nucleus of amygdala
CeA	Central nucleus of amygdala
CT	Computed tomography

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ILF Inferior longitudinal fasciculus
IQ Intelligence quotient
MRI Magnetic resonance imaging
SCR Skin conductance response
VTA Ventral tegmental area
WAIS Wechsler Adults Intelligence Scale

5.1 Introduction

5.1.1 Definition of Anhedonia

Anhedonia is defined as the inability to experience pleasure from events that are typically considered enjoyable [1]. It is not restricted only to enjoyable stimuli, but also to all kinds of emotions including sadness, fear, disgust, and anger. Anhedonia is regarded as a cardinal feature of affective disorders in psychiatry. However, through the assessment of various cases of anhedonia, several neuropsychological findings have revealed a new horizon regarding the emotional processing of each sensory modality. In this review, I will illustrate some striking cases of anhedonia with a selective loss of emotional responses in visual and auditory modalities.

5.1.1.1 Neuropsychological Approach

5.1.1.1.1 Neuropsychology

Neuropsychology is the study of the relationship between brain function and behavior [2]. It has been established by connecting symptoms with specific brain lesions. Paul Broca (1824–1880) has been called the founder of neuropsychology. In 1861, he reported a case that had been able to speak only the word “tan” for 21 years [3]. The patient’s name was Leborgne, but he was called Monsieur Tan. He could understand spoken language and his intellectual functions were normal. Broca thought as follows: “The patient suddenly became unable to speak. Possibly, a cerebrovascular attack occurred. Other mental functions were preserved. Therefore, that attack destroyed the brain region that participated in speaking. In other words, if I can know the site of lesion in Leborgne’s brain, we can know the localization of speaking in the human brain.” The patient suffered from phlegmonous cellulitis, and 1 week after the examination he died. Broca autopsied the patient, and ascertained an old infarction at the posteroinferior portion of the left frontal lobe. That was the first case of aphasia and of scientific evidence that the human brain had a localization of a specific cognitive function.

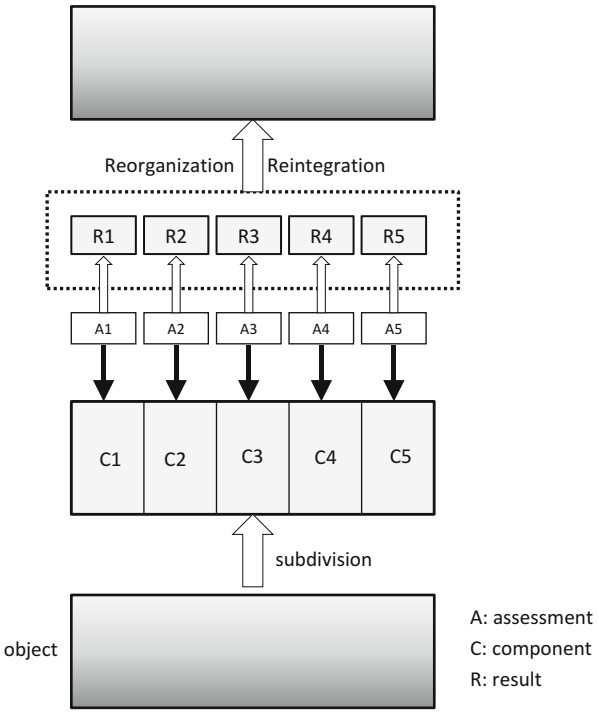

Fig. 5.1 Law of division

5.1.1.1.2 Three Principles of Neuropsychology

The Law of Division (Fig. 5.1)

The law of division was first described by Descartes in the seventeenth century, and is a fundamental principle of modern science even now. This law consists of three steps: subdivision, estimation, and reorganization or integration. In order to understand something, the object is subdivided as small as possible. The estimation is carried out to each subdivided component. Then, the results of all components are integrated and reorganized, and we can understand the object as a whole. Many neuropsychological tests are designed based on the law of division. For example, the IQ (intelligence quotient) is broadly used to show the intellect of a person. The IQ is acquired by the results of the Wechsler Adults Intelligence Scale (WAIS). The WAIS includes tasks regarding knowledge, calculations, figures, visuospatial skills, and others. Subjects perform each task, and the results are compared with those of standard data from their age group. The revised scores of all tasks are summed, and the total score is regarded as the intellect of that person. According to the law of division, the whole is the total sum of all parts. In other words, one plus one is always two.

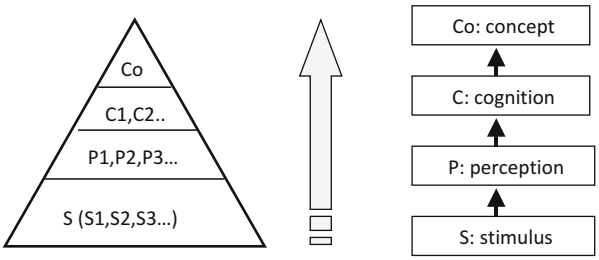

Fig. 5.2 Bottom up

Bottom Up (Fig. 5.2)

In the human brain, objects are recognized via serial partial processing. First, the stimulus is subdivided, and each subdivision is perceived. It is then recognized and finally, the concept is formed. In neuropsychology, this bottom up processing is called the "cognitive pyramid", with vision systems being the most studied. Each occipital field participates in the perception of a feature of the object: V3, V4, and V5 participate in spatial information, color, and movement, respectively. V3 and V5 belong to the parietal visual pathway that relates to the vision of movement. V4 connects to inferior temporal regions. This route is called the temporal visual pathway and participates in the vision of shapes. In the auditory system as well, sound is subdivided into two kinds of information at the level of the internal ear: pitch and volume. Pitch is perceived at the site of the basement membrane that registers the largest amplitude, and the amplitude itself codes the volume of that sound. Current research in neuropsychology is now climbing up the cognitive pyramid from the stage of perception to recognition step-by-step.

Of course, we also know that there is another form of mental processing in the human brain that may be even more important: top-down processing. In psychology, this is known as the German word Geschtalt. This conceptualization insists that an object has a meaning as a whole that cannot be divided into parts. The whole is more than the total sum of the parts, and one plus one is more than two. Although we realize its importance, the associated mental processing remains unknown, and we do not currently have the methodology to investigate it scientifically.

Double Dissociation (Fig. 5.3)

Information processing is performed in serial order, similar to a flow chart of a computer program. Now we know that due to an impairment of processing 'A' and 'B', the symptoms 'a' and 'b' occur, respectively. If there are patients with symptom 'a' and without 'b', and with 'b' without 'a', it is reasonably concluded that an independent processing of 'A' and 'B' occurs in the brain. This rule is called "double dissociation". For example, there are patients who cannot speak but have a preserved hearing of language, which is known as motor aphasia. On the contrary, other patients demonstrate intact speaking with the loss of hearing ability, termed sensory aphasia. Therefore, we regard that the ability of speaking and understanding

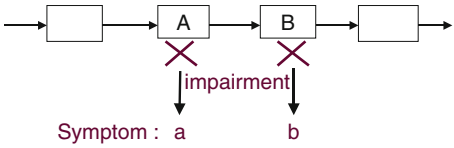

Fig. 5.3 Double dissociation

language is independent in the brain, and have independent neural bases, at least partially. Neuropsychology is built upon a large number of case studies that illustrate double dissociation.

5.2 Neural Basis of Emotion

5.2.1 Hierarchy of the Brain

There are some researchers who believe that the brain has a hierarchical organization. The first theory was proposed by John Hughlings Jackson (1835–1911). Jackson thought that the brain had two neural systems at higher and lower levels that had opposite functions. For example, the structure of the neural system is simple at the lower level, but complex at the higher level. The system is stable at the lower level, while unstable and easily injured at the higher level. It functions automatically and voluntarily at the low and high levels, respectively. Paul D. MacLean (1931–2007) was an important researcher who helped advance Jackson's theory. In 1990, MacLean published a book "The Triune Brain in Evolution", and insisted that the brain had three systems: a protoreptilian brain, a paleomammalian brain, and a neomammalian brain (Fig. 5.4). The protoreptilian brain consists of the brain stem, the mesobrain, and the basal ganglia, and exhibits functions related to the preservation of individuals and one's own species. The paleomammalian brain corresponds to the limbic system and is involved in emotional processing. This system first appeared during the higher evolution of mammals. The neomammalian brain includes the neocortex, which participates in complex mental activities, abstract thinking, and language, features observed only in higher mammals. MacLean suggested that the brains of higher organisms had been developed from protoreptilian to neomammalian structures, and this development could also be applied to the growth of each individual person. Emotion is usually accompanied by autonomic responses, and so in order to approach emotional processing in the brain we need to understand the neural structures of the limbic system.

5.2.2 Limbic System (Fig. 5.5)

The limbic system consists of the amygdala, hippocampus, parahippocampal gyrus, fornix, mammalian body, cingulate gyrus, and some thalamic nuclei. The amygdala

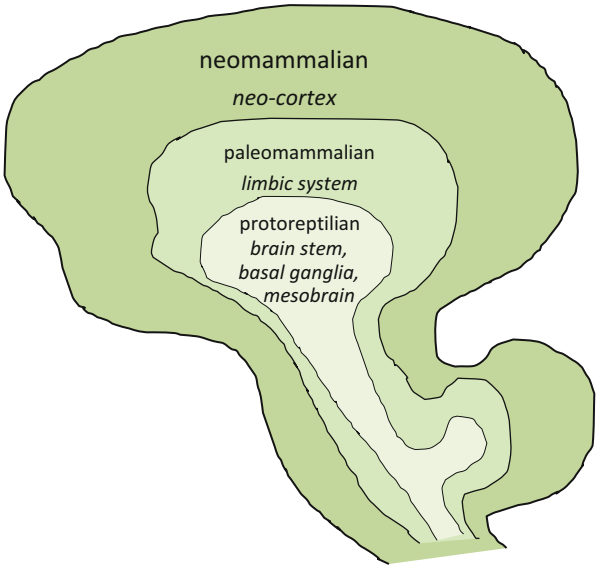

Fig. 5.4 Triune brain theory

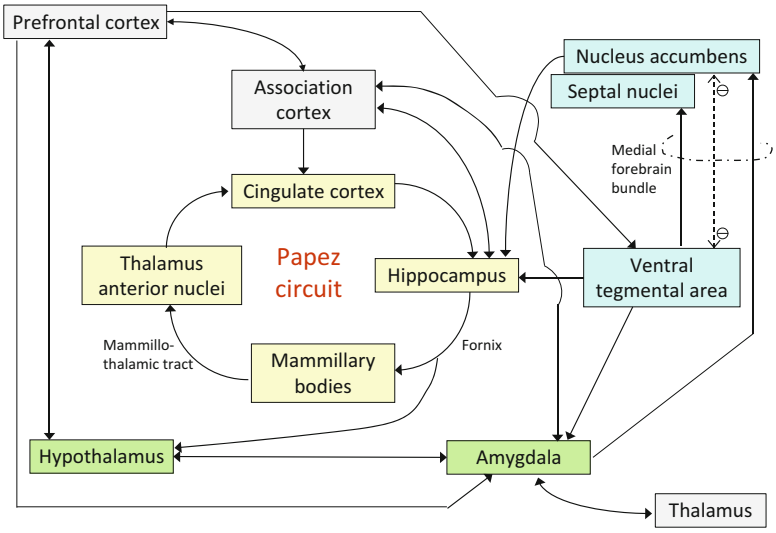

Fig. 5.5 Limbic system and reward circuitry

is the primary structure related to emotions, and is divided into three subnuclei: the central nucleus (CeA), corticomedial nucleus, and basolateral nucleus (BLA). The BLA has reciprocal projections between the associate cortices, and is responsible for attaching emotional significance to stimuli [4]. The CeA also has reciprocal projections between the brain stem, spinal cord, hypothalamus, and BLA. The CeA

regulates visceral responses to emotional stimuli. Thus, the amygdala receives all kinds of sensory information, judges its emotional significance, and produces visceral responses involuntarily. The parahippocampal gyrus, cingulate gyrus, anterior nucleus of the thalamus, and mammalian body belong to the Papez circuit, which is known to participate in memory. Historically, the Papez circuit was initially considered to be the primary neural structure of emotion. Since it is well known that stimuli that elicit strong emotions are more easily remembered, emotion and memory are closely related not only behaviorally but also anatomically.

5.2.3 Reward Circuitry (Fig. 5.5)

Animals including humans feel pleasure if their instinctive desires are satisfied. The brain regions whose stimulation evokes pleasurable feelings are called "pleasure centers" or "reward circuitry". For example, rats will work to obtain electrical stimulation of such regions in the absence of associated food or tangible rewards [5]. Reward circuitry participates in incentive-based learning, appropriate responses to stimuli, and the development of goal-directed behavior (Lippincott's Illustrated Reviews). Dopamine plays an important role in reward. The brain regions belonging to this reward circuitry include the ventral tegmental area (VTA), septal nuclei, and the nucleus accumbens. The medial forebrain bundle carries dopaminergic fibers projecting from the VTA to the nucleus accumbens. Dopaminergic fibers from the VTA also project to the hippocampus, amygdala, septal nuclei, and prefrontal cortex. The prefrontal cortex and the nucleus accumbens provide feedback fibers back to the VTA. Finally, reward circuitry also communicates with the hypothalamus to drive neuroendocrine and visceral responses.

5.2.4 Categorization of Anhedonia

Anhedonia can be categorized according to two points of view: mental processing and modality. Emotional processing might also have two domains: emotion perception and emotional experience [6, 7]. Emotion perception means the recognition of expressed emotions without necessarily feeling an emotion. Emotional experience is the subjective experience of emotion. These two domains can be independent from each other. We can, for instance, judge a piece of music as beautiful, but not be moved emotionally by it [8].

Other types of anhedonia are categorized by a modality or stimulus that becomes unable to evoke emotion. The loss of emotional responses related to vision is called "visual hypoemotionality". The selective loss of emotional responses to music is termed musical anhedonia or esthetic amusia by the present author [7].

There are two hypotheses regarding the mental processing of emotion. First, it is possible that emotion perception serially precedes emotional responses. In this case,

bottom-up processing would lead to emotional responses based on prior emotion perception. Another hypothesis favors parallel processing, such that these are independent processes in the brain, at least partially. It remains to be clarified which hypothesis is correct, although reported neuropsychological findings presented in the following paragraphs suggest that the latter hypothesis, parallel processing, might be more accurate.

5.3 Visual Hypoemotionality

5.3.1 First Report of Visual Hypoemotionality by Bauer [9]

The first case that showed a selective loss of emotional responses to visual stimuli was reported by Bauer [9]. The author named this symptom "visual hypoemotionality". The patient was a 39-year-old right-handed college graduate who had suffered from severe brain trauma in a motorcycle accident. Initial brain CT was not remarkable. On the next day, he underwent an orthopedic procedure to repair a knee injury. After that, brain CT showed large bilateral intraparenchymal hematomas in the inferior aspect of the posterior temporal lobes, involving the occipitotemporal gyrus (Fig. 5.6). The lesion was larger in the right hemisphere. As a result, he developed bilateral altitudinal hemianopsia, prosopagnosia, topographical disorientation, and a modality-specific inability to become emotionally aroused by visual cues. He complained that, as an assistant city planner, he was no longer able to appreciate subtle aesthetic differences between buildings. He also complained bitterly about his loss of emotional reaction to viewing pretty girls or erotic visual stimuli. Neurophysiological assessments revealed that, although healthy control patients exhibited significantly greater average skin conductance responses (SCRs) to nudes versus a landscape, the patient exhibited negligible differences

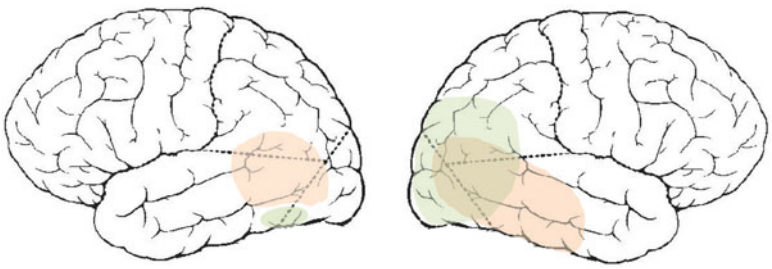

Fig. 5.6 Lesions of visual hypoemotionality. Brain lesions in Bauer's (*red*) and Habib's (*green*) patients. The lesions of the right side were larger than the left. At the level of the occipital white matter, the inferior longitudinal fasciculus (ILF) was bilaterally injured

between these two visual stimuli. Within the auditory modality, his mean SCR to sexual narratives was almost twice as great as his average SCR to non-emotional auditory stimuli. His lesion not only directly involved the visual association area of Brodmann area 18/19 but also impaired visual limbic connectivity via damage of the inferior longitudinal fasciculus (ILF). The ILF, via the temporal lobe, has input into both the basolateral limbic circuit (amygdala, mediodorsal thalamus, orbitofrontal cortex, uncinate fasciculus) and the medial limbic circuit of Papez (hippocampus, fornix, mammillary bodies, anterior thalamus, and cingulate). The author concluded that visual hypoemotionality in his patient was caused by a visual-limbic disconnection.

5.3.2 Second Case of Visual Hypoemotionality [10]

A few years after Bauer's case report, a paper relating a second case of visual hypoemotionality was published [10]. The patient was a 71-year-old right-handed woman. Following a cerebral infarction in the territory of the posterior cerebral arteries, she developed a left hemianopia, severe prosopagnosia, topographical disorientation, mild hemineglect, and visual hypoemotionality. A CT scan showed a large right occipital-temporal hypodensity and a much smaller subcortical infarction of the left occipital lobe. Previously, she had especially appreciated esthetics; she was fond of painting aquarelles and enjoyed taking care of many types of flowers. In contrast, after her cerebral accident, she complained about a lack of emotive reaction normally elicited by visual stimuli that formerly aroused a powerful feeling of well being or contentment. She said that the charm of flowers did not enter her mind anymore, and that landscapes could no longer convey their beauty to her. The right hemisphere infarction seemed to entail a complete isolation of the right temporal lobe from visual afference. The small infarction involving the deep white matter of the left occipital lobe was likely to damage the ILF, which is the main subcortical connection between the visual cortex and limbic structures. The author concluded that his patient's visual hypoemotionality was caused by a bilateral visual-limbic disconnection due to ILF damage.

5.3.3 Summary of These Two Cases

Following the report by Habib, there have been no other reports of visual hypoemotionality. The cases mentioned above have the following features in common: (i) bilateral occipital lesion greater in the right hemisphere, (ii) possible involvement of ILF, (iii) prosopagnosia, (iv) topographical disorientation, and (v) probable pathogenesis related to a visual-limbic disconnection.

5.4 Musical Anhedonia (Esthetic Amusia)

5.4.1 Case of Mazzoni [11]

Defective perception of music due to an altered capacity to discriminate the elementary components of musical stimuli (rhythm, pitch, timbre, intensity, and duration) produces an alteration in the esthetic enjoyment of and the emotional involvement in music [11]. However, there are two cases that have showed a selective loss of esthetic pleasure only in listening to music. The first case was reported by Mazzoni [11]. The patient was a 24-year-old male who was an amateur musician and a skillful guitarist. Due to an arterio-venous malformation (AVM) in the right temporo-parietal region, esthetic pleasure for the musical world had completely vanished. He could not perceive the structure of musical pieces clearly, and the relationship between the accompaniment and the soloist was indiscernible. Examinations of musical abilities (recognition and production of features of musical sounds, plus identification and/or reproduction of rhythm, melody, and harmony; vocal and instrumental performance; and listening to musical compositions) were normal. On hearing the pieces played on the piano, he complained, "…It's flat, it's no longer three-dimensional; it's only on two planes… there's no emotion". His difficulties increased as the presented compositions became more complex: "… this is even worse. I can distinguish the different instruments, but I can't perceive the whole". The author suggested that the patient might have lost the ability to convert musical perception into something emotionally meaningful, but also pointed out that disturbances of this type are difficult to view objectively because of their highly subjective nature.

5.4.2 Our Case [7]

Almost two decades later, the second case of a selective loss of musical emotion was reported, and the term *musical anhedonia* was used in this article for the first time. A 71-year-old right-handed retired teacher suffered an infarction in the right parietal lobe. He found himself unable to experience emotion in listening to music, even music that he had listened to pleasantly before the illness. He described the music as dull and lacking freshness. He also reported that music had become two-dimensional and seemed like a fish in a can. In neuropsychological assessments, his intellectual, memory, and constructional abilities were normal. Speech audiometry and recognition of environmental sounds were within normal limits. Neuromusicological assessments revealed no abnormalities in the perception of elementary components of music, expression, or emotional perception of music. Brain MRI identified the infarcted lesion in the right inferior parietal lobule. We call the symptom exhibited by our patient *musical anhedonia*, referring to a normal perception of elementary musical components and emotion perception coexisting with an impaired capacity to respond

Table 5.1 Double dissociation between emotion perception and emotional experience of music in reported cases

Author	Journal	Emotion of music		Site of lesion	Diagnosis
		Perception	Experience		
Mazzoni (1993) [11]	JNNP	○	×	rt temporoparietal	AVM, hemorrhage
Our case (2011) [7]	Neurocase	○	×	rt parietal	Cerebral infarction
Peretz (1999) [13]	Neurocase	×	○	bil temporal frontal	Aneurysms at bil MCA, post operation
Matthew (2009) [12]	Neurocase	×	○	bil temporal	Degeneration, atrophy

○ preserved, × injured, *AVM* arterio-venous malformation, *bil* bilateral, *MCA* middle cerebral artery, *rt* right

emotionally to music. However, from the perspective of an impairment of musical ability, this symptom can also be called *esthetic amusia*. We may reasonably conclude that the right parietal lobe might participate in emotional experiences while listening to music.

5.4.3 *Double Dissociation Between Perception and Experience of Musical Emotion*

Our and Mazzoni's case show that emotional experiences in listening to music can be selectively impaired. Two prior cases described patients with impaired perception of elementary musical components and emotion perception despite a preservation of emotional experiences related to music [12, 13]. This suggests the possibility of a double dissociation between emotion perception and emotional experience of music (Table 5.1). Therefore, it is reasonably concluded that these two cognitive domains have at least a partially independent neural basis in the brain.

The site of lesion in our and Mazzoni's case commonly includes the right parietal lobe. How can musical anhedonia (esthetic amusia) be caused by damage of that region? This is undetermined, but we may say that the pathological mechanism is a disconnection between music and emotional processing in the brain. As shown above, associate cortices, including auditory, have connections with the limbic system via the cingulate gyrus, hippocampus, and amygdala. The latter two structures also belong to reward circuitry that mediates the positive reinforcing effects of stimuli. The hippocampus, amygdala, and prefrontal cortex also have reciprocal projections between the hypothalamus that controls autonomic nervous system functions such as blood pressure, respiration, and body temperature. It is suggested that the neural network between the right parietal cortex and the limbic system (including reward circuitry) plays an important role in the appreciation of the esthetic pleasure of music.

5.5 Conclusion and Future Directions

I presented cases exhibiting a selective loss of emotional experiences with regard to vision and music, respectively termed visual hypoemotionality and music anhedonia (esthetic amusia). From these cases, the following conclusions are suggested: (i) the processing of emotion perception and emotional experience is independent, in other words parallel, in the brain; (ii) emotion experience may be selectively impaired in a sole sensory modality; (iii) anhedonia of vision and audition might be caused by a disconnection between visual and auditory association areas and the limbic system (including the reward circuit). This could be regarded as a disconnection between the paleomammalian and neomammalian brain in MacLean's triune theory; (iv) the right parietal lobe might play a crucial role in the esthetic appreciation of music.

Much still remains to be understood about anhedonia and emotional processing in the brain. First, are there cases with anhedonia of other sensory modalities, namely olfactory, gustatory, and somatosensory sensation? Second, music anhedonia (esthetic amusia) occurs with the preservation of emotional responses to other auditory stimuli, for example environmental sounds and prosody. Can visual hypoemotionality occur in such a category-specific manner? Third, can the pathological mechanism of visual hypoemotionality and music anhedonia (esthetic amusia) be explained solely as a disconnection syndrome? It is well known that the right hemisphere participates in global processing, while the left hemisphere mediates local processing [14] and the parietal lobe plays an important role in spatial processing. Is it possible that the right parietal lobe serves a central function in the production of musical beauty? Representing natural experiments, patients with brain damage shed light on fundamental aspects of brain function. I believe that future neuropsychological studies will continue to clarify the neural bases of emotion as well as the appreciation of beauty.

References

1. Loring DW. INS dictionary of neuropsychology. New York: Oxford University Press; 1999.
2. Kolb B, Whishaw IQ, editors. Fundamental of human neuropsychology. New York: W.H. Freeman; 1996.
3. Dronkers NF, Plaosamt O, Iba-Zizen MT, Cabanis EA. Paul Broca's historic cases: high resolution MR imaging of the brains of Leborne and Lelong. Brain. 2007;130:1432–41.
4. Krebs C, Weinberg J, Akesson E, editors. Lippincott's Illustrated reviews: neuroscience. Philadelphia: Lippincott Williams & Wilkins; 2012.
5. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol. 1954;47(6):419–27.
6. Juslin PN, Västfjäll D. Emotional responses to music: the need to consider underlying mechanisms. Behav Brain Sci. 2008;31:559–621.
7. Satoh M, Nakase T, Nagata K, Tomimoto H. Musical anhedonia: selective loss of emotion experience in listening to music. Neurocase. 2011;17(5):410–17.
8. Brattico E, Jacobsen T. Subjective appraisal of music. Neuroimaging evidence. Ann N Y Acad Sci. 2009;1169:308–17.

9. Bauer RM. Visual hypoemotionality as a symptom of visual-limbic disconnection in man. Arch Neurol. 1982;39:702–8.
10. Habib M. Visual hypoemotionality and prosopagnosia associated with right temporal lobe isolation. Neuropsychologia. 1986;24:577–82.
11. Mazzoni M, Moretti P, Pardossi L, Vista M, Muratorio A. A case of music imperception. J Neurol Neurosurg Psychiatry. 1993;56:322–4.
12. Matthews BR, Chang CC, May MD, Engstrom J, Miller BL. Pleasurable emotional response to music: a case of neurodegenerative generalized auditory agnosia. Neurocase. 2009; 15:248–59.
13. Peretz I, Gagnon L. Dissociation between recognition and emotional judgments for melodies. Neurocase. 1999;5:21–30.
14. Fink GR, Marshall JC, Halligan PW, Dolan RJ. Hemispheric asymmetries in global/local processing are modulated by perceptual salience. Neuropsychologia. 1999;37:31–40.

Chapter 6
Projecting Oneself into the Future, an Intervention for Improving Pleasure in Patients with Anhedonia

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Abstract In clinical practice, anhedonia and apathy are challenging symptoms of schizophrenia. Anhedonia in schizophrenia appears to be associated with impairment in anticipatory pleasure. However, the problem is complicated since comorbid depression occurs in 50 % of patients and the symptoms of the different disorders may overlap. This chapter presents an intervention to train anticipatory pleasure in patients with schizophrenia. This intervention has been evaluated in an exploratory pilot study. Results show that the patients improved on the anticipatory scale of the Temporal Experience of Pleasure Scale. Patients also increased their daily activities. The program is still being improved and should be tested in a controlled study.

Keywords Anhedonia • Schizophrenia • Anticipatory pleasure • Cognitive and behavioural therapy • Psychological intervention

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Abbreviation

TEPS Temporal Experience of Pleasure Scale

6.1 Introduction

Carole works in a hospital department. She is exasperated because she has now gone four times into Jack's room so that he will come take his shower and get his breakfast. He remains in his bed in his pyjamas. Each time she asks him to come, he says he is coming but he doesn't move. Gregory works in a nursing home. Today, he has organised a group sporting activity but after three turns through the residents' rooms, he has only managed to motivate two patients instead of the ten originally planned on. Gregory is frustrated. Jill is a community health psychiatric nurse, and for several months she has been trying to get Julian to leave his home. Instead he stays in all day smoking cannabis. Jill doesn't know what to do anymore.

Anhedonia, the difficulty of anticipating or experiencing pleasure, is a particularly stubborn and challenging symptom of schizophrenia. It is often association with apathy and reduced socializing. It is part of the range of negative symptoms of schizophrenia which are central features of the illness. According to recent literature reviews, it is necessary to distinguish negative symptoms associated to a factor of diminished experience (anhedonia, asocial behaviour and avolition) from those associated to a factor of restricted expression (blunted affect, alogia) [1, 2]. Negative symptoms are often difficult to evaluate because they may be primary and linked directly to the illness or secondary and have other causes [3]. For example, a person can be anhedonic because she is depressed, may withdraw from society because she feels persecuted, or appear to lack any will while he is actively fighting against auditory hallucinations. In the same way, the secondary effects of the use of antipsychotics such as akinesia can be confused with blunted affect or may lead to dysphoric reactions [4]. These negative symptoms largely contribute to decreased social [5] and professional [6] functioning. They are associated with a poor quality of community life [7]. A recent study shows that the syndrome of apathy-anhedonia tends to be associated with a poorer prognosis compared to symptoms showing a diminished expression, which suggests that it is a more severe aspect of the psychopathology [8].

It would appear that individuals differ in their capacity to experience anticipatory pleasure (defined as the capacity to feel pleasure in anticipation) and the experience of consummatory pleasure (defined as the pleasure experienced in the moment of a pleasant activity) [9]. Klein [10] has set up a distinction between anticipatory pleasure and consummatory pleasure in a theoretical text on anhedonia in depression. It would seem that anticipatory pleasure is more strictly linked to motivation and behaviours directed toward a goal and that consummatory pleasure is more strictly linked to satiety. Several studies underline that individuals with

schizophrenia are less active or involved in pleasant and positive activities compared to non-patients. Nevertheless, laboratory studies measuring the experience of actual pleasure when confronted with pleasurable stimuli have not shown that patients experience less pleasure than control subjects. One possible explanation for these differences in results could be that individuals with schizophrenia present a greater deficit for anticipatory pleasure than for consummatory pleasure [11]. Another study confirms this hypothesis by revealing that patients with schizophrenia report the same pleasure when engaged in pleasant activities compared to control subjects but they anticipate less joy for future activities [12]. In order to briefly measure the experiences of anticipated and consummated pleasure, Gard et al. [9] developed a self-administered scale of 18 items called the Temporal Experience of Pleasure Scale (TEPS). Three studies that used this scale show that individuals with schizophrenia exhibit a stronger reduction in anticipatory pleasure compared to consummatory pleasure with respect to control subjects [13–15]. An additional study indicates that the sub-scales prove to be stable over a period of 6 months [16]. Nevertheless, a fourth study did not replicate the previous results with TEPS [17]. Raffard et al. [18] demonstrated that individuals with schizophrenia have difficulty imagining pleasant events in the future. They also reported that apathy was associated with difficulties in imagining pleasant events that may take place in the future.

Both studying and understanding anhedonia becomes complex for different reasons. First of all, anywhere between 50 and 75 % of patients with schizophrenia exhibit low self-esteem [19, 20]. Also, half of all individuals with schizophrenia exhibit a concomitant affective disorder [21]. The difficulty of anticipating pleasure and the difficulty of experiencing pleasure can overlap because patients would be suffering from both depression and a diminished experience syndrome at the same time. In contrast, it appears that changes in capacities for planning are significantly more altered in patients with schizophrenia than those with unipolar depression [22].

Secondly, psychiatry has undergone an immense transformation over the past three decades, and we find ourselves now with three generations of extremely different patients. The first are patients who experienced institutionalisation. These individuals are currently over 50 years old. They learned to be submitted to their environment. They may have evolved into a deficit state and are generally followed up in adapted living environments like boarding houses, group homes or sheltered living apartments and workshops. They were treated with traditional antipsychotics and experienced extrapyramidal side effects. A second generation of patients who are now between 30 and 50 years old lived through multiple but brief hospitalisations. Most often, these individuals were treated with atypical antipsychotic medications. This generation experienced the establishment of patient laws which changed the constrained relationship between professionals and patients. They had much more access to illicit drugs than the previous generation. They are apt at living in more autonomous environments, often in their own homes. They benefitted from validated psychosocial treatments like social skills training or cognitive behavioural therapy. Over the last 10 years, a new generation of patient has appeared: these are

individuals who received early interventions related to their psychosis. Half of these patients have never been in hospital [23] and most have not received forced treatments. This generation of patients considers that intermediary structures like group homes or sheltered workshops are highly constraining or stigmatizing. They offer new challenges to community-health psychiatry services and lead us to develop new alternatives that are even closer to normal life within a community such as supported employment or housing.

In this context, anhedonia will take on very different forms. The anhedonia of a patient who began his illness in a constrained and under-stimulated institutional environment will be severely affected by iatrogenic environmental factors. The anhedonia of a patient who will have followed an early intervention programme focused on rehabilitation will be less affected by these iatrogenic factors. For example, a study by Cassidy et al. [24] shows that the patients suffering from a first psychotic episode who continue to consume cannabis during their treatment will exhibit a significant decrease of anticipatory pleasure compared to those who were able to remain abstinent. The clinical manifestations directly associated to the illness are probably purer in patients who received early interventions.

This is the context which motivated us to develop an intervention meant to improve anticipatory desire in schizophrenia [25].

6.2 Training for Anticipatory Pleasure

Instead of engaging patients in pleasant activities and hoping that this will make them more active, our intervention invites patients to imagine what the positive consequences will be in terms of pleasure, feelings of accomplishment or satisfaction when engaging in an activity. If the lack of activity is a result of depression, it is probably preferable to engage patients in pleasant activities [26–28] or in interventions meant to increase the frequency and intensity of emotions described as recently by Gregory Strauss [29]. In contrast, if the patient exhibits difficulty experiencing anticipatory pleasure on the TEPS, it is preferable to engage her in the programme of training for anticipatory pleasure as described below:

Julian has been living as a recluse in his home for several months; he no longer has the energy nor the desire to go out of his house. He spends his days sleeping and watching television. He says that he has lost all desire. He has a weak score for depression on the Calgary scale. Before becoming ill, he was a fan of hockey, but he is afraid to return to the ice skating rink. He is mostly afraid of the crowd. Some of his friends, with whom he played hockey, come to visit him sometimes in the evening. He has fond memories of the relationship he had with his sister. However, she is less available because she is in a relationship. Julian says that if he wanted to do something, he would be interested in doing a little sport. Before becoming ill, he

had begun an apprenticeship as a motorcycle mechanic: he really likes Harley Davidson bikes. With respect to personal hygiene, Julian is letting himself go; sometimes his body gives off a strong smell.

6.2.1 Inspire the Interest and Motivation for the Training

Together with the participant, the therapist will construct the arguments for training to anticipate pleasure and elicit the link between desire and motivation. This rational is developed through questioning. Example questions are: How do you stimulate yourself to engage in activities? What makes an activity more or less attractive? What does it mean to "motivate yourself?" How does a person motivate herself? It is important that the participant realizes that anticipating pleasure is what drives motivation.

6.2.2 Put Together a List of Pleasant Activities

Together, the participant and the therapist construct a list of pleasant activities from the past. This is a list of pleasant activities that the participant would like to start again, current activities that the person would like to do more of and new activities that he would like to be able to accomplish: activities may be quite simple or complex. Complex activities are divided into subtasks that are more easily completed. For example, the activity of going to a hockey game would be subdivided into:

- invite a friend to come watch a hockey match on TV
- go to see a training session of my local team
- go to see a local match with friends (less than 100 spectators).

It is important to score activities from zero to 10 as a function of the individual's desire to accomplish the activity and the effort needed: For example, "zero" means no desire and no necessary effort, "10" means the person really wants to accomplish the activity and a huge effort is needed to accomplish this task. Activities are then classed in decreasing order of desire/effort. The following Table 6.1 is an example of Julian's activity list.

6.2.3 Anticipating Pleasure

Since participants may be contaminated by unpleasant emotions [30], the therapist begins by putting the participant into a state of relaxation with a relaxation or a mindfulness exercise.

Table 6.1 List of activities for training Julien's anticipatory pleasure

Activities	Desire	Effort	Desire/effort
Invite a friend to come watch a hockey match on TV	6	2	3
Look at my motorcycle magazine	4	2	2
Discuss motorcycling with friends	4	2	2
Buy a kebab at the corner of the street	4	2	2
Go window-shopping at the Harley Davidson garage	7	4	1.75
Drink a coffee at the café across the street	4	3	1.33
Go to see a training session of my local team	5	4	1.25
Go to see a local match with friends (less than 100 spectators).	7	6	1.16
Invite my sister and her boyfriend to a meal	8	7	1.15
Buy my favourite motorcycle magazine	3	3	1
Go to see a hockey game	8	8	1
Go for a walk in the park with a girlfriend	8	9	.88
Take a shower	2	3	.66

6.2.4 Mindfulness Exercise, Awareness of One's Environment

The exercise takes from 5 to 10 min.

1. Close your eyes and relax.
2. Pay attention to your breathing without trying to control it and let yourself become relaxed (approximately 2 min).
3. I would now like you to visualise the space here where we are.
4. Visualise the colour of the walls… of the ceiling… of the floor… the arrangement of furniture and objects…
5. Try to remember the colours and textures…the walls…the furniture… the objects…the decorations…
6. Remember the knick-knacks and the paintings on the walls…Visualize their size, shape, colours, textures…
7. Try to remember your surroundings exactly… and to mentally reconstruct an image of the room…
8. Keep your eyes closed… when you have a good image of the room, give me a signal with your hand.
9. Slowly open your eyes and look around the room.

Discuss the effect of the exercise

The participant is then invited to imagine himself in an activity, moving up the list in terms of desire/effort ratio (from the lower to the higher desire/effort ratio). The therapist guides the participant to imagine the physical feelings associated with the activity, moving through the five senses (sight, hearing, smell, taste, and touch), the feeling of positive emotions and/or the feeling of accomplishment, depending on each selected activity. The participant is invited to remember positive experiences from the past with respect to each selected activity. For example: "Remember the smell of the best kebab you have ever tasted… smell the odour of grilled meat

in your nose… concentrate on this smell… try to make it as vibrant as possible…" The participant is then asked to anticipate positive emotions: "Concentrate on the feelings of pleasure you have when with your friend… You told me that you enjoyed hearing her voice… imagine the sound of that voice… You told me that you liked it when she smiled…imagine that you have just told a funny story and can hear her laughs… imagine that she is laughing… Go over the feelings in your body when she laughs… Scan your body from head to toe and list the pleasant sensations that you may experience…" Depending on the activity, the participant may be asked to anticipate a feeling of accomplishment. For example: "Re-experience the feeling of contentment you have from being in the shower… imagine that you feel fresh and clean… Try to fully feel this sensation in your body… Note the parts of your body that are associated with this feeling of contentment… Anticipate the feeling of gratification… Observe the sensation in your body… where is it located? In your head… in your stomach…? Let yourself feel these emotions completely…" If the participant has trouble feeling these sensations, describe the possibilities.

And the end of each exercise, discuss in detail how the exercise went for the participant.

6.2.5 Recommend Tasks to Be Accomplished Between Sessions

The therapist prescribes to the participant tasks to accomplish between sessions. The task may be for the participant to re-do one of the exercises from the session on his own. The tasks may be anything from listening to the recorded session on her own or writing down an exercise in anticipatory pleasure. For example, make a list of positive anticipations that could be done to help the participant get out of bed in the morning.

6.3 Conclusions and Future Directions

Currently, there is a tendency to replace mindfulness exercises with heart rate variability (HRV) biofeedback. The advantage of biofeedback is that it becomes possible then to know immediately if the person is relaxing. The exercises lead quickly to a state of relaxation. They consist of a series of vagal manoeuvres followed by a pleasant breathing to the heart. For example, here is an exercise developed by Charly Cungi [31], called the "crisis of calm".

1. Vagal manoeuvres
   - Breathe out the air in your lungs, calmly, like a "balloon deflating".
   - Breathe in a little bit of air, without pulling hard.
   - Hold this breath for a short moment in order to facilitate the exchange of air inside the lungs.
   - Let the air out of your lungs, without pushing.

2. Focus on breathing
   - Focus your attention on the mediastinum (the zone situated between the lungs at the sternum), and more specifically at the heart level, fairly high up on the chest.
3. Pay attention to your breathing during inhalation and exhalation.
   - Breathe slowly, softly, settle into a comfortable breathing rhythm.
4. Focus on the pleasant feeling in the body
5. Affective evocation
   - While maintaining pleasant breathing, name a pleasant feeling. This might be while thinking of someone you love, a particular place or object, etc.

Then, the person is invited to imagine herself in a pleasant event in the future and visualize it. The therapist can stimulate the participant's imagination by saying:

Concentrate on the experience of the pleasant event and the environment with as much detail as possible, including all that you can see, feel, and hear. After the exercise, which lasts for several minutes, the therapist asks the participant to describe the pleasant experience with as much detail as possible. The intervention is currently completed with techniques to increase the frequency and intensity of positive emotions [32, 33] as suggested by Gregory Strauss [29]. Focusing attention on the present pleasant experience and vividly remembering or anticipating positive events promote positive affect as well as communicating and celebrating positive events with other promotes life satisfaction [32].

Clinical experiences show that participants appreciate this type of training. Until now, this treatment has only been tested on an exploratory basis [25] and used in clinical practice with patients suffering from anhedonia and apathy. It should now be tested on a larger scale under controlled conditions and should involve neurocognitive, affective and social functioning evaluations.

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References

1. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr Bull. 2006;32:238–45.
2. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull. 2010;36:359–69.
3. Carpenter Jr WT, Heinrichs DW, Alphs LD. Treatment of negative symptoms. Schizophr Bull. 1985;11:440–52.
4. Marder SR. Subjective experiences on antipsychotic medications: synthesis and conclusions. Acta Psychiatr Scand Suppl. 2005;111:43–6.
5. Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr Res. 2009;113:189–99.

6. Tsang HW, Leung AY, Chung RC, Bell M, Cheung WM. Review on vocational predictors: a systematic review of predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. Aust N Z J Psychiatry. 2010;44:495–504.
7. Eack SM, Newhill CE. Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis. Schizophr Bull. 2007;33:1225–37.
8. Strauss GP, Horan WP, Kirkpatrick B, Fischer BA, Keller WR, Miski P, Buchanan RW, Green MF, Carpenter Jr WT. Deconstructing negative symptoms of schizophrenia: avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. J Psychiatr Res. 2013;47:783–90.
9. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.
10. Klein D. Depression and anhedonia. In: Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1984. p. 1–14.
11. Kring AM. Emotion in schizophrenia: old mystery, new understanding. Curr Dir Psychol Sci. 1999;8:160–3.
12. Gard DE, Kring AM, Germans MK, Werner K. Emotion in the daily life of patients with schizophrenia. Boulder: Society for Research in Psychopathology; 2000.
13. Favrod J, Ernst F, Giuliani F, Bonsack C. Validation of the temporal experience of pleasure scale (teps) in a French-speaking environment. L'Encéphale. 2009;35:241–8.
14. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:253–60.
15. Loas G, Monestes JL, Yon V, Thomas P, Gard DE. Anticipatory anhedonia in schizophrenia subjects. L'Encéphale. 2010;36:85–7.
16. Buck B, Lysaker PH. Consummatory and anticipatory anhedonia in schizophrenia: stability, and associations with emotional distress and social function over six months. Psychiatry Res. 2013;205:30–5.
17. Strauss GP, Wilbur RC, Warren KR, August SM, Gold JM. Anticipatory vs. consummatory pleasure: what is the nature of hedonic deficits in schizophrenia? Psychiatry Res. 2011;187:36–41.
18. Raffard S, Esposito F, Boulenger JP, Van der Linden M. Impaired ability to imagine future pleasant events is associated with apathy in schizophrenia. Psychiatry Res. 2013;209(3):393–400.
19. Moritz S, Veckenstedt R, Randjbar S, Vitzthum F, Karow A, Lincoln TM. Course and determinants of self-esteem in people diagnosed with schizophrenia during psychiatric treatment. Psychos Psychol Soc Integr Approach. 2010;2:144–53.
20. Bentall RP, Corcoran R, Howard R, Blackwood N, Kinderman P. Persecutory delusions: a review and theoretical integration. Clin Psychol Rev. 2001;21:1143–92.
21. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull. 2009;35:383–402.
22. Holt DV, Wolf J, Funke J, Weisbrod M, Kaiser S. Planning impairments in schizophrenia: specificity, task independence and functional relevance. Schizophr Res. 2013;149(1–3):174–9.
23. Baumann PS, Crespi S, Marion-Veyron R, Solida A, Thonney J, Favrod J, Bonsack C, Do KQ, Conus P. Treatment and early intervention in psychosis program (tipp-lausanne): implementation of an early intervention programme for psychosis in Switzerland. Early Interv Psychiatry. 2013;7(3):322–8.
24. Cassidy CM, Lepage M, Harvey PO, Malla A. Cannabis use and anticipatory pleasure as reported by subjects with early psychosis and community controls. Schizophr Res. 2012;137:39–44.
25. Favrod J, Giuliani F, Ernst F, Bonsack C. Anticipatory pleasure skills training: a new intervention to reduce anhedonia in schizophrenia. Perspect Psychiatr Care. 2010;46:171–81.
26. Lewinsohn PM. Engagement in pleasant activities and depression level. J Abnorm Psychol. 1975;84:729–31.

27. Lewinsohn PM, Graf M. Pleasant activities and depression. J Consult Clin Psychol. 1973;41: 261–8.
28. Cuijpers P, van Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. Clin Psychol Rev. 2007;27:318–26.
29. Strauss GP. Translating basic emotion research into novel psychosocial interventions for anhedonia. Schizophr Bull. 2013;39:737–9.
30. Horan WP, Green MF, Kring AM, Nuechterlein KH. Does anhedonia in schizophrenia reflect faulty memory for subjectively experienced emotions? J Abnorm Psychol. 2006;115: 496–508.
31. Cungi C, Deglon C. Cohérence cardiaque, nouvelles techniques pour faire face au stress. Paris: Retz; 2009.
32. Quoidbach J, Berry EV, Hansenne M, Mikolajczak M. Positive emotion regulation and well-being: comparing the impact of eight savoring and dampening strategies. Personal Individ Differ. 2010;49:368–73.
33. Bryant FB. The process of savoring: a new model of positive experience. Mahwah: Lawrence Erlbaum; 2007.

Part II
Neurobiological Advances

Chapter 7
Translational Models of Dopaminergic Mechanisms for Motivational Deficits in Anhedonic Patients

Michael T. Treadway and David H. Zald

Abstract Anhedonia is a core symptom of multiple psychiatric disorders, the neurobiological substrates of remain poorly understood. Despite significant preclinical advances in the identification of specific sub-components of reward processing, clinical definitions of anhedonia primarily emphasize reductions in pleasure and positive emotionality, while impaired motivation is often neglected. Here, we review recent evidence suggesting that motivational deficits may reflect an important dimension of symptomatology that is discrete from traditional definitions of anhedonia in terms of both behavior and pathophysiology. In summarizing this work, we highlight the use of translational models such as effort-based decision-making as important tools for elucidating the biological basis of motivational deficits in clinical populations. Finally, we touch on some of the implications of this work for improving diagnosis and treatment.

Keywords Anhedonia • Motivation • Effort • Depression • Schizophrenia • Dopamine • Ventral striatum • Insula

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Abbreviations

MDD	Major Depressive Disorder
DA	Dopamine
VS	Ventral striatum
BDI	Beck Depression Inventory
SHAPS	Snaith-Hamilton Pleasure Scale
FCPS	Fawcett-Clark Pleasure Scale
SANS	Scale of Negative Symptoms
TEPS	Temporal Experience of Pleasure Scale
EEfRT	Effort Expenditure for Rewards Task

7.1 Introduction

The term anhedonia—introduced to the clinical literature over 100 years ago—describes a devastating psychological state involving a near-total absence of positive emotion. Everyday activities such as eating, working, and socializing are experienced without the attendant pleasures of appetite, excitement, interest, motivation, or connection. In the last quarter-century, the anhedonia construct has emerged from relative obscurity to become a central feature in the current nosology of multiple psychiatric conditions, most notably in Major Depressive Disorder (MDD) and schizophrenia. This increased conceptual relevance has been mirrored by a steep rise in empirical research devoted to the understanding and treatment of anhedonic symptoms. Mounting interest in this particular symptom likely reflects the confluence of several distinct currents, which include influential theoretical frameworks regarding the diagnostic importance of anhedonia in MDD and schizophrenia [1, 2], the observation of comparatively poorer treatment outcomes for anhedonic symptoms [3], and a surge in preclinical discoveries regarding the molecular and systems-level mechanisms underlying reward processing generally (for reviews see [4–6]). This last trend is of particular importance as the field of psychiatry often relies on translational neuroscience approaches in its quest to elucidate the etiopathophysiology of mental disorders [7]. As such, the availability of a rich basic science literature is crucial.

Despite this heightened focus, many fundamental questions remain regarding the nature of anhedonic symptoms, their etiology, phenomenology, biological underpinnings, and specificity to psychiatric illness. Indeed, several recent theoretical reviews have called for a critical reexamination of the anhedonia construct [8–11]. Much of this critique has hinged on the question of what alterations in reward processing are included in a definition of anhedonia. Does anhedonia describe a singular problem in experiencing pleasure, or does it include deficiencies in a number of reward-related domains? The answer to this question has substantial implications for the theoretical conceptualization of anhedonia and related

constructs, for the assessment of psychopathology involving these symptoms, for understanding the neural substrates of psychiatric symptoms and for the treatment or reward processing abnormalities.

The need of clarity on this issue is highlighted by the diagnostic criteria for major depressive episode as enshrined in the DSM-IV and DSM-V. One can meet the A2 criteria for a depressive episode either by a loss of pleasure or a loss of interest. If pleasure and interest are reflections of a singular process, then this collapsing of terms should cause little problem. However, if pleasure and interest reflect different processes, they may have dramatically different pathophysiological substrates. That is to say, circuit-level mechanisms underlying interest, such as reward prediction, anticipation and motivation that relate to potential future rewards, may be distinct from those involved in the experience of pleasure, enjoyment, or satisfaction that occur following reward receipt [8, 11].

Unfortunately, most clinical measures of psychopathology and dimensional assessments of anhedonia fail to discriminate between these various domains of reward processing. While such measures have had a useful place in the context of clinical assessment and care, they may mask important behavioral and biological distinctions that are critical towards understanding pathophysiology.

7.2 The Many Dimensions of Anhedonic Symptoms

It has long been recognized that reinforcement involves multiple sub-processes, such as anticipation, motivation, prediction, subjective pleasure and satiety. It has only been more recently, however, that investigators have been able to clearly show that these sub-components are neurobiologically dissociable. That is to say, manipulations of distinct circuits and neurochemicals can produce isolated effects on a single dimension of reward-related behavior, such as an abolition of motivation without any change in hedonic responsiveness. Berridge and colleagues have previously described this phenomenon as a distinction between “wanting”, (defined as the motivation or drive to obtain a reinforcer) and ‘liking’, (defined as the subjective experience of pleasure that may arise upon consumption of the reinforcer) [12, 13], and we adopt this terminology here.

A key implication of this work is that a reduction in reward-seeking behavior may result from impairments in one or many sub-component processes, which in turn implies that they may have shared or unshared neurobiological origins across different individuals. Despite this new understanding of the biological divisions involved in reward and reinforcement in the preclinical literature, current clinical methods have largely continued to construe anhedonic symptoms along a unitary dimension with a focus on reduced hedonic capacity or positive emotionality. Consistent with this orientation, until recently, most clinical and laboratory measures of anhedonia have either exclusively focused on subject pleasure and/or positive feeling states, or treated sub-domains such as motivation and pleasure as being equivalent [14, 15].

7.3 Self-Report Measures of Anhedonia

To date, the assessment of anhedonic symptom severity has primarily been achieved through self-report instruments. A content review of items used in the most common anhedonia measures reveals that they unanimously emphasize the experience of pleasure in response to positive stimuli, with little or no attention to diminished drive or motivation. This emphasis on the experience of pleasure can be seen in the Chapman Anhedonia Scale [16], the Scale of Negative Symptoms (SANS; [17]), the Fawcett-Clark Pleasure Scale, (FCPS; [18]) and the Snaith-Hamilton Pleasure Scale (SHAPS; [19]). Symptom severity instruments specific to depression often assess anhedonia with a small number of items; a single question in the case of the 17-item Hamilton Depression Rating Scale [20], two items on the 21-item Beck Depression Inventory (BDI anhedonia scale; [21]) and four on the 30-item Inventory of Depressive Symptoms. Importantly, none of these scales have made an explicit attempt to dissociate between pleasure and motivational aspects of anhedonia. More recently, the Temporal Experience of Pleasure Scale (TEPS; [22]) was developed to assess anticipatory and consummatory pleasure. This scale is a promising advance, though it is unclear whether the experience of pleasure when anticipating rewards is an identical construct to reward motivation, and its application in clinical populations has resulted in some conflicting results [23, 24].

Finally, the Mood-Anxiety Symptoms Questionnaire (MASQ) developed by Watson and Clark [25, 26], includes a number of items related to lowered positive affect and interest, some of which appear related to aspects of anhedonia. However, these items are generally not treated separately from the larger scales that contain them, which remain relatively heterogeneous. Therefore, collapsing across these different forms of reward deficits may obfuscate the results, and may contribute to weaknesses in fitting a three-factor model across samples [27–29].

7.4 Behavioral Measures of Reward Domains

A number of studies have employed laboratory-based behavioral tasks in order to examine affective responses to positively-valenced stimuli in MDD. These studies have suggested that individuals with depression generally rate positively-valenced stimuli as being less positive, less arousing, or less able to affect their mood as compared to controls [30–38], although a larger number of studies have reported no group differences in these ratings [39–50].

The "sweet taste test" provides another laboratory approach to assessing hedonic capacity. During the sweet taste test, participants rate the pleasantness of different sucrose concentrations. Because sweet tastes at mild to moderate concentrations represent a natural reinforcer, hedonic responses to these sweet solutions should provide a good test of hedonic responsivity. Surprisingly, four separate studies using the sweet taste test, individuals with depression and matched controls have shown no differences in reported hedonic impact [51–54]. At least on the surface,

this suggests that there is no deficit in hedonic capacity to experience a natural reinforcer in MDD.

Similar dissociations between self-reported anhedonic symptoms and in-the-moment responses to laboratory stimuli have also been observed in schizophrenia patients. Gold and colleagues have demonstrated a striking distinction between self-reported anhedonia using the Chapman Anhedonia Scales, and affective reports of pleasure emotions in response to positively-valenced laboratory stimuli; while schizophrenia patients rated themselves as significantly more anhedonic according to the Chapman Scales, there affective ratings were identical to controls [15].

A limit to these laboratory measures is that they rely on verbal report, which may be subject to biases. Additional laboratory studies have emphasized behavioral measures to explore aspects of anhedonia in depression. One well-replicated finding has been that individuals with depression fail to develop a response bias towards rewarded stimuli [55–57]. These paradigms use discrimination tasks in which subjects must categorize a briefly presented stimulus as belonging to category A or B. Importantly, these paradigms use a pay-off matrix so that subjects are more rewarded for correctly guessing category A, as opposed to category B, with no punishment associated with incorrect guesses. Healthy control subjects typically develop a response bias toward the more rewarding option, whereas MDD patients do not. These elegant studies provide strong evidence for an insensitivity to reward-relevant information in MDD.

Further laboratory studies have also sought to assess discrete sub-components of reward processing, such as willingness to work for rewards. To isolate this construct behaviorally, a number of groups have recently employed various effort-based decision-making tasks in which subjects must expend physical or mental effort in order to earn varying levels of rewards. One such task developed by our group is the Effort-Expenditure for Rewards Task (EEfRT, pronounced "effort") [58]. During this task, participants perform a series of trials in which they are asked to choose between completing a "High Effort" and "Low Effort" task exchange for monetary compensation. Using the EEfRT and a similar effort based paradigm, two studies have found evidence for impairment in motivation for rewards in MDD [59, 60]. A similar pattern was observed in schizophrenia patients [61]. Critically, in each study differences in effort expenditure between anhedonic patients and controls were found to result from that fact that controls modulated their effort output as a function of how much reward was at stake, while patients did not. This suggests that rather than a pure effort-mobilization deficit, it may be the effective allocation of effort that is most impaired.

Taken together, the reviewed behavioral evidence suggests that although deficits in the experience of pleasure figure prominently in clinical diagnoses, the lack of consistent group differences in laboratory tests involving subjective responses to positive stimuli raise potential doubts as to whether a narrowly defined conceptualization of anhedonia as a specific deficit in the capacity to feel pleasure is accurate or useful in characterizing the most common reward processing abnormalities in depression and schizophrenia. In contrast, these behavioral studies have supported the claim that altered motivational states are common features of these disorders.

Indeed, these motivational deficits may be key drivers of deficient reward related behavior in these conditions, possibly to an even greater extent than an altered hedonic capacity.

7.5 Mapping Sub-domains of Reward Abnormalities to Distinct Neural Circuits

Because of the conceptual breadth of reward processing abnormalities, we have previously argued that circuit-level mapping of anhedonic pathophysiology will require disaggregating anhedonic behaviors into their constituent components. As described above, a number of behavioral studies have already begun to provide support for this approach, as anhedonic populations can exhibit either normal or abnormal symptom profiles depending on whether motivation or hedonic response is assessed. This distinction has important ramifications for the study of neurobiological mechanisms, as preclinical research has already demonstrated clear distinctions in neural systems responsible for motivation and pleasure.

This work began by drawing on animal models suggesting that the mesolimbic dopamine (DA) system may be selectively involved in reward motivation, but not hedonic response. The mesolimbic DA system encompasses a specific sub-population of DA neurons that innervate the ventral striatum (VS), a key region involved in the processing of reward-relevant information [62]. Evidence for the role of mesolimbic DA in motivation was provided by effort-based decision-making tasks in rodents. In these paradigms, animals must choose whether to consume freely available, but less desirable food rewards (Low Effort), or to exert physical effort in exchange for more palatable food rewards (High Effort). Healthy rats exhibit a strong preference for the High Effort option, while attenuation or blockade of DA—especially in the ventral striatum—results in a behavioral shift towards Low Effort options [5, 63]. Critically, DA blockade does not reduce overall consumption, highlighting a selective role in willingness to work rather than appetitive drive. Moreover, potentiation of DA produces the opposite effects, resulting in an increased willingness to work for preferred rewards [64]. In contrast to this strong evidence for DA in motivation, attenuation or even complete absence of DA appears to have little effect on measures of hedonic response, including sucrose preference and hedonic facial reactions (for a review, see [6]).

Using the EEfRT and similar tasks, human studies have begun to map out the role of mesolimbic DA circuitry in normal and abnormal reward motivation. Mirroring the effects of DA potentiation in rats, one study found that administration of the DA agonist *d*-amphetamine produced a dose-dependent increase in the willingness to work for rewards as assessed by the EEfRT [65]. Interestingly, these effects were strongest during trials for which probability of reward receipt was low, suggesting that DA may be involved in helping animals overcome probabilistic discounting as well as effort related response costs. Similar effects of DA enhancement using the DA precursor L-Dopa have been observed on measures of vigorous

effortful responding [66] as well reward anticipation and an optimism-bias [67, 68], two constructs that are closely related to motivation.

To further elucidate the role of DA function as a predictor of individual differences in motivation, a follow-up study used positron emission tomography (PET) imaging to test associations between amphetamine-induced DA release (a probe of DA system reactivity) and willingness to work for rewards on during the EEfRT [69]. Here we found that the magnitude of DA release in the striatum positively predicted the proportion of High Effort choices subjects made during low probability trials. Localization to this region is consistent with preclinical findings [5, 63] as well as human functional neuroimaging studies [70–72]. Intriguingly, our study also found a negative relationship between percentage of High Effort choices and DA release in the insula. While insula DA function has not traditionally been a focus for rodent models of effort-based decision-making, recent work suggests that insular DA receptor mRNA expression is predictive of effort-related behaviors [73]. Moreover, other imaging human imaging studies have observed insula activation when participants chose not to expend effort [74]. Although further investigation is necessary, these data suggest that the insula and striatum may play somewhat antagonistic roles in determining whether an individual is willing to overcome effort costs.

Similar convergence between clinical and preclinical studies has been observed in reinforcement learning studies. Using a rodent version of signal-detection task developed by Pizzagalli and colleagues, researchers found that a pharmacologic blockade of DA release abolished the development of a reward response bias, a pattern that mirrors behavioral effects in depressed patients [75]. In humans, DA PET imaging revealed that reinforcement learning during this task was associated with DA release medial prefrontal reward areas [76]. These findings compliment prior translational work using motivation, and further implicate DAergic systems in the pathophysiology and anhedonia.

Going forward, mapping distinct facets of anhedonia to specific circuits will be critical in the development of biological markers that can reliably aid in diagnosis and treatment prediction. As the DSM-based nosology has been found to lack a clear biological basis [77], the use of circuit-level measures will become increasingly important [78]. Ultimately, this approach will help contribute to a pathophysiologically based nosology of psychiatric symptoms.

7.6 Conclusions

The construct of anhedonia has been substantially revised since Ribot's original proposal over a century ago. As researcher and clinicians have increasingly appreciated the distinct sub-processes involved in reinforcement behavior, greater precision has been brought to bear on laboratory measures and assessment instruments used to diagnosis the presence and severity of anhedonic symptoms. More recently, the application of preclinical models of motivation and reward processing has served as

a useful guide in developing identifying neurobiological mechanisms that may underlie anhedonic behavior. We believe that this latter approach has substantial potential for rapidly enhancing our understanding of anhedonia, and thereby improving clinical treatment for this debilitating symptom.

References

1. Meehl PE. Hedonic capacity: some conjectures. Bull Menninger Clin. 1975;39:295–307.
2. Klein DF. Endogenomorphic depression. A conceptual and terminological revision. Arch Gen Psychiatry. 1974;31:447–54.
3. Shelton RC, Tomarken AJ. Can recovery from depression be achieved? Psychiatr Serv. 2001;52:1469–78.
4. Rushworth MF, Noonan MP, Boorman ED, Walton ME, Behrens TE. Frontal cortex and reward-guided learning and decision-making. Neuron. 2011;70:1054–69.
5. Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology (Berl). 2007;191:461–82.
6. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008;199:457–80.
7. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167:748–51.
8. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55.
9. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169(4):364–73.
10. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull. 2008;36:359–69.
11. Barch DM, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr Bull. 2010;36:919–34.
12. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998;28:309–69.
13. Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl). 2007;191:391–431.
14. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2010;35(3):537–55.
15. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull. 2008;34:835–47.
16. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374–82.
17. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry. 1982;39:784–8.
18. Fawcett J, Clark DC, Scheftner WA, Hedeker D. Differences between anhedonic and normally hedonic depressive states. Am J Psychiatry. 1983;140:1027–30.
19. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995;167:99–103.
20. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
21. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996;67:588–97.
22. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.

23. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:253–60.
24. Strauss GP, Wilbur RC, Warren KR, August SM, Gold JM. Anticipatory vs. consummatory pleasure: what is the nature of hedonic deficits in schizophrenia? Psychiatry Res. 2011;187:36–41.
25. Watson D, Clark LA, Weber K, Assenheimer JS, Strauss ME, McCormick RA. Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. J Abnorm Psychol. 1995;104:15–25.
26. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol. 1995;104:3–14.
27. Buckby JA, Cotton SM, Cosgrave EM, Killackey EJ, Yung AR. A factor analytic investigation of the Tripartite model of affect in a clinical sample of young Australians. BMC Psychiatry. 2008;8:79.
28. Burns DD, Eidelson RJ. Why are depression and anxiety correlated? A test of the tripartite model. J Consult Clin Psychol. 1998;66:461–73.
29. Kiernan G, Laurent J, Joiner Jr TE, Catanzaro SJ, MacLachlan M. Cross-cultural examination of the tripartite model with children: data from the Barretstown studies. J Pers Assess. 2001;77:359–79.
30. Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. J Abnorm Psychol. 1992;101:37–44.
31. Berenbaum H. Posed facial expressions of emotion in schizophrenia and depression. Psychol Med. 1992;22:929–37.
32. Wexler BE, Levenson L, Warrenburg S, Price LH. Decreased perceptual sensitivity to emotion-evoking stimuli in depression. Psychiatry Res. 1994;51:127–38.
33. Sigmon S, Nelson-Gray R. Sensitivity to aversive events in depression: antecedent, concomitant, or consequent? J Psycholopathol Behav Assess. 1992;14:225–46.
34. Dunn BD, Dalgleish T, Lawrence AD, Cusack R, Ogilvie AD. Categorical and dimensional reports of experienced affect to emotion-inducing pictures in depression. J Abnorm Psychol. 2004;113:654–60.
35. Rottenberg J, Gross JJ, Gotlib IH. Emotion context insensitivity in major depressive disorder. J Abnorm Psychol. 2005;114:627–39.
36. Rottenberg J, Kasch KL, Gross JJ, Gotlib IH. Sadness and amusement reactivity differentially predict concurrent and prospective functioning in major depressive disorder. Emotion. 2002;2:135–46.
37. Sloan DM, Strauss ME, Wisner KL. Diminished response to pleasant stimuli by depressed women. J Abnorm Psychol. 2001;110:488–93.
38. Sloan DM, Strauss ME, Quirk SW, Sajatovic M. Subjective and expressive emotional responses in depression. J Affect Disord. 1997;46:135–41.
39. Allen NB, Trinder J, Brennan C. Affective startle modulation in clinical depression: preliminary findings. Biol Psychiatry. 1999;46:542–50.
40. Renneberg B, Heyn K, Gebhard R, Bachmann S. Facial expression of emotions in borderline personality disorder and depression. J Behav Ther Exp Psychiatry. 2005;36:183–96.
41. Gehricke J, Shapiro D. Reduced facial expression and social context in major depression: discrepancies between facial muscle activity and self-reported emotion. Psychiatry Res. 2000;95:157–67.
42. Kaviani H, Gray JA, Checkley SA, Raven PW, Wilson GD, Kumari V. Affective modulation of the startle response in depression: influence of the severity of depression, anhedonia, and anxiety. J Affect Disord. 2004;83:21–31.
43. Tremeau F, Malaspina D, Duval F, Correa H, Hager-Budny M, Coin-Bariou L, et al. Facial expressiveness in patients with schizophrenia compared to depressed patients and nonpatient comparison subjects. Am J Psychiatry. 2005;162:92–101.
44. Mitterschiffthaler MT, Kumari V, Malhi GS, Brown RG, Giampietro VP, Brammer MJ, et al. Neural response to pleasant stimuli in anhedonia: an fMRI study. Neuroreport. 2003;14:177–82.

45. Tsai JL, Pole N, Levenson RW, Munoz RF. The effects of depression on the emotional responses of Spanish-speaking Latinas. Cultur Divers Ethnic Minor Psychol. 2003;9:49–63.
46. Dichter GS, Tomarken AJ, Shelton RC, Sutton SK. Early- and late-onset startle modulation in unipolar depression. Psychophysiology. 2004;41:433–40.
47. Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005;58:843–53.
48. Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. Biol Psychiatry. 2005;58:495–503.
49. Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, et al. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. Biol Psychiatry. 2005;57:201–9.
50. Forbes EE, Dahl RE. Neural systems of positive affect: relevance to understanding child and adolescent depression? Dev Psychopathol. 2005;17:827–50.
51. Kazes M, Danion JM, Grange D, Pradignac A, Simon C, Burrus-Mehl F, et al. Eating behaviour and depression before and after antidepressant treatment: a prospective, naturalistic study. J Affect Disord. 1994;30:193–207.
52. Dichter GS, Smoski MJ, Kampov-Polevoy AB, Gallop R, Garbutt JC. Unipolar depression does not moderate responses to the Sweet Taste Test. Depress Anxiety. 2010;27(9):859–63.
53. Amsterdam JD, Settle RG, Doty RL, Abelman E, Winokur A. Taste and smell perception in depression. Biol Psychiatry. 1987;22:1481–5.
54. Berlin I, Givry-Steiner L, Lecrubier Y, Puech AJ. Measures of anhedonia and hedonic responses to sucrose in depressive and scizophrenic patients in comparison with healthy subjects. Eur Psychiatry. 1998;13:303–9.
55. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. J Psychiatr Res. 2008;43:76–87.
56. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol Psychiatry. 2005;57:319–27.
57. Henriques JB, Glowacki JM, Davidson RJ. Reward fails to alter response bias in depression. J Abnorm Psychol. 1994;103:460–6.
58. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. PLoS One. 2009;4:e6598.
59. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J Abnorm Psychol. 2012;121(3):553–8.
60. Clery-Melin ML, Schmidt L, Lafargue G, Baup N, Fossati P, Pessiglione M. Why don't you try harder? An investigation of effort production in major depression. PLoS One. 2011;6:e23178.
61. Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK, Frank MJ. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. Biol Psychiatry. 2012;74(2):130–6.
62. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35:4–26.
63. Cousins MS, Salamone JD. Nucleus accumbens dopamine depletions in rats affect relative response allocation in a novel cost/benefit procedure. Pharmacol Biochem Behav. 1994;49:85–91.
64. Bardgett ME, Depenbrock M, Downs N, Points M, Green L. Dopamine modulates effort-based decision making in rats. Behav Neurosci. 2009;123:242–51.
65. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. J Neurosci. 2011;31:16597–602.
66. Beierholm U, Guitart-Masip M, Economides M, Chowdhury R, Düzel E, Dolan R, et al. Dopamine modulates reward-related vigor. Neuropsychopharmacology. 2013;38(8):1495–503.

67. Sharot T, Guitart-Masip M, Korn CW, Chowdhury R, Dolan RJ. How dopamine enhances an optimism bias in humans. Curr Biol. 2012;22(16):1477–81.
68. Sharot T, Shiner T, Brown AC, Fan J, Dolan RJ. Dopamine enhances expectation of pleasure in humans. Curr Biol. 2009;19:2077–80.
69. Treadway MT, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, et al. Dopaminergic mechanisms of individual differences in human effort-based decision-making. J Neurosci. 2012;32:6170–6.
70. Kurniawan IT, Seymour B, Talmi D, Yoshida W, Chater N, Dolan RJ. Choosing to make an effort: the role of striatum in signaling physical effort of a chosen action. J Neurophysiol. 2010;104:313–21.
71. Croxson PL, Walton ME, O'Reilly JX, Behrens TE, Rushworth MF. Effort-based cost-benefit valuation and the human brain. J Neurosci. 2009;29:4531–41.
72. Schmidt L, Lebreton M, Clery-Melin ML, Daunizeau J, Pessiglione M. Neural mechanisms underlying motivation of mental versus physical effort. PLoS Biol. 2012;10:e1001266.
73. Simon NW, Beas BS, Montgomery KS, Haberman RP, Bizon JL, Setlow B. Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. Eur J Neurosci. 2013;37(11):1779–88.
74. Prevost C, Pessiglione M, Metereau E, Clery-Melin ML, Dreher JC. Separate valuation subsystems for delay and effort decision costs. J Neurosci. 2010;30:14080–90.
75. Der-Avakian A, D'Souza MS, Pizzagalli DA, Markou A. Assessment of reward responsiveness in the response bias probabilistic reward task in rats: implications for cross-species translational research. Transl Psychiatry. 2013;3:e297.
76. Vrieze E, Ceccarini J, Pizzagalli DA, Bormans G, Vandenbulcke M, Demyttenaere K, et al. Measuring extrastriatal dopamine release during a reward learning task. Hum Brain Mapp. 2013;34(3):575–86.
77. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol Psychiatry. 2012;17:1174–9.
78. Akil H, Brenner S, Kandel E, Kendler KS, King MC, Scolnick E, et al. Medicine. The future of psychiatric research: genomes and neural circuits. Science. 2010;327:1580–1.

Chapter 8
Brain Systems for the Pleasure of Food and Other Primary Rewards

Fabian Grabenhorst

Abstract The orbitofrontal cortex, anterior cingulate cortex, and amygdala are key components of the reward and pleasure systems of the human brain. Investigations with functional magnetic resonance imaging (fMRI) of how these brain systems respond to food and other primary, sensory rewards can reveal basic principles of their function in reward, experienced pleasure, decision-making, and behavior. Here I review recent advances that have been made with this approach, with the aim to characterize the functional specializations of the orbitofrontal cortex, anterior cingulate cortex and amygdala in reward, pleasure and decision-making. The specific aims are (i) to show that the orbitofrontal cortex, anterior cingulate cortex, and amygdala are principal structures in the human brain for reward and pleasure; (ii) to describe their roles in information processing for rewards; (iii) to outline some key principles according to which human reward and pleasure systems operate; (iv) to consider the relationship between these reward systems and the decision systems in the ventromedial prefrontal cortex; and (v) to illustrate with specific examples how this approach to reward and pleasure is also relevant to applied disciplines including food design, food marketing, health policy, and clinical conditions in which hedonic responses to rewards are altered.

Keywords Value • Emotion • Decision-making • Economic choice • Human brain • Orbitofrontal cortex • Amygdala • Anterior cingulate cortex • Ventromedial prefrontal cortex • Functional MRI • Oral fat texture • Food labeling • Taste • Flavor • Odor • Touch

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8.1 Introduction

The capacity to feel pleasure in response to rewards is an important part of human conscious experience. Experienced pleasure is central to an individual's well-being and a guide for our decision-making and behavior. Anhedonia, a key symptom in major depression, is defined in terms of a loss of experienced pleasure. What happens in our brains when we experience pleasure, for example while tasting a delicious food? How are the different components of the food, its sensory, physical features as well as its subjective hedonic properties, represented in the brain? How do neural representations of reward value and pleasure influence our decisions and actions? Here, I argue that we can approach these questions by investigating the brain processing of primary rewards, including food and other sensory stimuli. Understanding the neural processes that occur when primary rewards are consumed can provide important insights not only into the determinants of experienced pleasure but also into the determinants of choice and reward-based behavior [1].

The approach described here, centered on the neural processing of primary rewards at the time of consumption, is complementary to approaches that consider neural processing of value at the moment of choice, that is, at the time when value-based decisions are made. The latter approach is taken in the fields of decision neuroscience and neuroeconomics [2–4]. The sensory nature of rewards is sometimes neglected in these fields, and the focus is on value derived from abstract variables including reward probability, delay, or social factors. However, our daily lives revolve around primary, sensory rewards. For example, we may sample different foods in the market square to choose our lunch or sip different types of ale in the pub to choose our next drink. In order to understand the decision process in these situations, and also in more complex ones, we need to consider how the brain represents reward value and experienced pleasure when primary rewards are consumed. Thus, examining how the brain's reward systems respond to the different sensory components of a reward at the time of consumption, and the interactions that may occur between these components, can inform our understanding of the brain mechanisms for reward, pleasure, decision-making, and related disorders [1].

The aim of this chapter is to develop a theme of how sensory information about primary rewards is transformed, over a series of neural processing stages, into brain representations of reward value, pleasure, and reward-based choices and actions. The specific aims are (i) to show that the orbitofrontal cortex, anterior cingulate cortex, and amygdala are principal structures in the human brain for reward and pleasure; (ii) to describe their roles in information processing for rewards; (iii) to outline some key principles according to which human reward and pleasure systems operate; (iv) to consider the relationship between reward/pleasure systems and the decision systems in the ventromedial prefrontal cortex; and (v) to illustrate with specific examples how this approach to reward and pleasure is also relevant to applied disciplines including food design, food marketing, health policy, and clinical conditions in which hedonic responses to rewards are altered. The specific examples considered include the brain processing of oral fat texture, which is a prototypical

primary reward implicated in overeating and obesity [5, 6]; food labeling as an external, cognitive influence on pleasure and choice [7, 8]; and hedonic complexity, which is defined as the simultaneous presence of pleasant and unpleasant components in a reward [9, 10]. Finally, the relevance of this approach for understanding conditions with abnormal reward processing and reduced experienced pleasure, such as anhedonia, will be considered.

8.2 An Approach to Pleasure Based on Rewards

When considering the brain systems for pleasure and related emotional states, a starting point is to ask in what situations we experience pleasure, and why. A useful approach to these questions is provided by theories of emotion based on reward processing. From earlier approaches [11–13], Rolls has developed the theory that emotions are states elicited by rewards, or, more generally, by reinforcers [14–17]. In animal learning theory and psychology, a reward is defined as anything that an individual, will work for – when a stimulus or event increases the probability of a response, it acts instrumentally as a reward. Thus, rewards can be conceptualized as goals for behavior. Accordingly, the theory of emotion based on rewards holds that emotions are states elicited by goals [17, 18]. This resonates with our intuitive understanding of emotions: we typically have emotions when we anticipate, attain or fail to attain our goals. Within this framework, pleasure can be understood as the conscious affective state produced by rewards, which can be measured using subjective ratings [1, 17, 19, 20].

Why, then, do rewards elicit emotions and other affective states such as pleasure? The approach to emotion based on reward [17] is grounded in evolutionary, Darwinian theory: Primary rewards, such as sweet taste and warm touch, are conceptualized as gene-specified (i.e. unlearned) goals for action built into us during evolution by natural selection to direct our behavior to stimuli that are important for survival and reproduction [1, 17]. Affective states are elicited by primary rewards when these are anticipated, obtained, omitted or terminated – and example being the pleasure produced by tasting a piece of chocolate – or by initially neutral stimuli that have become associated with primary rewards. The central function of rewards and related affective states can be understood as introducing flexibility into behavior: Specification of the goals for actions, rather than specification of the actions directly, is an efficient and adaptive way to enable behavior to be guided flexibly towards rewards by selecting to most appropriate action to obtain a reward in a given context [17].

Thus, rewards not only guide and often determine our behavior but also elicit pleasure and other affective states. This reward-based approach to pleasure provides an answer to the questions of what types of stimuli produce pleasure, and why. (For a complementary approach to emotion and pleasure based on action systems in the brain see Panksepp [21].) It also lays the foundation for the empirical investigation of emotion and subjective affective states, for it allows the definition of a basic set

of sensory stimuli that are primary rewards and that can be presented to humans to reproducibly elicit affective states, including pleasure. Further, the brain systems that can be shown to respond to and process these affective stimuli are implicated in having clear information-processing roles in reward and pleasure [1, 17].

8.3 Experienced Pleasure as an Influence on Decisions and Behavior

What role does experienced pleasure play in decision-making and behavior? Intuitively, a link between subjective pleasure and behavior seems obvious: we seek stimuli that give us pleasure and avoid those that give us displeasure. Cabanac [19, 22] provided both empirical evidence and theoretical analysis for the role of pleasure in behavior. The evidence suggests that affective responses to sensory stimuli depend on internal physiological state, for example one's state of satiety or body temperature, and that individuals tend to maximize pleasure when different affective stimuli are pitted against each other [19, 22]. On this basis, Cabanac [22] proposed that pleasure provides a common currency in which different, conflicting motivations can be compared to make adaptive decisions. From this perspective, experienced pleasure and the expected pleasure associated with specific choice options or courses of action seem to play a principal role in guiding human behavior.

However, humans do not always behave in a way that maximizes experienced pleasure. They frequently have inaccurate knowledge and make inaccurate predictions about their affective responses to outcomes [23, 24]. To account for such discrepancies between experienced pleasure and behavioral choices, Kahneman and Tversky [23] introduced the concept of *experienced utility*, which can be measured on a moment-by-moment basis as subjective pleasantness. Experienced utility is a hedonic interpretation of the economic concept of utility and is empirically distinct from *decision utility*, which is measured in terms of decisions weights as inferred from observed choices. Thus, Kahneman's approach conceptualizes experienced utility as an alternative criterion for evaluating outcomes, which may not necessarily correspond fully to decision utility, i.e. what is chosen.

In a related approach, we [1] suggested that subjective pleasure may primarily reflect conscious influences on decisions and behavior. As pleasure is a consciously experienced state, the correlation between reported pleasure and choice may be strongest when behavior is produced via a conscious route, which may involve rational (i.e. reasoning) thoughts about multi-step plans [1, 17, 25, 26]. By contrast, our choices are not always guided by consciously represented factors, for example in situations in which behavior is controlled by implicit Pavlovian or habit systems, and the correlation between reported pleasure and choice may be relatively low in these cases. From this perspective, affective responses to primary rewards may become conscious by virtue of entering a special processing system, for example when reasoning about whether an experienced reward such as a pleasant touch

should be continued or terminated [27]. If this limited-capacity conscious system is not engaged with other reasoning processes, then simple rewards may, while the system is monitoring events in the world, enter it and become conscious, for example during simple reward consumption [18]. Experienced pleasure may therefore reflect processing by a reasoning, conscious system which may involve the prefrontal cortex, as opposed to implicit Pavlovian or habit systems in the amygdala and basal ganglia [7, 17, 18, 28, 29]. Thus, the conjecture is that experienced pleasure may be linked to the operation of a conscious, goal-directed decision system, and therefore may provide insight into the determinants of behavior at least partly independently of what can be inferred from observed choices alone.

8.4 Brain Systems for Reward and Pleasure: Sensory Analysis, Reward Value, and Decision-Making in a Three-Tiered Neural Architecture

Tracing the sensory signals produced by primary rewards through different neural processing stages can reveal basic principles of how the reward and pleasure systems of the human brain operate. For example, neural activity in the orbitofrontal cortex, a brain area known for its roles in reward and pleasure, can be compared to activity in areas that project to it, and to activity in areas to which the orbitofrontal cortex in turn projects. In the present chapter, this approach provides the basis for a model of how information in the sensory input regions is transformed into representations of reward value and pleasure, and then to representations involved in decision-making about rewards. This leads to the concept of three tiers of neural processing, which provides a framework in terms of neuroanatomical connections. The framework has been developed by Rolls and extended by Grabenhorst and Rolls [1, 17, 18, 30]. It is illustrated in Fig. 8.1 and summarizes the sensory pathways that lead into principal reward systems including the orbitofrontal cortex and amygdala, which analyze and represent the reward value of stimuli, and to structures to which they connect, including the anterior cingulate cortex, medial prefrontal cortex and striatum. The framework also incorporates how inputs related to cognitive, attentional and linguistic processing, originating beyond the orbitofrontal cortex and amygdala, can modulate affective processing in reward areas to influence how we feel and decide about rewards.

8.4.1 Tier 1: Sensory Representations Independent of Reward Value

The first processing stage of the three-tiered architecture consists of cortical areas in the different sensory systems in which stimuli are represented as objects (Fig. 8.1). Information processing in Tier 1 is concerned with what stimulus is present, i.e. its

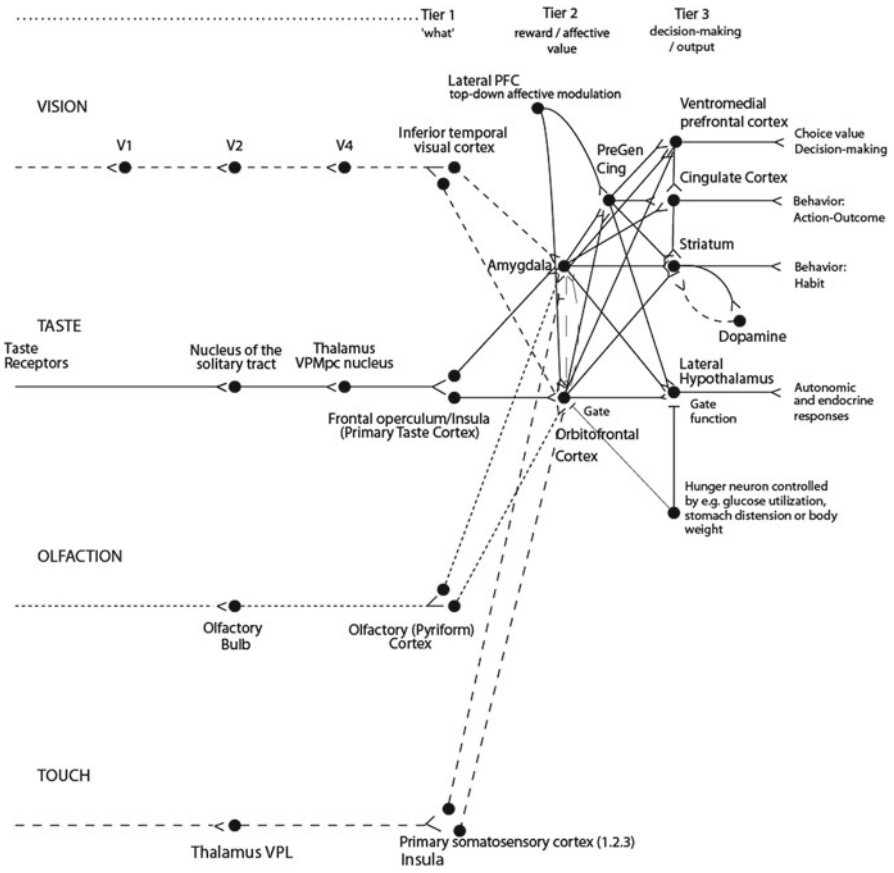

Fig. 8.1 Organization of cortical processing for reward value and pleasure. The Tier 1 brain regions up to and including the column headed by the inferior temporal visual cortex represent neuronally the sensory nature of rewards, i.e. 'what' stimulus/object is present, but not its reward or affective value. Tier 2 represents the reward value of stimuli and associated subjective pleasure, and includes the orbitofrontal cortex, amygdala, and anterior cingulate cortex. Tier 3 constitutes output systems for rewards including value-based choices in the ventromedial prefrontal cortex. The secondary taste and olfactory cortices are within the orbitofrontal cortex. V1 – primary visual cortex. V4 – visual cortical area V4. PreGen Cing – pregenual cingulate cortex. "Gate" refers to the finding that inputs such as the taste, smell, and sight of food in regions where reward value is represented only produce effects when an appetite for the stimulus (modulated for example by hunger) is present [17]. Lateral PFC: lateral prefrontal cortex, a source for top-down attentional and cognitive modulation of affective value (Adapted with permission from Ref. [1])

sensory and physical characteristics including stimulus intensity and identity. These sensory brain representations reflect the identity of objects but not their hedonic, rewarding properties. This has been shown in human functional brain imaging studies, for example using functional magnetic resonance imaging (fMRI), in which activations to sensory rewards in these brain areas correlated with reports of stimulus intensity. For example, activations to a range of taste and flavor stimuli in an

anterior part of the insula, which corresponds to the primary taste cortex in humans, correlated with the subjective intensity of the stimuli but not with their pleasantness [8]. The same part of the insula was more strongly activated by a more highly concentrated 0.4 M monosodium glutamate taste stimulus compared to 0.1 M stimulus, even though the more highly concentrated stimulus was rated as significantly less pleasant. Similar results have been obtained in the piriform, primary olfactory cortex for odors [10, 31] and in the posterior insula and secondary somatosensory cortex for somatosensory and thermal stimuli [32, 33]. Consistently, single neurons in the monkey primary taste cortex and also at earlier processing stages of the gustatory system reflect basic taste qualities but are not modulated in their activity by motivational state, for example when the animal is fed to satiety [34–36]. Thus, hedonically neutral representations of stimuli, distributed across sensory brain systems, provide the perceptual basis for our affective responses to rewards. This separation of sensory from hedonic processing is useful for it allows us to identify and respond to objects in the environment independently of whether we like them.

Single neuron recordings in monkeys can provide details on the type of information represented in the brain areas in Tier 1. In the inferior temporal cortex, the final stage of the "what"-visual pathway, neurons respond to visual objects independent of their view, orientation, and position on the retina [37]. This type of object identity representation is highly appropriate as an input for reward-decoding brain systems – usually, the value of an object is determined by its identity – and for associating visual stimuli with primary rewards [17]. Thus, the computational goal of the sensory processing performed in Tier 1 can be conceptualized as building representations of the identity of stimuli and objects in the world from which their reward value can be easily decoded and which can be interfaced with neural systems for learning and deciding about rewards [1, 17, 18].

8.4.2 Tier 2: Reward and Pleasure in the Brain

The second processing stage in the proposed framework includes brain areas that receive inputs from the sensory systems in Tier 1 and from these inputs compute and represent the reward or affective value of stimuli and events. These brain areas include the orbitofrontal cortex, the amygdala, and the anterior, perigenual cingulate cortex (Fig. 8.1). We next consider the functional specializations of each of these brain areas.

8.4.2.1 The Orbitofrontal Cortex: The Value and Pleasure of Sensory Rewards

The orbitofrontal cortex forms part of the ventral frontal lobe located above the bony roof of the eye sockets (Fig. 8.2a). It is known as a key structure for reward processing in primates including humans [1, 18, 30, 39, 40]. In humans, it is also

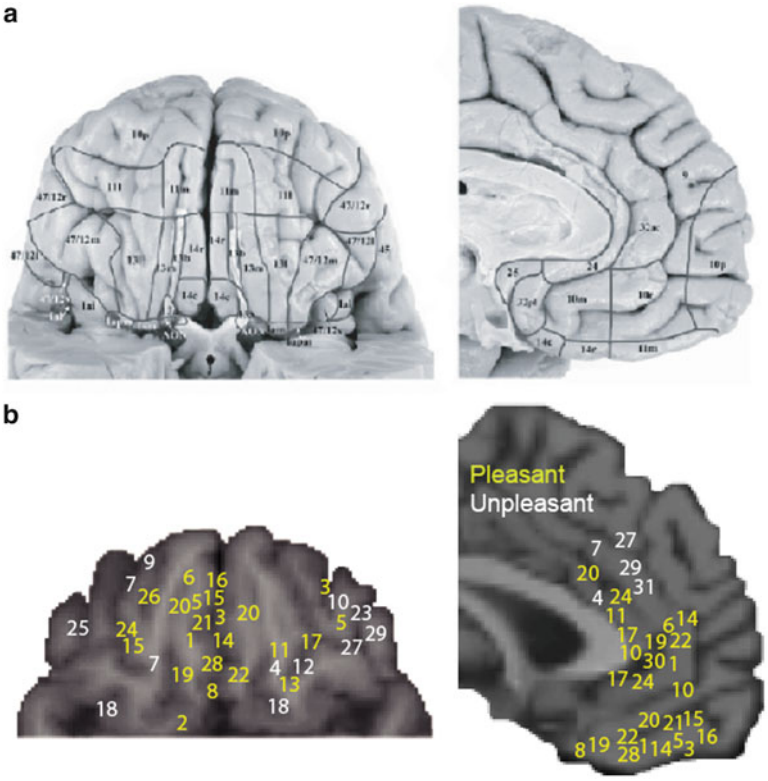

Fig. 8.2 Reward and pleasure systems in the human orbitofrontal cortex and anterior, perigenual cingulate cortex. (**a**) Architectonic subdivisions of the human orbitofrontal cortex (*left*, ventral view) and medial prefrontal cortex (*right*, sagittal view) after Öngür, Ferry and Price (Adapted with permission from Ref. [38]). (**b**) Maps of subjective pleasure in the human orbitofrontal cortex and anterior cingulate cortex. *Yellow numbers* refer to sites where activations produced by different sensory stimuli in neuroimaging studies correlated with the experienced pleasantness associated with the stimuli. *White numbers* refer to sites where activations correlated with subjective unpleasantness. The numbers refer to effects found in specific studies. Taste: *1, 2*; odor: *3–10*; flavor: *11–16*; oral texture: *17, 18*; chocolate: *19*; water: *20*; wine: *21*; oral temperature: *22, 23*; somatosensory temperature: *24, 25*; the sight of touch: *26, 27*; facial attractiveness: *28, 29*; erotic pictures: *30*; laser-induced pain: *31*. For detailed references see Grabenhorst and Rolls [1] (Adapted with permission from Ref. [1])

implicated in the experienced pleasure produced by different types of sensory rewards [1, 18, 40]. This is shown clearly in human neuroimaging studies in which orbitofrontal cortex activation by sensory stimuli tracks trial-by-trial reports of experienced pleasantness (Figs. 8.2b and 8.3a). Neuronal recordings in monkeys have shown that reward representations in the orbitofrontal cortex encode the detailed sensory nature of each reward. For example, neurons in the monkey orbitofrontal cortex encode the taste, odor, visual, oral texture, oral fat, temperature and viscosity features of foods, either unimodally or in multimodal combinations

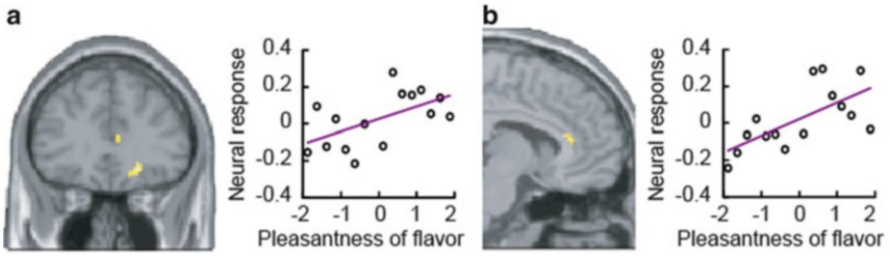

Fig. 8.3 Representations of the experienced pleasure of food flavor in the human orbitofrontal cortex and anterior cingulate cortex. Healthy, mildly hungry volunteers consumed liquid food stimuli (milkshakes) that varied in flavor while we measured their brain activity using functional MRI [5]. On every trial when a food stimulus was consumed, the volunteers provided ratings of subjective experienced pleasure. Neural activations in the medial orbitofrontal cortex (**a**) and anterior, pregenual cingulate cortex (**b**) produced by the liquid food stimuli tracked these trial-by-trial ratings of flavor pleasantness (but not of control ratings such as fattiness). The scatter plots show the relationship between pleasantness ratings and neural response magnitude averaged across all subjects (Adapted with permission from Ref. [5])

[18, 41–44]. This neuronal representation of food stimuli in the orbitofrontal cortex is highly distinct and finely tuned, for orbitofrontal cortex neurons can respond to relatively similar oral stimuli in very specialized ways that reflect subtle differences in a sensory feature, such as taste or oral texture [41]. This rich, detailed and distributed representation of sensory rewards may provide the neuronal basis for learning about specific rewards, having appetite or satiation for specific rewards, and deciding about or making behavioral responses to specific rewards. Thus, rather than representing the value or pleasure associated with rewards in any general way, the orbitofrontal cortex provides a hedonic representation that is linked to the sensory specifics of a reward. We next consider its functions in more detail.

8.4.2.1.1 Anatomical Connections of the Orbitofrontal Cortex

To understand the functions of the orbitofrontal cortex, it is helpful to consider its connections with other parts of the brain. Conceptually, the orbitofrontal cortex can be thought of as receiving inputs from the modality-specific "what" sensory cortical pathways in Tier 1 that provide information about the identity and sensory features of stimuli (Fig. 8.1). Rolls and colleagues [45] discovered a taste area in the lateral part of the monkey orbitofrontal cortex which contains taste responsive neurons, and showed anatomically that this was the secondary taste cortex in that it receives a major projection from the primary taste cortex [46]. This region projects on to more anterior areas of the orbitofrontal cortex [46]. Thus, anatomically and physiologically, the orbitofrontal cortex contains the secondary taste cortex. Taste neurons are also found more medially [42, 47–50]. The orbitofrontal cortex also contains an area with olfactory neurons [42] and receives direct inputs from the

primary olfactory, piriform cortex [51–55]. Thus, the orbitofrontal cortex also contains the secondary olfactory cortex. Visual inputs reach the orbitofrontal cortex from the inferior temporal cortex, the cortex in the superior temporal sulcus, and the temporal pole [52, 56–58]. There are also neurons in the orbitofrontal cortex with responses to oral somatosensory stimuli such as the texture of food [43, 59], and there are inputs from somatosensory cortical areas and from the insula [58, 60]. The orbitofrontal cortex also receives inputs from the amygdala [51] and the mediodorsal nucleus of the thalamus [61]. These connections provide some routes via which the affective representations of sensory stimuli in the orbitofrontal cortex can be generated. Many intrinsic connections exist between orbitofrontal subregions [61], and these may provide the basis for multisensory convergence, i.e. convergence of sensory inputs from different modalities, onto individual neurons [17, 62]. Collectively, the afferents to the orbitofrontal cortex convey detailed information about primary rewards, including the taste and texture of oral stimuli, and about potential secondary rewards, such as visual and olfactory stimuli.

The orbitofrontal cortex has outputs to temporal lobe areas, such as the amygdala [63], to the cingulate cortex [64, 65], ventral striatum [66] and head of the caudate nucleus [67, 68], the ventromedial prefrontal cortex [55], entorhinal and perirhinal cortex [63, 69], preoptic region, lateral hypothalamus, and the ventral tegmental area [70, 71]. These connections provide routes via which the orbitofrontal cortex can influence emotion, decision-making and behavior. By contrast, the orbitofrontal cortex is only weakly connected with cortical motor areas [58]. Correspondingly, its neuronal responses do not reflect specific movements required to obtain a reward [18, 72, 73]. This suggests an intermediate role in information processing that is situated between sensory input and motor output but more closely linked to the sensory input side.

8.4.2.1.2 The Orbitofrontal Cortex and Reward

Receiving inputs from Tier 1, the orbitofrontal cortex in Tier 2 is the first stage of cortical processing in which reward value is explicitly represented. This is supported by evidence that orbitofrontal neurons decrease their responses to food when its reward value is reduced by feeding to satiety [74]; that orbitofrontal neurons are activated by reward self-stimulation sites in the brain and that these self-stimulation effects reduce with satiety [75, 76]; that orbitofrontal neurons with visual responses rapidly learn and reverse their responses to visual stimuli depending on whether the stimulus is associated with a reward or punisher [77, 78]; and that activations in humans are produced by affective taste, olfactory, oral texture, somatosensory, visual, social, and monetary stimuli [1, 18]. Further, activations produced by liquid food stimuli in human orbitofrontal cortex decrease when the food is consumed to satiety [79]. Damage to the orbitofrontal cortex also produces changes in reward-guided behavior in both humans and monkeys, including changes in food choice [80, 81] and changes in experienced affective state in humans [82]. Direct evidence for a role of the orbitofrontal cortex in experienced pleasantness is provided by

fMRI studies showing that activity in the orbitofrontal cortex correlates with the subjective pleasantness produced by taste, odor, flavor, oral texture, visual, temperature, somatosensory touch and other sensory rewards (Fig. 8.2b) [1, 5, 8, 32, 79, 83, 84]. For example, Fig. 8.3a shows that the subjective pleasantness of the flavor of liquid food stimuli at the time when these stimuli are consumed is represented by neural activity in the orbitofrontal cortex [5]. Thus, the human orbitofrontal cortex responds to a wide range of different rewards and represents their value and the subjective correlate of reward value, experienced pleasantness.

8.4.2.1.3 The Orbitofrontal Cortex and Decisions

The orbitofrontal cortex also seems to play a fundamental role in reward-guided, economic decisions. Tremblay and Schultz [85] found that orbitofrontal cortex neurons responded to food rewards in a manner that reflected the monkey's relative preferences for the different foods. For example, over blocks of trials in which different rewards were available, some neurons would increase or decrease their responses to the physically identical reward, depending on whether the other available reward was relatively more or less preferred. Thus, the reward system in the orbitofrontal cortex seems to rescale, even over relatively short periods of time, depending on the distribution of available rewards [86, 87]. More recently, Padoa-Schioppa and Assad [72] showed that in monkeys choosing between different types of juice reward, orbitofrontal cortex neurons encoded the economic value that guided the monkeys' choices in a manner that reflected a trade-off between juice quality and quantity. Different neurons encoded the value of individual choice options, a pre-decision variable and suitable input for a decision mechanism, or the value of the chosen option, a post-decision variable suitable for comparing expected and obtained outcomes. In further studies, orbitofrontal cortex neurons have been shown to carry information about other, more abstract decision variables, such as reward probability, magnitude, and effort (though effort was encoded to a lesser extent compared with the cingulate cortex) [88], as well as reward risk, defined as the variance in the distribution of reward values on offer [89]. These findings suggest that value representations in the orbitofrontal cortex provide a substrate not only for affective responses, including pleasure, to primary rewards, but also for making value-based decisions about rewards.

8.4.2.1.4 Summary: Roles of the Orbitofrontal Cortex in Reward and Pleasure

In summary, the orbitofrontal cortex is a brain system that responds to primary rewards such as foods in a manner which reflects both their reward value and their detailed sensory properties. Prime examples are orbitofrontal cortex neurons that are tuned to different combinations of taste, odor, oral texture and oral temperature [43]. In addition, the orbitofrontal cortex also contains more abstract representations of economic value suitable to guide economic choices. Activation of the

human orbitofrontal cortex by different rewards reflects experienced pleasure (Figs. 8.2b and 8.3a). Thus, the human capacities for rich affective experiences and adaptive behavior may to a large extend depend on the capacities of the orbitofrontal cortex to analyze, decode and represent primary rewards, learn associations between primary rewards and other stimuli, and detect changes in rewards [17]. Accordingly, understanding the representation of reward in the orbitofrontal cortex, and the factors that activate the orbitofrontal cortex may provide important insights into human values and pleasures.

8.4.2.2 The Amygdala: Reward Value, Emotion, and Implicit Influences on Behavior

The amygdala is a collection of cell masses located in the medial temporal lobe and is a principal brain structure for reward and emotion. It was first described by German anatomist Carl Friedrich Burdach in his 1819 monograph "Vom Baue und Leben des Gehirns" [90] and named *Mandelkern (nucleus amygdalae)*, presumably after its basolateral complex, which is shaped like an almond. The amygdala is structurally and functionally complex and consists of several subnuclei. However, these are often difficult to distinguish in human neuroimaging studies; in the present chapter, we therefore consider the amygdala as a whole. In terms of its anatomical connections, the amygdala receives sensory information about rewards and other stimuli from the different brain systems in Tier 1. The amygdala thus shares some of the anatomical connections of the orbitofrontal cortex, and is also directly connected with the orbitofrontal cortex. Consequently, it is implicated in similar types of affective processing and reward-related functions. However, there are also clear functional differences between the amygdala and orbitofrontal cortex.

8.4.2.2.1 Anatomical Connections of the Amygdala

Similar to the orbitofrontal cortex, the amygdala receives sensory inputs from cortical areas in Tier 1 (Fig. 8.1). Olfactory inputs to the amygdala originate in the primary olfactory cortex and even at earlier stages of the olfactory system [54]. Taste inputs originate in the ventral posterior medial nucleus of the thalamus and the anterior insular primary taste cortex [91]. Projections conveying somatosensory information reach the amygdala from the posterior insular cortex [92]. The amygdala receives visual inputs from higher order visual cortices which represent the identity of objects [91]. The amygdala is also directly connected with the orbitofrontal and medial prefrontal cortex [63, 91]. The outputs of the amygdala are directed towards brain systems involved in decision-making, action selection, attention, memory and autonomic responses [17, 91, 93–96], and these connections provide routes for the amygdala to influence emotion, cognition and behavior.

8.4.2.2.2 The Amygdala and Reward

Traditionally known for its role in fear conditioning and negative emotion [29, 97–99], it is now clear that the amygdala also plays an important role in reward processing [17, 94, 100–102]. For example, single neurons in the primate amygdala learn and update the reward value associated with visual cues [100, 102] and reflect the magnitude of consumed liquid rewards [103]. Amygdala lesions in monkeys produce deficits in choosing between objects when choices have to be based on the current value of foods associated with each object [94]. Amygdala lesions also produce changes in food preferences, in that lesioned monkeys select unpalatable foods that normal animals would avoid [104].

In both human and non-human primates, the amygdala is implicated in reward processing partly by its role in representing the sensory features of food rewards including their taste, odor, flavor, temperature, texture and fat content [5, 83, 105–108]. However, in contrast to the orbitofrontal cortex, the neuronal representation of sensory food properties in the amygdala is less distinct and more broadly tuned, in that amygdala neurons tend to have more similar responses to different stimuli. The amygdala is also implicated in motivational state, though its function in satiety at the neuronal level is less clear than for the orbitofrontal cortex [105, 109–111]. In humans, activations in the amygdala are produced by a range of food stimuli with different sensory properties [5, 83, 106, 112]. Some neuroimaging studies using taste [106] and olfactory [113] stimuli have shown amygdala engagement by intense stimuli independent of stimulus pleasantness. However, the amygdala does not seem to represent intensity independent of value in any simple way. In an explicit test of the amygdala's role in valence vs. intensity processing, it was found that the amygdala distinguished high intensity from low intensity odors only when these had affective value (i.e. when they were either pleasant or unpleasant) but not when they were neutral [114]. Thus, the amygdala seems to respond to affective stimuli in a manner that reflects interactions between intensity and valence.

What is the amygdala's role with respect to experienced pleasure produced by sensory rewards? Compared to the orbitofrontal cortex (and the perigenual cingulate cortex, as discussed below), amygdala activation by primary rewards in neuroimaging studies is not as consistently related to moment-by-moment ratings of experienced pleasure. To some extent this could be due to potentially reduced signal sensitivity in medial temporal lobe areas when fMRI imaging parameters are optimized for the orbitofrontal cortex. However, in several studies in which basic responses to sensory rewards were detected in both orbitofrontal cortex and amygdala (suggesting adequate signal sensitivity), correlations with subjective pleasantness were found in orbitofrontal cortex but not the amygdala [5, 83]. Consistently, whereas orbitofrontal cortex lesions impair subjective hedonic and emotional experiences [82], amygdala lesions do not seem to produce similar impairments [115] with the possible exception of an attenuated experience of fear [116]. Thus, compared with the orbitofrontal cortex, the amygdala may be less directly involved in experienced pleasure, and its reward responses may be used for different functions.

8.4.2.2.3 The Amygdala, Pavlovian Learning of Values, and Implicit Influences on Behavior

Rather than representing experienced pleasure, the role of the amygdala in reward-related behavior may lie primarily in the learning and updating of values, and in allowing these learned values to guide behavior [17, 29, 101, 117, 118]. Current theories of amygdala function emphasize its involvement in Pavlovian learning processes and its potential to influence behavior and decision-making by virtue of its stored reward and punishment associations [99, 101]. According to one computational hypothesis [17, 102], neuronal networks in the amygdala may perform a pattern association function to link stimuli with primary rewards and punishers. These views are supported by clear evidence that amygdala neurons in primates learn and update associations of neutral (visual) stimuli with reward and punishment in Pavlovian learning situations [100, 102]. The conditioned responses and learned values resulting from these processes seem to influence decision-making and behavior in an implicit, covert way [119]. For example, patients with lesions of the amygdala failed to acquire conditioned preferences for visual stimuli that were paired with food rewards [120]. The conditioning procedure was administered incidentally during performance of a distracting task so that healthy control participants acquired conditioned preferences without awareness of the conditioning procedure. Further, Pavlovian-instrumental transfer, in which a conditioned stimulus that predicts a reward can enhance the vigor of instrumental responses, has been shown to involve the amygdala in both rodents and humans [121–123]. In another example, patients with amygdala lesions failed to acquire autonomic responses to affective stimuli in a conditioning procedure, even though they could report the details and contingencies of the conditioning process [124]. The amygdala is also implicated in framing effects during decision-making in which decisions about otherwise identical (i.e. rationally equivalent) choice options are influenced by the way in which the choice options are described [125]. This suggests that the amygdala is involved when conditioned values or contextual cues guide behavior.

One possible route for the amygdala to influence behavior is via its connection with the striatum, a brain system known for its role in implicit habitual behavior [126]. Further, connections between the amygdala and prefrontal cortex may provide a route for the amygdala to bias decision processes on the basis of conditioned values and stimulus-reward associations [99, 127]. Another way for the amygdala to guide behavior is via its outputs to the basal forebrain, a key structure in the control of attention and vigilance. Moreover, the amygdala has direct connections to autonomic effector structures in the brain stem. Via this route, the amygdala can control and influence the autonomic components of emotion. The evidence above, together with other studies [124, 128], thus suggests involvement of the human amygdala in Pavlovian learning involving affective stimuli and in covertly influencing behavior and emotion on the basis of learned associations.

8.4.2.2.4 The Amygdala and Economic Choice

The amygdala is not only a key structure of the brain's reward and emotional learning systems but it is also involved in reward-based, economic decisions. In humans, Urbach-Wiethe disease, a rare genetic condition associated with selective damage to the amygdala, is related to changes in decision-making under conditions of ambiguity [127] and risk [129] as well as changed autonomic responses during decision-making. Existing theories of the amygdala view its role in decisions as restricted mainly to the evaluation of choice options [99, 101, 127], rather than extending to the decision process itself. Although this view ties in well with known amygdala functions in reward [94, 102, 130], Pavlovian learning [100, 131], and emotion [97, 99, 101, 118, 132–134], the information carried by single neurons in the primate amygdala during economic decision-making has not been systematically explored. In the absence of such data, it may be premature to discard a more direct role for the amygdala in decision processes.

To address this fundamental question, Grabenhorst, Hernadi and Schultz carried out a neurophysiological investigation on the amygdala's role in economic decisions [135]. In this study, monkeys made repeated choices to save liquid rewards with interest over consecutive trials until they decided to spend the saved reward for consumption [135]. During trial-by-trial economic saving, single neurons in the amygdala predicted the choices that the monkeys were going to make on a given trial with remarkable accuracy. Multiple regression analysis showed that many of these amygdala neurons reflected the monkeys' choices but not the economic value on which the choices were based. This suggested a representation of the identity of the chosen option rather than a value signal, i.e. a representation of the output of a decision mechanism, rather than of its input. Importantly, these choice signals occurred early in trials even before the monkeys knew which response to make to implement their choice, suggesting an abstract, action-independent representation of economic choice in the amygdala. This finding indicates that the role of the amygdala in economic choice may significantly extend beyond its evaluative functions. We suggested [135] that rather than informing decision mechanisms in downstream brain systems, the amygdala itself may implement a decision process that computes choices from locally represented value information.

8.4.2.2.5 Summary: Amygdala Function in Reward-Guided Behavior

The amygdala is at a similar stage in information processing as the orbitofrontal cortex and it is implicated in similar affective and value-related functions. Indeed, both areas interact during value-guided behavior [94]. However, compared to the orbitofrontal cortex, the amygdala is less directly implicated in experienced pleasure. The amygdala's functional specialization may be to allow Pavlovian learned

(conditioned) associations and other contextual biases to influence affective state, decision-making and behavior. These influences may be mediated largely via implicit routes operating outside of our awareness. Finally, recent evidence for encoding of economic choices beyond value signals by primate amygdala neurons [135] suggests a more direct role for the amygdala in decision-making than previously thought.

8.4.2.3 The Anterior Cingulate Cortex: Reward Representations as an Interface for Affective Responses and Actions

The cingulate cortex occupies the parts of the medial wall of the cerebral hemispheres that surround the corpus callosum (Fig. 8.2a). On anatomical, connectional and functional grounds it can be divided into different subregions. Here we focus on the anterior or perigenual cingulate cortex, located around the anterior (genu) part of the corpus callosum, as this part is most consistently implicated in representations of primary rewards and pleasure (Fig. 8.2b). It can be distinguished from a mid-cingulate region, which contains the cingulate motor areas involved in action-reinforcer associations and movement preparation [136], and a posterior cingulate region involved, among other functions, in self-relevant information processing and episodic memory [137].

8.4.2.3.1 Anatomical Connections of the Anterior Cingulate Cortex

The pregenual and subgenual cingulate areas have connections with the amygdala, insula, medial and lateral temporal cortex, the medial and lateral parts of the orbitofrontal cortex, and other parts of anterior and posterior cingulate cortex [52, 136, 138, 139]. The subgenual and pregenual cingulate areas are also heavily interconnected with each other [136]. In contrast to the amygdala and orbitofrontal cortex, the anterior cingulate cortex receives little direct input from sensory systems in Tier 1 that could provide information about primary sensory rewards [58]. Thus, information about sensory rewards and their affective value may reach the anterior cingulate cortex indirectly via afferents from the amygdala and orbitofrontal cortex. Both the pregenual and subgenual cingulate areas have strong outputs to the hypothalamus, ventral midbrain, and the periaqueductal gray [55, 63, 140], providing potential output pathways for the anterior cingulate cortex to influence autonomic and endocrine functions. Projections from the anterior cingulate cortex also reach the ventromedial striatum [66]. The anterior cingulate areas project into the mid-cingulate cortex, which contains the cingulate motor areas and which is involved in preparing actions and linking actions to rewards [136]. Compared to the orbitofrontal cortex, this profile of connectivity suggests a position in information processing which is further removed from the sensory input systems in Tier 1 and more closely related to autonomic and motor output systems.

8.4.2.3.2 The Anterior Cingulate Cortex and Reward

The anterior, perigenual cingulate cortex is involved in reward processing and experienced pleasure as shown by activations in human neuroimaging studies (Figs. 8.2b and 8.3b). For example, Fig. 8.3b shows that the subjective pleasantness of the flavor of liquid food stimuli at the time when these stimuli are consumed is represented by neural activity in the anterior cingulate cortex [5]. Neuroimaging studies have shown that the human anterior cingulate cortex responds to a range of pleasant and unpleasant stimuli, and that these responses frequently correlate with subjective ratings of pleasure. Pleasant or unpleasant somatosensory touch applied to the hand activates the anterior cingulate cortex [33]. The pregenual cingulate cortex also reflects the experienced pleasure or displeasure of warm, pleasant or cold, unpleasant touch to the hand [32]. The pregenual cingulate cortex is activated in humans by pleasant sweet [141] and umami [8, 142] taste and shows supralinear activation to the pleasant combination of umami taste and a consonant vegetable odor [142], as well as the combined sight and taste of chocolate in chocolate cravers [143], suggesting that this brain area responds strongly to food stimuli that are highly pleasant. The anterior cingulate cortex is also activated by water when it is rewarding, that is when subjects are thirsty, and reflects the subjective pleasantness of water [144]. In monkeys, there is evidence that primary reinforcers are represented in the primate pregenual cingulate cortex, in that a small proportion of neurons have taste responses that are mostly tuned to sweet taste [50]. These findings suggest that the anterior cingulate cortex responds similar to the orbitofrontal cortex in neuroimaging studies involving sensory rewards and provides similar representations of reward value and experienced pleasantness.

8.4.2.3.3 Comparing Orbitofrontal Cortex and Anterior Cingulate Cortex Functions in Reward, Pleasure and Choice

If activations in both orbitofrontal cortex and anterior cingulate cortex reflect the affective value of rewards, what might be the difference in information processing between these two areas? We suggested [1, 18, 145] that information about the value of rewards is projected from the orbitofrontal cortex to the anterior cingulate cortex (its pregenual and dorsal anterior parts). The pregenual and dorsal anterior cingulate cortex can then be conceptualized as an interface which allows information about rewards and outcomes to be linked, via longitudinal connections running in the cingulum fibre bundle [136], to information about actions represented in the mid-cingulate cortex.

Bringing together information about specific rewards with information about actions is important for associating actions with the value of their outcomes and for selecting the correct action that will lead to a desired reward [146, 147]. Thus, the function of the anterior cingulate cortex as a neural interface could be to support decisions about which actions to select on the basis of reinforcement and to enable learning of action-reinforcer associations. This is consistent with the finding that

lesions to the monkey rostral cingulate motor area impair performance when responses have to be selected on the basis of current reward associations [148], and evidence that lesions of anterior cingulate cortex also impair reward-guided action selection [149, 150]. Further, neuroimaging studies have shown that the anterior cingulate cortex is active when outcome information guides choices [151]. Single neurons in the monkey anterior cingulate cortex encode information about both actions and outcomes including reward prediction errors for actions [152, 153]. For example, Luk and Wallis [152] found that when information about different outcomes (types of juice) had to be associated on a trial-by-trial basis with different responses (types of lever movement), neurons in anterior cingulate cortex encoded information about both specific outcomes and specific actions. In a different study, Seo and Lee [154] found that dorsal anterior cingulate cortex neurons encoded a signal related to the history of rewards received in previous trials, consistent with a role for this region in learning the value of actions. Interestingly, in both of these studies there was little evidence for encoding of choices, indicating that a choice mechanism between rewards may not be implemented in anterior cingulate cortex.

A recent neurophysiological study provided key insights into the functional specialization of the anterior cingulate cortex compared to the orbitofrontal cortex. Cai and Padoa-Schioppa [155] recorded from neurons in the anterior cingulate cortex while monkeys chose between different types of juice rewards offered in different quantities. The study used the same paradigm and statistical analysis techniques previously used for recordings from the orbitofrontal cortex [72]. Similar to neurons in orbitofrontal cortex, some cingulate cortex neurons encoded post-decision variables, including the subjective value of the chosen option and the identity of the chosen juice. However, in contrast to the orbitofrontal cortex, cingulate cortex neurons did not encode pre-decision variables related to the value of individual choice offers. Further, neuronal activity in one part of the anterior cingulate cortex was spatially selective and reflected the chosen action as determined by the economic choice – a type of neuronal signal not observed in the orbitofrontal cortex. Cai and Padoa-Schioppa concluded from their results that economic decision processes, i.e. value comparisons between economic stimuli or "goods", seem to take place upstream of the anterior cingulate cortex [155].

Taken, together results from lesion and neurophysiological investigations provide support for the hypothesis that the anterior cingulate cortex may receive information about rewards and their values from the orbitofrontal cortex and act as an interface to link value and reward representations to action representations.

8.4.2.3.4 Relationship Between Reward-Based and Cognitive Functions of the Anterior Cingulate Cortex

Some of the proposed cognitive functions of the anterior cingulate cortex [156, 157] may be related to its role in representing rewards and their values. For example, parts of the anterior cingulate cortex are implicated in response conflict detection and monitoring for conflict [156, 157]. A system for conflict detection may become engaged by

hedonically complex rewards that contain both pleasant and unpleasant components at the same time, as we have observed for a hedonically complex odor mixture [10].

The anterior cingulate cortex is also specifically involved in navigating complex decision environments in which more than two alternative courses of action are available, as is required in ecological foraging [158, 159]. It has been suggested that during foraging, the anterior cingulate cortex may provide value representations in a special reference frame which entails the search for and evaluation of multiple choice alternatives [159]. This implies a valuation mechanism in the anterior cingulate cortex that is specialized for evaluating multiple courses of actions. It seems possible that in situations in which primary rewards are delivered to subjects in an fMRI scanner in the absence of foraging requirements or choice alternatives [8, 10, 27, 32, 160], such a mechanism might simply reflect the value or subjective pleasure of the consumed reward.

8.4.2.3.5 Participation of the Anterior Cingulate Cortex in Autonomic Function and Emotion

Parts of the anterior cingulate cortex seem to constitute a special output system for emotions, feelings, and their autonomic correlates: The subgenual cingulate cortex is, via its outputs to the hypothalamus and brainstem autonomic effector regions, implicated in the autonomic component of emotional states [61, 161–164]. Electrical stimulation of the anterior cingulate cortex induces emotional feelings and related autonomic changes including changes in respiration, blood pressure, facial flushing, and salivation [137]. Neural activity in the anterior cingulate cortex correlates with measures of autonomic arousal [165] and activations are found in relation to interoceptive awareness, for example when subjects make judgments about their heartbeat [166]. The subcallosal part of the cingulate cortex is also implicated in depression in that stimulation in this brain region alleviates depressive symptoms [167, 168]. Further, emotional changes follow damage to the anterior cingulate cortex and related areas in humans [82]. Thus, this part of the anterior cingulate cortex seems to participate in regulating the somatic and autonomic correlates of emotion.

8.4.2.3.6 Summary: Reward-Related Functions of the Anterior Cingulate Cortex

The anterior cingulate cortex provides representations of the reward value and subjective pleasure of many sensory rewards, which it may receive from the orbitofrontal cortex and amygdala. These value representations may provide the inputs for an associative learning system in the mid-cingulate cortex that links goals or outcomes to actions, and which may participate in the selection of actions based on expected outcomes. The subgenual region of the anterior cingulate cortex participates in the control of autonomic and somatic responses to affective stimuli. The anterior cingulate cortex may therefore provide an interface that links reward and value representations to output system for emotional responses and actions.

8.4.2.4 Rules of Operation of the Orbitofrontal Cortex and Anterior Cingulate Cortex in Reward and Pleasure

Our analysis so far suggests that the orbitofrontal cortex and anterior cingulate cortex are two principal brain systems involved in experienced pleasure in humans. We next examine some specific rules of operation of these reward and pleasure systems. We focus on recent developments in understanding how reward and pleasure are represented in these brain systems, how valuation signals in these systems are scaled, how they adapt to context and how they are modulated by top-down processes.

8.4.2.4.1 Reward-Specific Representations and Hedonic Maps

The evidence described in the previous sections shows that the value and experienced pleasantness of a range of sensory rewards are represented in the orbitofrontal cortex and anterior cingulate cortex, including pleasant taste [169], pleasant touch [33, 170], pleasant odor [10, 31, 84], pleasant flavor [8, 79, 83, 142], and pleasant thermal stimuli [32, 171]. Does this mean that the representation in these regions is of something general, such as general pleasantness? Although the functional imaging evidence does not address this directly, single neuron recordings in monkeys can provide a clear answer. Single neurons in the orbitofrontal cortex encode different specific rewards [17, 18]. They do this by responding to different combinations of taste, olfactory, somatosensory, thermal and visual stimuli. For example, orbitofrontal cortex neurons with responses to oral stimuli respond in some cases only to oral temperature, and in other cases to temperature and/or capsaicin and/or taste and/or viscosity and/or gritty texture and/or fat texture [41]. Thus the representation at the neuronal level in the orbitofrontal cortex is of the specific details of each sensory stimulus [17, 172], but in a way in which the hedonic value is made explicit in the representation, in that for example some neurons decrease their response to a food stimulus when that food is fed to satiety [74]. Part of the adaptive utility of this reward-specific representation is that it provides the basis for sensory-specific satiety as implemented by a decrease in the responsiveness of reward-specific neurons [18]. This is a fundamental property of reward systems that helps to ensure that a variety of different rewards is selected over time [17].

There is some indication that pleasant and unpleasant stimuli are represented in different parts of the orbitofrontal and anterior cingulate cortices, which may suggest the existence of hedonic maps (or "pleasure maps") in the human brain. Specifically, different types of reward tend to be represented in the human medial orbitofrontal cortex and pregenual anterior cingulate cortex, and different types of punisher tend to be represented in the lateral orbitofrontal cortex and dorsal part of anterior cingulate cortex (see Fig. 8.2b). This topological organization with different types of specific reward represented close together in the orbitofrontal cortex may allow for comparison between different rewards implemented by lateral inhibition as part of a process of scaling different specific rewards to the same range [17]. A topological organization of reward and punishment systems may also be

important to provide partly separate inputs into brain systems for learning, choice, and cost-benefit analysis.

8.4.2.4.2 The Orbitofrontal Cortex Implements a Common Scaling for Different Types of Reward

The orbitofrontal cortex represents the value of a range of different rewards, often in close proximity to each other. For example, in a recent fMRI study, the same parts of the human orbitofrontal cortex and pregenual cingulate cortex represented the pleasantness of fundamentally different primary rewards, taste in the mouth and warmth on the hand [160]. What are the functional implications of brain systems that bring representations of different types of rewards into anatomical proximity? According to one theory of orbitofrontal cortex function [17], this organization enables a comparison of the value of different types of reward, which is implemented by local lateral inhibition mediated by inhibitory interneurons. In this view, the currently most strongly activated excitatory neurons representing one type of reward would reduce the activity of less strongly activated neurons corresponding to representations of alternative rewards. The functional consequences of this architecture are contrast enhancement and local scaling of reward value and these properties can arise if different rewards are represented in the same general region of cortex. This type of organization also has implications for neural decision processes as considered next.

Economic decision theory [173] implies that decision-makers convert the value of different goods into a common scale of utility. Ecological [174], psychological [22], and neuroscientific approaches [175] similarly suggest that the values of different kinds of rewards are converted into a common currency. We have argued [17, 18] that different specific rewards must be represented on the same scale, but not converted into a common currency, as the specific goal that is selected in a decision process must still be identifiable so that the appropriate action to obtain that particular goal can be chosen [17, 18]. Thus, the key difference between the two concepts of common neural currency of value vs. common neural scaling of value lies in the specificity with which rewards are represented at the level of single neurons: While a common currency view implies convergence of different types of rewards onto the same neurons (a process in which information about reward identity is lost), a common scaling view implies that different rewards are represented by different neurons (thereby retaining reward identity in information processing), with the activity of the different neurons scaled to be in the same value range.

What specific advantages does a common scaling of different rewards confer? With our current computational understanding of how decisions are made in attractor neural networks [176–179], it is important that different rewards are expressed on a similar scale for decision-making networks to operate correctly while at the same time retaining information about the identity of the specific reward. The computational reason is that one type of reward (e.g. food reward) should not dominate all other types of reward and always win in the competition, as

this would be maladaptive. Making different rewards approximately equally rewarding makes it likely that a range of different rewards will be selected over time (and depending on factors such as motivational state), which is adaptive and essential for survival and reproduction [17]. The exact scaling into a decision-making attractor network will be set by the number of inputs from each source, their firing rates, and the strengths of the synapses that introduce the different inputs into the decision-making network [62, 176, 178, 179].

8.4.2.4.3 The Orbitofrontal Cortex Represents Value in Both Relative and Absolute Terms

For decision-making to be adaptive, it seems desirable that the brain represents the value of rewards both in absolute and relative terms. A neural representation of the absolute value of rewards should be independent of the value of other available rewards. Conceptually, such absolute value representations are closely related to transitivity, a fundamental property of economic choice which concerns the internal consistency of an individual's choice pattern [180]. Accordingly, a representation of value that is invariant with respect to the current reward context provides a foundation for establishing stable preferences and consistent choice behavior. However, a representation of relative value, in which the value of a reward depends on the current reward environment, may also be useful in decision-making. For example, when choosing between two rewards on a "single-shot" trial, it may be helpful to allow the neuronal activity in a decision system in the brain to increase to the more valued option, and to decrease to the other, as a result of competitive interactions in attractor networks [176–179]. We have also suggested that having an overshoot of the relative reward value, as found in positive contrast effects [181, 182], may be a useful heuristic built into the brain that facilitates local hill-climbing up reward gradients by helping an organism lock on well to a more valuable goal if it has recently become better than other options. Conversely, negative contrast, in which a reward becomes transiently relatively undervalued after the reward value has decreased, may be useful in helping organisms to unlock from a recently devalued goal, and this may encourage the organism to explore the environment for other alternative goals.

The current evidence suggests that both, representations of relative and absolute value may be found in the orbitofrontal cortex. A recent study provided evidence for absolute value coding in the orbitofrontal cortex, in that neuronal responses that encoded the value of a specific stimulus did not depend on what other stimuli were available at the same time [180]. It was suggested that transitivity, a fundamental trait of economic choice, is reflected by the neuronal activity in the orbitofrontal cortex [180]. This type of encoding contrasts with value-related signals found in the parietal cortex, where neurons encode the subjective value associated with specific eye movements in a way that is relative to the value of the other options that are available [183]. However, there is also evidence for relative encoding of value in the orbitofrontal cortex, in that neuronal responses to a food reward can depend on the

value of the other reward that is available in a block of trials [85]. Two recent studies demonstrated that neurons in the orbitofrontal cortex adapt the sensitivity with which reward value is encoded to the range of values that are available at a given time [86, 87]. This reflects an adaptive scaling of reward value over certain periods of time, evident also in positive and negative contrast effects, that makes the system optimally sensitive to the local reward gradient, by dynamically altering the sensitivity of the reward system so that small changes can be detected [17]. The same underlying mechanism may contribute to the adjustment of different types of reward to the same scale described in the preceding section.

Given that representations of both absolute value and relative value are needed for economic decision-making, we [31] tested explicitly whether both types of representation are present simultaneously in the human orbitofrontal cortex. In a task in which two odors were successively delivered on each trial, we found that fMRI activations to the second odor in an antero-lateral part of the orbitofrontal cortex tracked its relative pleasantness, in that activations reflected not only the pleasantness of the current (second) odor but also the pleasantness of the immediately preceding (first) odor on that trial. By contrast, activations in the medial and mid-orbitofrontal cortex tracked the absolute pleasantness of the second odor in that the activation was irrespective of the pleasantness of the preceding odor. Thus, reward responses in different parts of the orbitofrontal cortex seem to differ in their sensitivity to other available rewards. Accordingly, both relative and absolute subjective value signals, both of which provide important inputs to decision-making processes, are separately and simultaneously represented in the human orbitofrontal cortex.

Interestingly, we also found at the behavioral level that subjects rated an odor as more pleasant when it was preceded by a relatively less pleasant odor [31]. This suggests that one way in which the pleasantness or attractiveness of a reward can be increased is by preceding it with a less pleasant or even unpleasant stimulus.

One neuronal mechanism that might implement relative reward in the orbitofrontal cortex could consist of an attractor neuronal network in which the inputs are the two rewards to be compared. However, to implement positive contrast effects over delays as in some of the experiments described above, a neuronal mechanism might involve some adaptation. In this situation, if there is overlap in the representations of two successive rewards, then there will be less activation to the second reward if it is preceded by another reward. On the other hand, if the reward is preceded by a punisher with no overlap in the representation, then the response to the reward will be large because there will be no adaptation of the reward representation. A system that does not show these contrast effects might have very selective tuning for different rewards, so that there is little overlap in the representation of the first and second rewards.

8.4.2.4.4 Cognitive and Attentional Influences on Value and Pleasure Are Expressed in Orbitofrontal Cortex and Anterior Cingulate Cortex

How do cognition and attention affect valuation and neural representations of value? One possibility is that value representations ascend from the orbitofrontal cortex

and anterior cingulate cortex to higher language-related cortical systems, and there become entwined with cognitive representations. In fact, there is a much more direct mechanism. Cognitive descriptions at the highest, linguistic, level of processing (e.g. "rich delicious flavor") or attentional instructions at the same, linguistic level (e.g. "pay attention to pleasantness") have a top-down modulatory influence on value representations in the orbitofrontal cortex and anterior cingulate cortex of odor [184], taste and flavor [8], and touch [170] stimuli by increasing or decreasing neural responses to these rewards. Thus, cognition and attention have top-down influences on the first parts of the cortex in which value is represented (Tier 2), and modulate the effects of the bottom-up sensory inputs.

Recent studies have identified the lateral prefrontal cortex (a region implicated in attentional control, see Fig. 8.1 [62, 185]) as a site of origin for these top-down influences. In one study, activity in lateral prefrontal cortex correlated with value signals in ventral anterior cingulate cortex during self-controlled choices about food consumption [186]. Using fMRI and functional connectivity analyses, we recently showed that activity in different parts of lateral prefrontal cortex differentially correlated with activations to a taste stimulus in the orbitofrontal cortex or anterior insula, depending on whether attention was focused on the pleasantness or intensity of the taste [187]. Notably, activations of connected structures in whole cortical processing streams were modulated, including the affective stream (Tier 2 of Fig. 8.1, including orbitofrontal cortex and anterior cingulate cortex) or the discriminative object stream (Tier 1 of Fig. 8.1, including the insula). To account for this observation, we extended the concept of biased competition [188] and its underlying neuronal mechanisms [189] in which top-down signals influence inhibitory competition within a brain area, to a biased activation theory of top-down attention [187], in which activations in whole processing streams may be modulated by top-down signals.

These advances have implications for a number of areas related to neuroeconomics and decision-making, including the design of studies in which attentional instructions may influence which brain systems become engaged, as well as situations in which affective processing may be usefully modulated, for example in the control of the effects of the reward value of food and its role in obesity, and in addiction.

8.4.3 Tier 3: From Valuation to Choice in the Ventromedial Prefrontal Cortex

The operational principles described above may enable reward systems to provide representations of the value of primary and other sensory rewards that are appropriately scaled as inputs for neural decision systems. By providing this "evidence" for value-based decision-making, reward and pleasure systems may promote a progression through the reward space (and "pleasure space") in the environment to find the range of rewards necessary for survival, reproduction and well-being [1, 17].

We next consider the brain mechanisms for decisions about primary rewards that occur at subsequent processing stages in Tier 3: How and where in the brain are neural value representations transformed into choices?

8.4.3.1 Decision-Related Activity in a Ventromedial Region of the Prefrontal Cortex

A large body of evidence from human functional neuroimaging studies has implicated a ventromedial region of the prefrontal cortex in value-guided decision-making (Fig. 8.4a). This functionally defined ventromedial region is located at the intersection of the medial orbitofrontal cortex, anterior cingulate cortex and medial prefrontal cortex area 10, and partly overlaps with each of these structures.

The areas comprising the ventromedial prefrontal region are heavily connected with each other and with other regions of the pregenual, subgenual and dorsal anterior cingulate cortex, and parts of the orbitofrontal cortex [64, 192]. In addition, the ventromedial prefrontal region has connections with the dorsolateral prefrontal cortex and the inferior frontal gyrus [192], which are involved in a range of cognitive functions including working memory [193], perceptual decision-making [194], and the integration of reward and cognitive processes [195]. Thus the ventromedial prefrontal region is connected with the orbitofrontal cortex and the pregenual and dorsal anterior cingulate cortex where representations of different types of reinforcers are found, and these can potentially provide input to processing performed in the ventromedial area. Projection sites of the ventromedial prefrontal cortex include, in addition to other prefrontal areas, output systems for behavioral and autonomic responses such as the medial caudate nucleus, ventral striatum and periaqueductal gray [65, 66] as well as the amygdala [192].

As illustrated in Fig. 8.4a, studies using neuroeconomic and computational approaches have revealed that neural activity in the ventromedial prefrontal region correlates with the expected value of choice options during decision-making and other, related decision parameters [183, 196, 197]. For example, measures of the expected 'goal value' of choice options can be derived from an individual's choices between different rewards, such as when subjects bid money for goods they wish to acquire (i.e. willingness to pay), and these can be used as regressors for fMRI signals [186, 198–201]. Using this approach, neural correlates of decision values or goal values for different types of expected rewards, including food items, non-food consumables, monetary gambles, and lottery tickets, have been found at the time of choice in the ventromedial prefrontal region (Fig. 8.4a).

A common theme that has emerged from these studies is that the ventromedial prefrontal area provides a system for choices about different types of rewards and for different types of decisions, including in the social domain. However, as can be seen from Fig. 8.4a, there is considerable variability in the anatomical location of decision-related effects in the ventromedial prefrontal cortex. Moreover, activity in this region has been linked to a wide range of valuation and choice signals which incorporate information about temporal delay [202–204], uncertainty [205], price

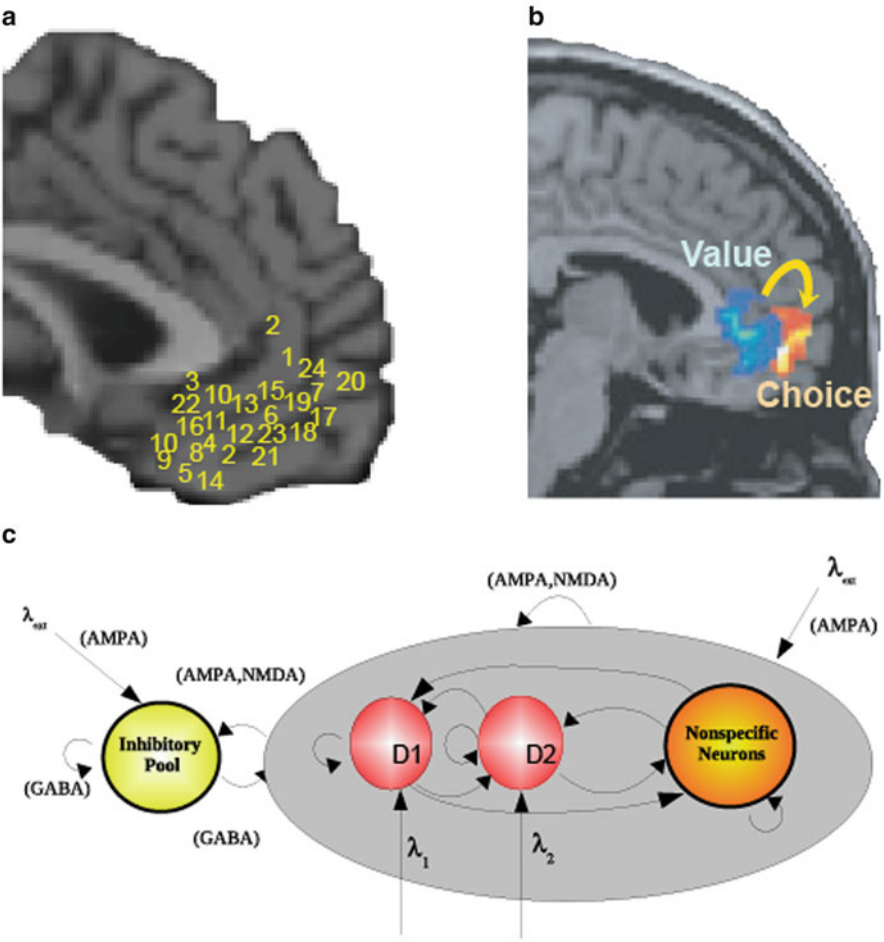

Fig. 8.4 From reward value to choice in the ventromedial prefrontal cortex. (**a**) A ventromedial region of the prefrontal cortex is frequently activated in neuroimaging studies of decision-making. In this map of activation foci, each number represents a specific effect found in one study. For example, activations in this ventromedial region have been associated with *1*: subjective value during decisions between immediate and delayed rewards; *4*: expected value during probabilistic decision-making; *5*: expected value based on social advice and own experience; *7*: price differential during purchasing decisions; *8*: willingness to pay for food items; *15*: subjective value of charitable donations; *16*: decision value for exchanging monetary against social rewards; *17*: preference decisions about thermal somatosensory stimuli; *18*: preference decisions about odors. (For complete references to the studies see [1]) (Adapted with permission from Ref. [1]). (**b**) One neuroimaging study specifically compared reward valuation processes with reward-based choice at the time of reward consumption [27]. When subjects evaluated the experienced pleasantness of thermal somatosensory stimuli applied to the hand (warm pleasant, cold unpleasant or warm-cold mixture stimuli), activity in the pregenual cingulate cortex (shown in *blue*) scaled with the trial-by-trial pleasantness ratings. By contrast, when subjects made binary choices about whether the thermal stimulus should be repeated, a more anterior part of the ventromedial region became engaged (*red* activation). Activity in this anterior ventromedial area also showed higher activity on easy

or value differential [206, 207], social advice [208], and monetary expected value [209]. This heterogeneity of findings raises the question of whether a common denominator for the functional role of the ventromedial prefrontal cortex in value-based decision-making can be identified or, alternatively, whether different subregions make functionally distinct contributions to decision-making. Here, insights are available from studies that examined the involvement of the ventromedial prefrontal area in decision-making about primary rewards, as described next.

8.4.3.2 Decisions About Primary Rewards Engage the Ventromedial Prefrontal Region

Typically, in the decision studies summarized above, individuals chose between abstract choice options that were presented visually and in which relevant decision variables were represented symbolically. However, in everyday life we often make choices on the basis of experienced pleasure while we consume a sensory reward. For example, we may sample the different sensory components of a food – its smell, taste, texture and temperature – before deciding whether or not to consume it. To investigate the brain systems underlying decisions about basic, primary rewards, we performed a series of neuroimaging studies in which individuals chose between affective stimuli based on their immediate experience of these stimuli.

Warm and cold stimuli have subjective affective components such as feeling pleasant or unpleasant, and these components may have adaptive value: approach to warmth and avoidance of cold may be reinforcers, or goals for action, built into us during evolution to direct our behavior to stimuli that are important for survival [17, 22]. Indeed, warm and cold stimuli may be prototypical primary reinforcers, and investigation of their neural processing may provide a fruitful approach to understanding the brain mechanisms of emotion and decision-making. When taking a decision about a reward or punisher, a representation of the affective value may be formed, and this may be followed by a decision process about whether to accept or work for that amount of reward. A key question concerns the extent to which affective representations in the brain are also involved in the decision process itself, or, alternatively, whether valuation and decision are to some extent anatomically separable processes.

To address this question, we performed a functional MRI experiment in which thermal stimuli that differed in affective value were repeatedly applied to the hand

Fig. 8.4 (continued) compared with difficult trials and tracked trial-by-trial decision confidence, two computationally derived criteria for a neural decision system [190, 191]. Thus, different parts of ventromedial prefrontal cortex may play different roles in value-based decisions [1] (Adapted with permission from Ref. [27]). (**c**) Computational model for a decision system that might be implemented in the ventromedial prefrontal cortex in an attractor or autoassociation network architecture [190]. Two populations of neurons (D1 and D2) represent the choice alternatives. The "evidence" (i.e. the subjective value) for decision 1 is applied via the λ_1, and for decision 2 via the λ_2 inputs. When λ_1 and λ_2 are applied, each neuronal population competes through the inhibitory interneurons (not shown), until one wins the competition, and the network falls into one of the high firing rate attractor states that represents the decision (Adapted with permission from Ref. [1])

[27]. Every time one of these affective thermal stimuli was delivered, subjects either rated their experienced pleasure or, on different trials, decided whether or not the stimulus should be repeated [27]. The choices were of consequence to the subjects, as one random choice would be selected and implemented at the end of the experiment. The imaging results revealed an interesting functional separation among subareas within the ventromedial prefrontal region (Fig. 8.4b): Whereas activity in the pregenual cingulate cortex and medial orbitofrontal cortex reflected the moment-by-moment ratings of experienced pleasure, an adjoining but more anterior part of the ventromedial prefrontal cortex was implicated in decision processes. This anterior part of the ventromedial region, which likely incorporated parts of the frontopolar medial area 10, was implicated in decision processes by the following criteria [27, 190]: First, it was more engaged when subjects made decisions about the thermal rewards compared to when they evaluated the stimuli without making a decision. Second, activity in the anterior ventromedial region was higher for easy decisions, for example when deciding whether or not to re-experience a very pleasant warm touch to the hand, compared to more difficult decisions, for example when deciding whether or not to re-experience a mixture of pleasant warm and unpleasant cold touch. Third, neural activity scaled with a trial-by-trial indicator of decision confidence (derived from the absolute difference in subjective pleasantness between choice options). Biophysically realistic simulations of decision systems in the brain predict that a brain area that implements a choice process should show just these patterns of activity: higher activity for easy compared to difficult decisions and choice-by-choice tracking of decision confidence [190]. Intuitively, the reason for this is that when the evidence in favor of one choice option is strong (i.e. when the absolute value difference between options is large), the population of neurons tuned to represent the evidence for the dominant option will inhibit the neuronal population representing the alternative option more strongly compared to when the evidence is weak [190, 194, 210, 211]. We have validated in simulations that this would lead to an increase in the fMRI signal on easy compared to difficult decision trials [190, 191].

Thus, the findings from this investigation using thermal stimuli as rewards and choice options suggest that the ventromedial prefrontal cortex is engaged by decisions about primary rewards, and in particular seems to implement a competitive decision process between choice options. Similar and confirmatory findings in the ventromedial prefrontal cortex have been obtained in an olfactory decision task, in which subjects made preference choices between affective odors [190, 191, 212]. In summary, these neuroimaging experiments on valuation and choice about primary rewards implicate the ventromedial prefrontal cortex in a specific decision mechanism. The computations involved in this mechanism are considered next.

8.4.3.3 A Computational Theory of Ventromedial Prefrontal Cortex Function

To explain the involvement of the ventromedial prefrontal cortex, it has been suggested that this part of the frontal lobe represents a common valuation signal that underlies different types of decisions as well as decisions about different types

of goods [183, 200, 203, 213]. A related account [214] suggests that whereas the orbitofrontal cortex encodes the value of specific rewards, the ventromedial prefrontal cortex plays a more specific role in value-guided decision-making about which of several options to pursue by encoding the expected value of the chosen option [208, 215, 216].

We have proposed an alternative account [1, 18, 27, 179, 190, 191] which suggests that whereas the orbitofrontal and pregenual cingulate cortices represent the value of rewards as inputs for a value-based choice process, the ventromedial prefrontal region is involved in the choice process beyond valuation, as has been found in the studies that have contrasted choice with valuation described above [27, 212]. Part of this proposal is that the ventromedial prefrontal cortex is involved in decision-making by implementing a competition between different rewards, with the computational mechanism described below. This choice process operates on the representation of rewarding *stimuli* (or goods, in economic terms), and thus takes place before the process of action selection.

This proposal is based in part on the evidence that neuronal activity in the adjacent orbitofrontal cortex is related to the reward value of stimuli, and that actions such as whether any response should be made, or a lick response, or a touch response, a right-left response are not represented in the orbitofrontal cortex [17, 62, 72, 73, 130]. Indeed, using an experimental design that temporally dissociated stimulus and action information in a value-based choice task, it has been demonstrated that correlates of chosen stimulus value can be found in the ventromedial prefrontal region even before action information is available [217]. Thus, we suggested that the role of the ventromedial prefrontal cortex is to transform continuously scaled representations of the value of choice option into a categorical representation of identity of the chosen option. This process uses a computational mechanism in which the winner in the choice competition is the chosen stimulus, which can then be used as the goal for action to guide action selection. These decision computations are described next. Notably, this computational view on the role of the ventromedial prefrontal cortex in decision-making is fundamentally different from the proposal made by Damasio and colleagues [218] according to which the ventromedial prefrontal cortex is involved in generating somatic markers (changes in the autonomic, endocrine, skeletomotor responses) which are then sensed in the insular and somatosensory cortices and thereby reflect the value of choice options and "weigh in" on the decision process.

A computational theory of how the ventromedial prefrontal region (and other cortical areas) may implement a decision process can be formulated at the mechanistic level of the operation of populations of neurons with biologically plausible dynamics [176–179, 210]. In the attractor (or autoassociation) network architecture shown in Fig. 8.4c, the evidence for decision 1 and 2 is applied separately into the decision network via the λ_1 the λ_2 inputs, respectively. These separate inputs, which can represent the value of two alternative choice options, excite neuronal populations in the decision network, which then engage in competition with each other. When λ_1 and λ_2 are applied, each neuronal population competes through inhibitory interneurons (not shown), until one population wins the competition,

and the network falls into one of the high firing rate attractors that represent the alternative decisions. Thus, biasing inputs to each population of neurons allow for competition via inhibitory neurons, and positive feedback implemented by recurrent collateral excitatory connections leads one population to transition from low or intermediate firing rates to a high firing rate. The population that wins the competition suppresses the other population via the inhibitory neurons, so that we end up with a binary outcome that represents the choice made [62, 176, 210]. This attractor-based integrate-and-fire model of decision-making makes specific predictions about the neuronal signature of a choice system in the brain as described above. The confirmation of these predictions for the anterior ventromedial prefrontal area, but not for the orbitofrontal cortex where the evidence indicates that value is represented, provides strong support for this neuronal mechanism of decision-making in the brain [190, 191].

8.4.3.4 Different Output Systems for Emotion and Reward-Guided Behavior

As described above we have suggested [1, 18] that information about the value of outcomes and expected outcomes is signalled by the orbitofrontal cortex to the perigenual cingulate cortex which allows this outcome information to be linked to action representations in the mid-cingulate cortex, thereby contributing to action-outcome learning and action selection [62, 146, 219]. Why then are there also outputs from the orbitofrontal cortex to the ventromedial prefrontal region, both directly [64] and via the pregenual cingulate cortex [64, 65]? We suggest that when a binary decision between rewarding stimuli must be made, the ventromedial prefrontal cortex becomes involved. If it is simply a case of linking an action to a reward, and thus deciding which response to perform, the mid-cingulate cortex may be engaged. But if a prior decision must be made, not about which action to make to obtain an outcome, but instead between different outcomes, then this may require participation of the ventromedial prefrontal area [27, 212]. The implication is that there are different decision systems in the brain, and that we must specify exactly what type of decision is required when relating a brain area to decision-making.

The suggestion that different cortical areas may implement different types of decisions is consistent with current computational approaches to decision-making as described in the previous section. An important concept is that choices may be made in the brain by attractor neural networks in which each attractor state, consisting of a set of neurons firing with high rates, represents one of the choices [176–179, 190, 210]. Given that the neural architecture involved in this process – local excitatory recurrent collateral connections between pyramidal cells and inhibitory interneurons that implement feedback inhibition – is prototypical of the cerebral cortex, decision processes of this type could take place in many different

cortical areas, implementing choices locally between whatever information is represented in a cortical area [62].

What determines whether a cortical brain area is involved in decision computations? We have proposed that if there is a strong forward input to the pyramidal cells, the firing rates will tend to reflect on a continuous scale the magnitude of the forward input [18]. Alternatively, if the recurrent collaterals are particularly efficacious in one area, this will tend to make the cortical area more likely to produce "choices", that is to end up in a stable state with high firing rates for a winning population, with other cells inhibited. Thus, some cortical areas may be more likely to represent inputs on a continuous scale, for example providing approximately linear representations of reward value or expected value, whereas other areas may operate more non-linearly, taking as inputs these value signals and falling into an attractor state.

In addition to the decision system for rewarding stimuli in the ventromedial prefrontal cortex and a decision system for actions linked to specific rewards in the mid-cingulate cortex there are other output systems for emotion and reward-related behavior. Some of these systems are less directly related to experienced pleasure and therefore not further discussed here. These systems are included in the framework in Fig. 8.1 and involve the striatum for behaviour based on habits and systems in the brain stem for reflexes and autonomic responses [17, 126].

8.5 What Makes Different Rewards Pleasant and Attractive? – Potential Implications for Food Design, Marketing, Health Policy and Anhedonia

The advances in understanding reward and pleasure systems summarized above were made in many cases using primary rewards, such as foods, as experimental stimuli. One advantage of using such complex, natural rewards is that the results have a clear relationship to the world outside the laboratory, and thus have ecological validity. In fact, many of the studies can be taken to have implications for improving the design of foods and other rewards, and for food marketing and health policy. For example, a current challenge in food design is to reproduce the pleasantness of oral texture produced by high fat foods but without also reproducing the high-energy load of such foods. Here it may be helpful to consider how the reward systems of the brain respond to oral fat in pleasant foods and how these brain systems incorporate both sensory and contextual information into their reward and pleasure signals. In this section, I will illustrate this approach with several examples, by describing investigations that were designed to yield general insights into brain function, but which also have implications for applied fields including food design, marketing, and health policy, and which may also be relevant for understanding conditions in which affective responses to pleasant stimuli are impaired, as in anhedonia.

8.5.1 Oral Fat Texture in Foods: A Prototypical Primary Reward

The sensory properties of food are important determinants of the reward value of food and oversensitivity of the brain's reward systems to these sensory properties may be a driving factor in overeating and obesity [1, 105, 220–223]. One of the sensory properties of food which contributes to its palatability and pleasantness is its oral fat texture, that is, the mouth-feel of fat [5, 224]. Fat is an important component of the human diet as it is both a high-value energy source and source of essential fatty acids. Typically, foods rich in fat are also highly palatable and the likely reason for this is an innate mechanism that makes energy-rich foods particularly attractive to us. Although highly adaptive under conditions when fat-rich foods are sparse, this mechanism causes problems in modern societies in which fat-rich foods are abundant and their consumption is promoted by advertising and other marketing actions. Indeed, fat is frequently over-consumed as part of highly pleasant, energy-rich foods and is a likely contributing factor to obesity [224, 225].

What makes oral fat pleasant? How do the brain's reward systems respond to oral fat? Until recently, little was known about how oral fat texture and its pleasantness are represented in the brain. This is an important issue, as evidence on the neural representation of the reward value of oral fat would provide a basis for investigations of whether the brains of obese people differ, inter alia, in their responsiveness to the reward value of oral fat texture. Such evidence would also help in the design of foods that mimic the pleasant texture of oral fat, yet have low energy content.

8.5.1.1 Brain Representations of Oral Texture, Including Fat Texture

Pioneering investigations to examine the representation of oral fat in the brain to understand the principles of its neural processing were carried out by Rolls and colleagues using single neuron recordings in macaque monkeys (for a detailed review, see [226]). These investigations showed that at the level of single neurons there is a representation of oral fat in the primary taste cortex in the anterior insula, in the secondary taste cortex of the orbitofrontal cortex, and in the amygdala [41, 44, 59, 108, 227]. Thus, areas in the primate brain that process the taste of foods also provide representations of its fat content and texture [228]. Another key finding of these studies was that the neuronal encoding of fat may occur via a texture-specific channel rather than a chemical channel: Neurons that responded to oral fat also responded to non-fatty oils that were similar in texture to the fat stimuli used [44, 227]. Thus, one way in which the brain's reward system may detect the presence of fat in foods is by its texture. Further, in some neurons information about fat texture converged with other sensory information including taste and oral temperature, and in the orbitofrontal cortex also with the sight and odor of food [41, 44, 108, 227].

The first evidence on the representation of food texture and oral fat in the human brain was provided by de Araujo and Rolls [141]. Building on the earlier neurophysiological studies, they tested human brain responses, measured with fMRI,

to a range of oral stimuli that differed in fat content and viscosity. The study showed that the anterior insular cortex responded to the viscosity of non-fatty oral stimuli as well as to fatty vegetable oils. Fatty stimuli also produced activation in a mid-insular region posterior to the taste area, in the hypothalamus, ventral striatum, and parts of the cingulate cortex. Remarkably, the pregenual cingulate cortex responded both to the delivery of oral fat and the delivery of non-fatty sucrose solution, indicating a potential role in processing the hedonic component of oral fat.

8.5.1.2 What Makes Oral Fat Pleasant? – How the Human Brain Represents the Reward Value of Fat in the Mouth

Although the investigations described above implicated different brain areas in the representation of oral fat, it remained unclear which of these brain areas were specifically related to the rewarding, hedonic properties of oral fat including subjective pleasantness. To address this question, Grabenhorst and colleagues [5] examined neural activity while subjects consumed liquid food stimuli that differed both in fat content and in flavor. The rationale was that the reward value of fat texture frequently depends on other sensory components of a food. For example, many people like a creamy texture in combination with a "sweet" flavor, as in vanilla ice cream or strawberries with cream, which is a popular summer snack in England. By contrast, some people are repelled by creamy texture in combination with savory flavors, as in avocado cream.

In the study by Grabenhorst et al. [5], a factorial design helped to distinguish brain responses to foods that were both pleasant in flavor and high in fat content from those that were also pleasant in flavor but low in fat content and less pleasant flavored foods with high fat content. Further, every time subjects consumed a small amount of one of the liquid food stimuli, they reported the experienced pleasantness of the oral texture and, on separate scales, the pleasantness of the flavor, as well as of the fattiness of the stimulus. As subjects were trained in providing independent ratings of these sensory properties, this procedure helped to identify parts of the brain in which neural activity at the time of consumption was related to the moment-by-moment changes in experienced pleasure.

We found that the reward systems of the medial orbitofrontal cortex and pregenual cingulate cortex responded to the food stimuli in a manner that correlated with the subjective pleasantness of the oral fat texture (Fig. 8.5a, b) [5]. This showed for the first time that neural activity in these reward areas in humans is directly related to the hedonic feelings produced by having fat in the mouth. In nearby places in both orbitofrontal and anterior cingulate cortex activations also correlated with the subjective pleasantness of the flavor component of the food. (Parameters for texture pleasantness and flavor pleasantness were estimated simultaneously in a multiple regression model – this ensured that neural activations in these adjacent parts of orbitofrontal and pregenual cingulate cortex were related to unique variance components in the texture and flavor pleasantness ratings.) These brain areas thus represent both the pleasantness of fat texture and the pleasantness of flavor. Bringing together representations of the sensory properties of food in the brain is likely to be important in determining the palatability of a food, which can be enhanced by particular combinations of the

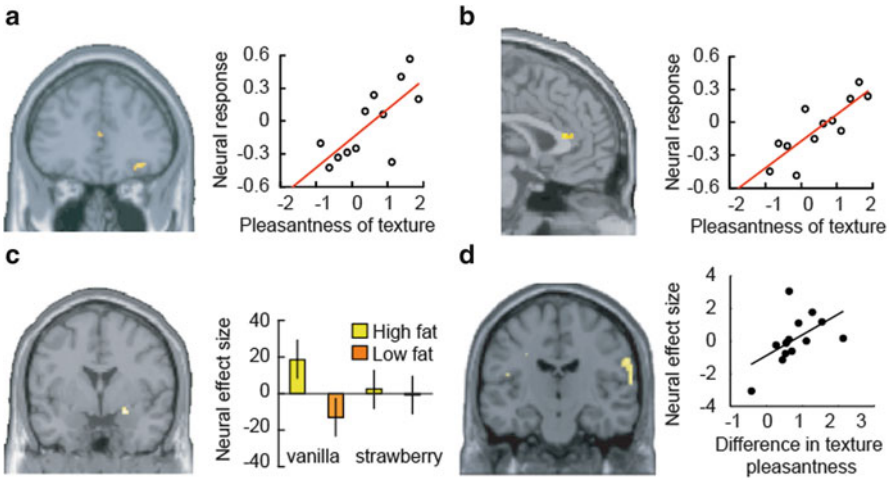

Fig. 8.5 How the brain represents the reward value of fat texture in the mouth [5, 6]. Healthy, mildly hungry volunteers consumed a range of dairy drinks that differed in fat content and flavor. Neural activity in the reward systems in the orbitofrontal cortex (**a**) and pregenual cingulate cortex (**b**) at the time of consumption correlated with the experienced pleasantness of the oral texture (the mouth-feel) of the food stimuli [5]. (**c**) The amygdala responded differentially for high- and low-fat stimuli but only if these had a pleasant, vanilla flavor, and not for stimuli with a less pleasant strawberry flavor. (**d**) The oral part of the somatosensory cortex was functionally coupled to the orbitofrontal cortex area shown in (**a**), in which activations were related to texture pleasantness [6]. Activity between these two brain areas was more strongly correlated during consumption of pleasant-flavored high-fat foods compared with low-fat food of the same flavor. *Right*: The effect size of this neural coupling predicted differences between individuals in their liking for the high-fat compared to the low-fat foods (Adapted with permission from Refs. [5] and [6])

sensory properties, including sweet and fat, as occurs in foods such as ice cream and chocolate. This convergence in a common brain area provides for neurons to be activated by particular combinations of taste and oral texture, and thus for particular combinations of taste and oral texture to become pleasant or unpleasant, and to show sensory-specific satiety [17]. In addition to the orbitofrontal and pregenual cingulate cortex, the amygdala was found to distinguish the high fat and low fat versions specifically of the pleasant-flavored food [5] (Fig. 8.5c). This hedonic-specific amygdala activation by oral fat may contribute to the affective response to high fat foods and may allow fat rewards to implicitly influence behavior.

8.5.1.3 A Role for the Oral Somatosensory Cortex in the Reward Value of Fat Texture

In a subsequent investigation, Grabenhorst and Rolls [6] found that the human somatosensory cortex is involved in oral fat processing via functional coupling to the orbitofrontal cortex, where the pleasantness of fat texture is represented.

It was found that somatosensory cortex activity was more strongly correlated with orbitofrontal cortex activity during the consumption of a high fat food with a pleasant (vanilla) flavor compared to a low fat food with the same flavor (Fig. 8.5d). This effect was not found in control analyses using high fat foods with a less pleasant flavor or pleasant-flavored low fat foods. Thus, the finding is that a combination of high fat with a pleasant, sweet flavor specifically enhances coupling between the region that represents pleasant fat texture, the orbitofrontal cortex, and the somatosensory cortex, a sensory brain system which processes the physical characteristics of stimuli.

Unlike in the orbitofrontal cortex, activity in somatosensory cortex was not directly related to subjective fat texture pleasantness or flavor pleasantness [6]. Thus there was no indication of a hedonic representation per se in this part of the brain. Instead, somatosensory cortex activity correlated with ratings of subjective fattiness, suggesting a representation of the sensory properties of oral fat. This places the somatosensory cortex at a similar processing stage as the anterior insular (primary taste) cortex, where the pleasantness at least of taste is not represented neuronally in the primate brain [105, 172], and where fMRI signals are typically related to sensory properties of oral stimuli rather than their pleasantness [1, 8, 106, 169].

An interesting finding was that, across subjects, the strength of the functional coupling between somatosensory cortex and orbitofrontal cortex explained inter-individual variation in texture pleasantness evaluations (Fig. 8.5d). That is, while subjects consumed the different oral fat stimuli, functional coupling between the sensory and reward areas of the brain predicted their subsequent liking of the high fat foods compared to the low fat foods. This finding may in future studies serve as an indicator to test the potency of novel food stimuli. It could also aid in the identification of dysfunction in these brain circuits in specific clinical groups, for example in individuals with eating disorders or anhedonia.

8.5.1.4 Implications for Overeating, Obesity, and the Design of Foods

The findings summarized above extend known functions of the human orbitofrontal cortex, anterior cingulate cortex, amygdala and oral somatosensory cortex to the processing of pleasant-flavored oral fat. They also implicate functional coupling between the somatosensory cortex and reward structures as a candidate neural mechanism that could be important in appetite, overeating and obesity. The functional coupling between the orbitofrontal cortex and oral somatosensory cortex occurred specifically during the consumption of foods that had both high fat content and a pleasant flavor. This is consistent with evidence that oral fat is particularly pleasant when combined with consonant flavors [224], and liking for such foods can predict weight gain [229]. Previous human imaging studies reported activations in somatosensory cortex by different types of food stimuli [230–233] and suggested links to obesity [234, 235]. Obese individuals show higher resting state activity of oral somatosensory cortex [234]. Youths and adults at risk for obesity show higher activation of somatosensory cortex by food stimuli [235, 236]. Based on anatomical connections, Kaas and

colleagues suggested an involvement of somatosensory cortex in both oral tactile and taste processing [237–239]. Our findings extend this view to incorporate a specific role in the processing of oral fat texture. Stice and colleagues [236] posited that altered somatosensory cortex responses in individuals at risk for obesity could reflect enhanced preferences for oral fat. Consistent with this proposal, we found that although the representation of oral fat in somatosensory cortex appears to be of its sensory properties, the oral somatosensory cortex is implicated in processing related to the hedonic analysis of fat texture via its functional coupling with the orbitofrontal cortex region where fat pleasantness is represented; and that inter-individual variation in this coupling explained variation in hedonic preferences between individuals. The present findings indicate, therefore, that alterations in the functional coupling between oral somatosensory cortex and reward structures may constitute a neural mechanism that could contribute to individual differences in liking for high fat foods, and therefore to overeating and obesity.

Interestingly, in a recent investigation, Eldgehaidy and colleagues [230] confirmed our earlier findings of activations by oral fat stimuli in the insular, somatosensory and cingulate cortex as well as the amygdala, despite using rather different stimuli, stimulus delivery and analysis protocols. They found that inter-individual differences in the ability to discriminate fat content in food were related to activation differences in some of these areas. This complements our finding that differences in coupling strength between orbitofrontal cortex and oral somatosensory cortex were related to differences in hedonic liking of high fat stimuli [6]. It will be important in future studies to investigate in more detail how activation of the brain's reward system by oral fat and texture stimuli is related to inter-individual differences on other measures of food liking, including food preferences as revealed by choices, and direct ratings of the overall experienced pleasantness of stimuli.

The findings described here on the representation of oral fat texture in the brain are potentially of relevance to understanding some of the factors underlying the obesity epidemic [240, 241], and how sensory properties of food such as oral fat texture become represented in terms of the subjective hedonic value, become related to the hypothalamic molecular mechanisms that reflect peripheral hunger and satiety signals [242, 243], and can contribute to driving excessive food intake [17, 105, 220–223, 235, 244, 245]. Understanding the brain representations in the human brain of oral fat [141, 230], and its pleasantness [5], may help unravel possible differences in how neural reward systems in obese vs. lean people respond to oral fat, a driver of food intake, and in the design of foods that produce the mouth-feel of fat yet have low energy content.

8.5.2 Food Labeling in Marketing and Health Policy: Cognitive Influences on the Pleasure of Foods

Our affective responses to foods and other rewards do not only depend on their sensory properties, but also on cognitive and linguistic processing. Whether or not we like a sensory stimulus depends on how we think about it. This simple observation

raises interesting and fundamental questions with respect to the brain processing of rewards: Do for example linguistic descriptions influence brain representations of food rewards only in higher-order, cognitive brain systems? Or, alternatively, do these cognitive influences produce top-down biasing of early sensory representations? Our choices about foods are also frequently guided by abstract information conveyed through language. For example, in everyday life, such information impinges on us in the form of food labels. In marketing, food labels are used to direct consumers' preferences towards specific brands [246, 247]. Food labeling is also the major health policy strategy to counter rising obesity rates and associated costs to health care systems [248–250]. A prime example is the recently enacted national calorie labeling law in the United States. Despite this prevalence of food labels in our daily lives, their underlying neural and psychological mechanisms are not well understood.

In psychology and linguistics, language-based information processing is seen as closely linked to explicit, conscious thought [251, 252]. This could suggest that food labels provide input to deliberate, conscious decision-making. Indeed, label-based health policy strategies tacitly adopt this view. Based on traditional economic theory, these strategies assume that by providing detailed nutritional information, food labeling will necessarily help individuals make better, healthier choices [249]. Yet, although widely implemented, evidence for the efficacy of nutritional labeling is mixed [248, 250].

By contrast, the utility of simple, intuitive labels in food marketing is well known [247]. Psychological and behavioral economic theories suggest that marketing actions activate automatic biases and emotions, which form integral parts of the human decision-making faculty [23, 247, 253], and which involve implicit emotional brain systems including the amygdala [97–99, 119, 254]. Thus, from a health policy perspective, the design of labels that capitalize on these biases and engage the same neural systems could offer a promising approach for promoting healthier choices. Rather than instilling explicit nutritional knowledge, such labels could implicitly guide consumers towards healthier choices, in line with "libertarian paternalism" as a guiding principle for policy interventions [255, 256].

Recent neuroimaging studies have provided insights into how labels influence hedonic representations of food in the brain and how labels may guide neural decision processes about foods, as described next.

8.5.2.1 Influences of Food Labels on Affective Responses to Taste and Flavor

In a pioneering study by McClure and colleagues [257], the influence of brand identity cues on drinks preferences was related to activation of the hippocampus at the time the brand cue was shown, potentially reflecting the recall of cultural, brand-specific memories. However, influences of labels on hedonic experience related to primary rewards at the time of food consumption may involve different brain

systems. We therefore used functional MRI in healthy, mildly hungry volunteers to investigate how top-down cognitive effects from the language level can influence hedonic representations in the brain of both taste and flavor (i.e. combined taste and olfactory) stimuli.

The key point of the experimental design was to investigate how subjective evaluations and brain activations to the identical sensory stimulus, a liquid taste or flavor stimulus, could be modulated when it was paired with semantically different word labels. The word labels were designed to influence the subjective pleasantness of the stimulus without influencing its intensity. To make the findings relevant to the brain mechanisms of food reward and thus the control of food intake we used taste and flavor stimuli that are present in many foods. The pure taste stimulus consisted of 0.1 M monosodium glutamate which produces the taste of umami. For the flavor stimulus we added a consonant vegetable odor to the taste stimulus. Umami taste is found in a diversity of foods rich in glutamate like fish, meat, milk, and some vegetables including tomatoes and mushrooms, and is enhanced by some ribonucleotides (including inosine and guanosine nucleotides) [258, 259], which are present in for example meat and some fish [260]. We explicitly compared whether cognitive modulation effects are present in areas that represent the intensity but not the pleasantness of taste and flavor such as the insular primary taste cortex [79, 261, 262], or in areas where neural activations are related to the reward value, that is the pleasantness, of taste and flavor such as the orbitofrontal cortex and pregenual cingulate cortex.

At the behavioral level, we found that subjects rated the identical taste stimulus as significantly more pleasant when a positive label was provided ("rich and delicious taste") compared to a neutral label ("monosodium glutamate"). Similarly, the identical flavor stimulus was rated as significantly more pleasant when labeled as "rich and delicious flavor" compared to a less positive label ("boiled vegetable water"). As a control, similar differences in intensity ratings were not found. To investigate the underlying brain mechanisms, we measured neural activity while subjects consumed the taste and flavor stimulus and compared activations to the identical stimulus under the two label conditions. To localize brain areas related to hedonic or sensory processing, we also correlated brain activity with trial-by-trial ratings of experienced pleasantness and intensity. We found that neural responses to the identical sensory (taste or flavor) stimulus were enhanced in the medial orbitofrontal cortex and pregenual cingulate cortex when a positive label was provided. Both brain areas also tracked the subjective pleasantness ratings of the stimuli, confirming a role in hedonic processing. By contrast, a similar modulation effect by the word labels was not found at an earlier, sensory processing stage in the anterior insula: here, neural responses to the stimuli reflected their intensity but not their pleasantness, and were unaffected by presentation of the different labels.

The implication of these data is that simple word labels can alter the subjective pleasantness of the identical food stimulus, and that this modulation is expressed in reward areas such as the orbitofrontal cortex and pregenual cingulate cortex. These results are supported by similar findings in other sensory modalities. For example, word labels have been shown to modulate neural responses to odors and

somatosensory stimuli in the orbitofrontal cortex and amygdala, in studies that used similar experimental designs to the one just described [170, 184]. Moreover, simpler marketing actions that do not involve a linguistic level of processing seem to influence food liking via the same neural mechanism: Plassmann and colleagues [263] showed that pairing the identical red wine with different price tags resulted in enhanced liking and enhanced responses in the medial orbitofrontal cortex when subjects believed they were consuming an expensive wine. Thus, cognition modulates the affective representations of taste and flavor by a top-down influence on the first cortical areas that represent the affective value of taste and flavor. Cognitive factors can thus have a fundamental influence on how the hedonic value of the taste and flavor of a food is represented early in cortical processing, and in this way may be important in the selection and consumption of foods.

8.5.2.2 Attentional Instructions Modulate Brain Processing of Foods

In a related series of studies, we found that attentional instructions (e.g. "pay attention to pleasantness" or "pay attention to intensity") have similar top-down modulatory influences on reward representations of taste and olfactory stimuli in the medial orbitofrontal and anterior cingulate cortex [169, 264]. Thus, cognition and attention have top-down influences on the first part of the cortex in which value is represented (Tier 2), and modulate the effects of the bottom-up sensory inputs. Extending these findings, a recent study showed that explicit instructions to consider healthiness influenced prefrontal cortex activity and increased healthy food choices [265], similar to the effects of deliberate self-control [186].

8.5.2.3 How Food Labels Influence Food Liking and Food Preferences

The design of food labels in marketing and health policy could benefit from a principled, mechanistic understanding of the brain systems for food valuation and choice, and of the physiology of the specific biases according to which these systems operate. However, the neural mechanisms mediating the influence of incidental labels on food choice in the absence of explicit instructions have remained largely unclear, even though these constitute the main category of labels in marketing and health policy [247, 250, 266]. In a recent study, we used functional MRI to investigate how simple, incidental food labels influence food choices and related neural activity. Healthy, mildly hungry subjects who were of normal weight and not dieting performed a food evaluation task and a food choice task [8]. The main experimental manipulation was to pair pictures of identical foods with simple labels that emphasized either taste benefits or health-related food properties. In contrast to the studies described above, the focus here was to study how food labels influence neural activity and behavior in response to foods prior to consumption, at the time of choice. Accordingly, subjects made choices about food stimuli that were presented visually, similar to choosing between foods in the supermarket.

Behaviorally, we found that simple labels designed to enhance the attractiveness of foods lead subjects to give higher ratings of expected pleasantness, compared to labels that focused on the health-relevant properties of foods. By contrast, a similar effect was not found for expected healthiness ratings; subjects' evaluations of food healthiness were unaffected regardless of whether labels explicated health-relevant food properties or promoted the attractiveness of foods. However, although health labels did not influence subjective ratings of healthiness, they did exert an influence on food preference choices: When foods were shown together with labels that described their health properties (e.g. "rich in fat" or "low in carbohydrates"), subjects were significantly less likely to select foods that they found very attractive but also relatively unhealthy (Fig. 8.6). A logistic regression analysis confirmed that when health labels were shown, healthiness considerations had a significant weight on the subjects' choices. In fact, choices for pleasant but unhealthy foods were reduced in the health label condition by almost 40 %. Thus, simple incidentally presented labels without explicit instructions guided the subjects' choices towards healthier food items. What is the brain mechanism behind this effect?

Using functional MRI, we measured subjects' brain responses while they rated and chose between foods in the different label conditions. As a first novel finding, we found that simple, incidental labels which promoted the taste benefits of foods similar to marketing strategies, increased the neural encoding of expected taste pleasantness in the amygdala. Similarly, labels that indicated potential health costs of foods, in line with health policy aims, increased the neural encoding of health costs in the amygdala, even in the absence of changes in reported healthiness judgments (Fig. 8.6a). Thus, label-based marketing and health policy strategies may influence subjective evaluations of visual food stimuli via a common neural mechanism: Depending on the information conveyed by the label such strategies bias the responsiveness of the amygdala, a key component of the brain's valuation system, towards either the appetitive, hedonic properties of foods or potential health costs. It was suggested that this differential relationship between amygdala activity and taste pleasantness or health costs reflects the biasing of a valuation signal encoded by neuronal populations within the amygdala [103, 135, 267]. Thus, our findings suggested that abstract, linguistic labels designed to emphasize either the hedonic or health-related aspects of foods could bias the amygdala's valuation signal.

A second novel finding was that the amygdala was actively involved during decision-making when incidental labels guided food choices. Although the enhanced healthiness valuations in the amygdala by the labels were not immediately expressed in reported healthiness judgments, they predicted behavioral shifts towards subsequent healthier choices (Fig. 8.6b, c). In other words, when health labels increased the representations of health costs in the amygdala (at a time when subjects evaluated the foods but did not make choices) the strength of this effect in the brain predicted subsequent reductions in behavioral choices for unhealthy foods. This may indicate that, rather than passively tracking food evaluations, the amygdala may be actively involved in decision-making about foods. Consistent with this interpretation, at the time of choice, the amygdala encoded a health-based decision variable when health labels were shown and its activity was associated

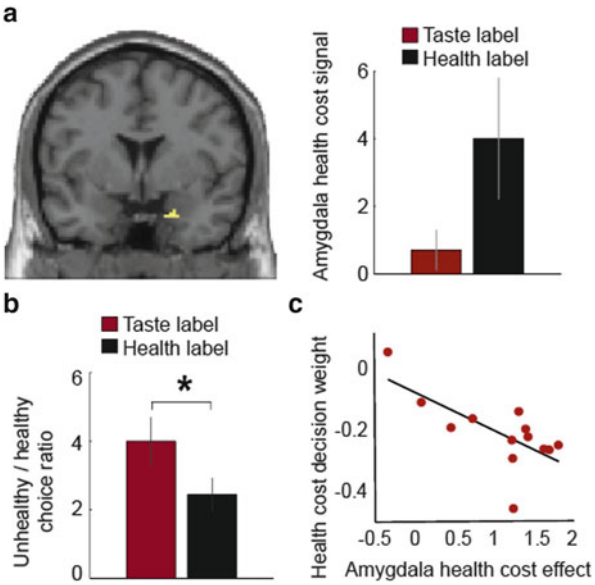

Fig. 8.6 Food labels promote healthy choices by biasing the amygdala's valuation signal [7]. Healthy, mildly hungry subjects evaluated and, on different trials, chose between different food items that were visually presented to them. The foods were accompanied by labels that either marketed the food's pleasantness (e.g. "crispy-savory" for French fries) or described the food's health-relevant properties (e.g. "high in fat"). (**a**) Neural activity in the amygdala during food evaluation represented the subjects' evaluations of food healthiness, but only when an appropriate health label was shown. (When a label promoting taste pleasantness was shown, the amygdala represented taste pleasantness evaluations.) *Right*: Effect size for health cost representation in the amygdala under the two label conditions. (**b**) Choice data: When health labels were shown, subjects made significantly fewer choices for subjectively pleasant but unhealthy foods, compared to when marketing-style taste labels were shown. Thus, simple incidental labels promoted healthy food choices. (**c**) Amygdala susceptibility to health labels across individuals predicted reductions in unhealthy choices: The magnitude of the health cost effect in the amygdala shown in (**a**), produced by the health labels at the time when subjects evaluated the foods, predicted subsequent reductions in unhealthy choices (measured by logistic regression weights of healthiness on choices; negative weights indicate that health costs reduced the likelihood that a food would be chosen) (Adapted with permission from Ref. [7])

with low confidence in decisions. The observed coding of decision variables could indicate amygdala participation in a decision process which translates valuations into choices [127, 129, 190, 194]. Given the amygdala's function in gating attention towards significant events [97, 98, 119, 268], these effects might also reflect modulation of other brain systems with known roles in decisions, including the prefrontal cortex and striatum.

These findings highlight the potential utility of simple, incidental food labels in health policy and marketing. The results indicate that such labels engage a key emotional brain system and bias its evaluations towards appetitive or health properties

of foods. From a public health perspective, these results lend weight to the efficacy of libertarian-paternalistic policy proposals to guide consumers towards decisions that will ultimately benefit them [248, 256]. However, they also indicate the need for careful ethical consideration and public disclosure [256] when using such labels in health policy. Likewise, our findings substantiate demands [247] for regulation of specific types of food marketing strategies.

8.5.3 *Hedonic Complexity: A Counterintuitive Property of Potent Natural Rewards*

Many natural rewards are hedonically complex in that they contain both individually pleasant and unpleasant components. A striking example is the pleasant floral scent of jasmine, which as it occurs naturally in *Jasminum grandiflorum* contains typically 2–3 %, and sometimes more than 10 %, of indole, a chemical which on its own at the same concentration is usually rated as unpleasant and has an animal-like smell [269]. One remarkable property of such hedonically complex stimuli is that the presence of an individually unpleasant component in an overall pleasant mixture can enhance the pleasantness or attractiveness of the mixture. For example, a vegetable odor that is unpleasant on its own may in combination with the taste of monosodium glutamate produce a consonant flavor that is experienced as delicious and highly pleasant [142]. This is counter-intuitive, but appears to happen in natural odors [270]. Professional perfumers know that adding a small quantity of an unpleasant odor to an otherwise pleasant perfume can enhance its overall impact. Examples quoted by perfumers and flavorists include perfumes with sulfur components that on their own are unpleasant – resembling cat urine – but give a lift to and may even impart a fruity component to complex odor mixtures as in tropical fruits and Sauternes wine. Another example is that adding musk odor (such as civet or castor glandular secretions [270]), unpleasant on its own, to a pleasant odor may, for at least some people, enhance the attractiveness of a perfume and may capture attention. Another example is that wintergreen contains methyl salicylate, which on its own is unpleasant. The addition of trace amounts of pepper to strawberries is also a good demonstration as to how a not overly pleasant culinary ingredient, in this case a trigeminal stimulus, may enhance the aroma of a sweet dish. Thus, odors with mixed hedonic components are key for success in perfumery with certain creations, and the same principle is also important in the multisensory effects used in fine cuisine.

What mechanisms might be responsible for the enhanced attractiveness of hedonically complex mixtures? How do pleasant and unpleasant stimuli combine in the brain? This question is also of general interest in relation to understanding reward-based decision processes and cost-benefit analysis in the brain's decision systems. In a series of neuroimaging studies, described next, we examined the brain processing of hedonically complex stimuli.

8.5.3.1 Odor Mixtures: How the Brain Combines Pleasant and Unpleasant Olfactory Stimuli

Given the close relationship between olfaction and emotion, odors play a central role in making many sensory stimuli pleasant and attractive, for example in food selection and social affiliative behavior [17, 271]. Many odors we encounter are mixtures that are hedonically complex having affectively positive and negative components. However, it is unclear how the pleasant and unpleasant components of such mixtures are analyzed by the human brain, what the rules are for the neural representations of such mixtures, and how the representations may be related to verbal reports on the affective value of the mixtures. When humans smell an odor mixture, to what extent does the brain represent separately the different affective components of the mixture? Research on the neural representation of odor mixtures in animals has shown that the interactions include suppression, and the formation of new representations that are different from the components [271–274]. These interactions may take place at various stages of the olfactory pathways including the olfactory bulb, and areas that receive inputs from the olfactory tract including the piriform cortex [272, 273]. Overall, little is known about the interactions between the pleasant and unpleasant components of sensory stimuli in any modality. Olfaction provides a good model for investigation because it has been shown that affectively positive odors are represented in partly different brain regions than affectively unpleasant odors [84, 113].

In the first neuroimaging study on odor mixtures in humans, we investigated brain responses to a naturally occurring, hedonically complex jasmine odor mixture, and both its individually pleasant and unpleasant components [10]. The unpleasant component was the chemical indole, used in a concentration that occurs naturally in jasmine, which on its own has an unpleasant, animal-like smell. The pleasant component of the mixture was a chemically well-defined model of the natural jasmine odor but without the indole component. The odors were matched in intensity, as determined by individual ratings of the subjects, but, importantly, differed in subjective pleasantness: Whereas both the jasmine odor without the unpleasant component and the hedonically complex mixture (jasmine including indole) were rated as very pleasant, the indole odor by itself was rated as unpleasant.

The brain responses found to the hedonically complex jasmine odor mixture and to its individually pleasant and unpleasant components could be characterized as falling into three main types [10] (Fig. 8.7). First, the activations in the primary olfactory area, the piriform cortex, were correlated with subjective ratings of odor intensity ratings but not experienced pleasantness. Moreover, neural responses in this region to the different olfactory stimuli were overall quite similar in magnitude, perhaps reflecting the fact that the odors were matched in their intensity. Thus, there was no indication of special interactions between the mixture's components in the primary olfactory cortex. Second, the responses in secondary olfactory areas in the medial and mid-orbitofrontal cortex, which are reward structures, were correlated with the pleasantness of the stimuli rather than their intensity. Further, these areas had activations to the hedonically complex jasmine mixture and its individually

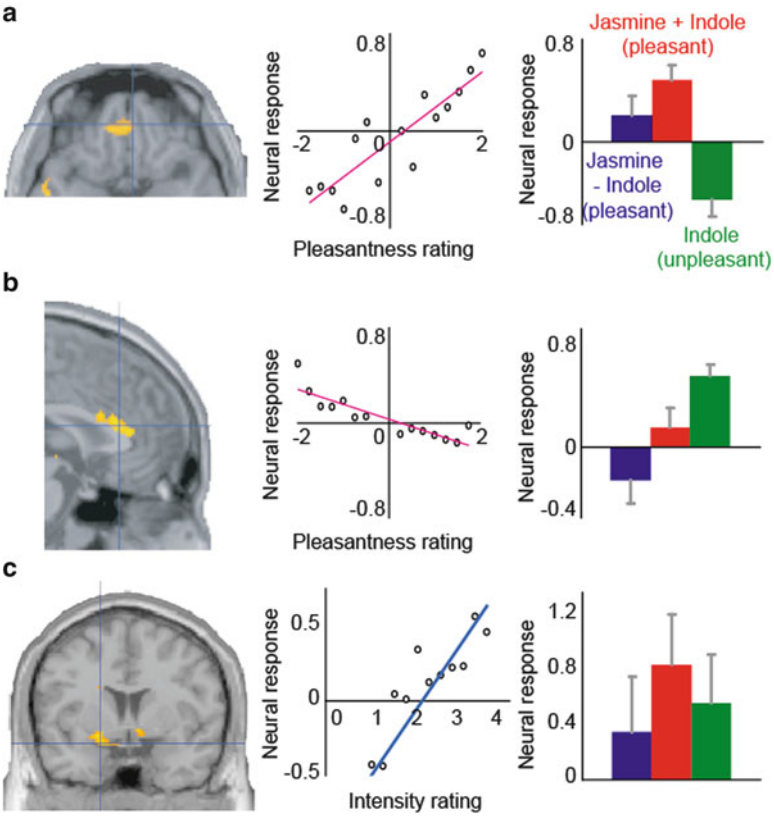

Fig. 8.7 The emotion produced by a hedonically complex odor mixture [10]: Brain responses to an overall pleasant natural jasmine odor mixture that contains both individually pleasant and unpleasant components. Different parts of the brain's reward system responded to this hedonically complex natural odor by emphasizing either its pleasant or unpleasant components. (**a**) Activity in the medial orbitofrontal cortex while subjects smelled the different odor stimuli correlated with ratings of experienced pleasantness (brain map and scatter plot in the middle). Interestingly, as shown in the bar graph on the *right*, the medial orbitofrontal cortex showed a stronger response to the mixture with pleasant and unpleasant components (Jasmine + Indole) than to the pleasant component on its own (Jasmine − Indole), an effect not reported by the subjects in their ratings. Thus, the medial orbitofrontal cortex responded to the mixture by emphasizing its pleasant component. (**b**) Activity in the dorsal anterior cingulate cortex correlated negatively with experienced pleasantness. In contrast to the medial orbitofrontal cortex, the response to the mixture (Jasmine + Indole) in this part of the brain was more similar to the activation produced by its unpleasant component (Indole) than the pleasant component (Jasmine − Indole). Thus, the anterior cingulate cortex responded to the mixture by emphasizing its aversive component. (**c**) Responses in the piriform primary olfactory cortex correlated with subjective odor intensity but not pleasantness. All odors activated the piriform cortex in a similar manner, suggesting a representation of the sensory but not the hedonic properties of the odors (Adapted with permission from Ref. [10])

pleasant component that were relatively similar and large. By contrast, the unpleasant component indole on its own produced a deactivation. Thus, in brain regions that represent the pleasantness of odors, the mixture and its pleasant component produced similar activations [10]. Third, a striking finding was that, in brain regions in which activations were correlated with the unpleasantness of the stimuli, such as the dorsal part of the anterior cingulate cortex and a posterior mid-orbitofrontal cortex region, the magnitude of the activations to the mixture was intermediate between those produced by its pleasant and unpleasant components. In fact, whereas the pleasant component produced a deactivation in these areas, the hedonically complex mixture produced a positive response. The implication is that in these brain regions potentially unpleasant aspects of the indole in the mixture are represented, even though these unpleasant aspects were not expressed in ratings of the overall pleasantness of the mixture. In contrast, in brain regions that represent the pleasantness of odors, the pleasant aspects of the mixture appear to be represented).

These findings [10] suggest that different parts of the brain's reward system respond differently to the hedonically complex mixture, either emphasizing its pleasant or unpleasant components. Accordingly, the brain can simultaneously and independently represent the positive and the negative hedonic value of an odor mixture with pleasant and unpleasant components. The finding that the mixture produced a larger activation in the medial orbitofrontal cortex (which represents the pleasantness of odors and other stimuli [84, 113, 184]) is of interest in relation to the fact that some individuals find that adding an unpleasant component to a pleasant odor may enhance its appeal, with verbal descriptions sometimes referring to enhanced attractiveness or body. A possibility is that even if on average the mixture did not receive increased pleasantness ratings, the larger activations in the medial orbitofrontal cortex might represent preferences that are not conscious, but can influence decision-making and behavior. Thus, the results of this study [10] indicate that one brain mechanism which may underlie the attractiveness of hedonically complex stimuli is a principle by which brain areas that represent the pleasantness of stimuli can do this in a way that is partly independent of unpleasant components, thereby emphasizing the pleasant component of a hedonically complex mixture.

8.5.3.2 A Hedonically Complex Odor Captures the Brain's Attention

Another hypothesis for a mechanism that may contribute to the pleasantness or enhanced impact of a hedonically complex mixture is that the interaction between the pleasant and unpleasant components could allow the mixture to capture attention [9]. In other words, the interactions occurring in a hedonically complex mixture may engage brain mechanisms related to attention, which may enhance and prolong the activation of the brain by the mixture. We tested this hypothesis by examining whether brain areas in which attention enhances neural activation to odors are also activated particularly effectively by a hedonically complex odor mixture, even in the absence of explicit attentional instructions. If some brain regions are activated similarly by attention to odor and a hedonically complex odor

mixture, then this could be evidence that brain processing related to attentional capture may contribute to the efficacy of olfactory mixtures in enhancing subjective pleasantness. One candidate region where this effect might be expressed is the lateral prefrontal cortex, which is involved in attention across different sensory modalities [185, 275, 276]. Further, jasmine odor has been shown to elicit an enhanced early component of the contingent negative variation, a slow cortical potential which occurs between a warning stimulus and an imperative stimulus, specifically over left frontal areas [277]. Thus, attentional capture could be an interesting way in which some natural as well as other volatile chemical stimuli (including perfumes that contain extracts of natural materials, such as civet cat musk gland secretions) can produce strong and lasting subjective pleasantness, can contribute to making other stimuli pleasant and attractive, and thus may influence subjective preference, emotion, and choice.

To investigate the effects of hedonic complexity on brain systems involved in attention, we compared neural responses to a hedonically complex odor mixture, presented in the absence of attentional instructions, with neural responses produced by a pleasant odor to which subjects explicitly directed their attention [9]. Our findings showed that neural activity in the superior frontal gyrus, a lateral prefrontal area previously implicated in attention, was modulated both by explicit attention to odor (in that it had enhanced activations when subjects paid selective attention either to its pleasantness or intensity) and when indole was added to jasmine to produce a hedonically complex mixture (i.e. subjects smelled the hedonically complex mixture without selective attention requirements) (Fig. 8.8). Thus, the superior frontal gyrus is a brain area in which a hedonically complex stimulus with both pleasant and unpleasant components may, even in the absence of explicit attentional demands, produce effects related to attentional capture because of the unusual combination of pleasant and unpleasant components.

An interesting finding was that the magnitude of the attentional capture effect in the superior frontal gyrus, measured across subjects, was related to the subjective hedonic complexity of the mixture, defined as the absolute difference in rated pleasantness between its pleasant and unpleasant components [9]. Thus, participants for whom the mixture was more hedonically complex showed a stronger attentional capture effect in the brain. As a control, a similar effect was not found for differences in intensity. Accordingly, the capacity of the mixture to produce attentional capture in the brain may be explained by the interactions between its pleasant and unpleasant components, and its magnitude was related to inter-individual differences in subjective hedonic complexity.

What might be the nature of this attentional capture effect? The superior frontal gyrus does not represent the pleasantness of the odors involved, so it does not contribute as a hedonic analyzer. Nor is it an olfactory region as it did not respond to the other odors without explicit attention in any way different from a clean air control stimulus. However, by reflecting attentional capture to the complex hedonic mixture, the superior frontal gyrus may prolong and enhance brain processing of the hedonically complex mixture. Where could such an effect be expressed in the brain, as a result of top-down effects from the prefrontal cortex [62, 278]? A likely candidate

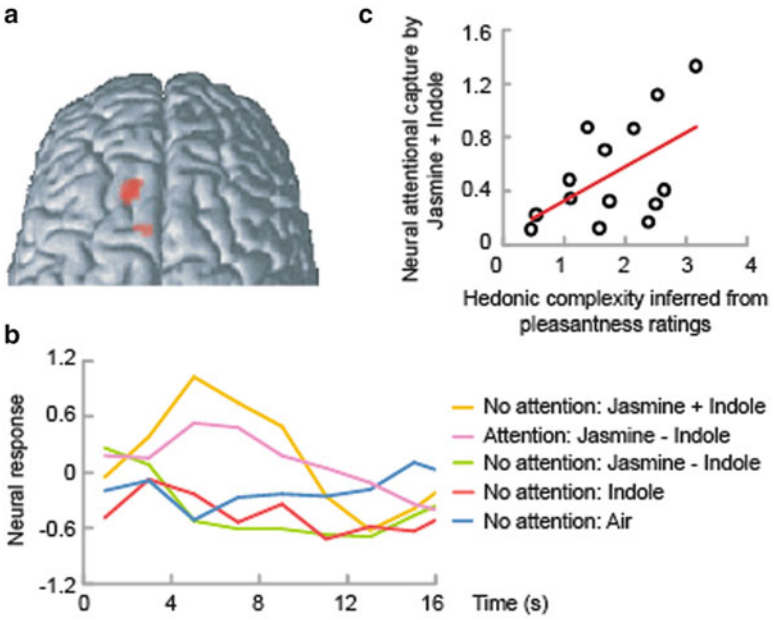

Fig. 8.8 A hedonically complex odor mixture captures the brain's attention [9]. A specific part of the frontal lobe, the superior frontal gyrus, was engaged in similar ways by deliberately paying attention to a simple pleasant odor (Jasmine – Indole) and by a hedonically complex odor mixture without attention requirements (Jasmine + Indole). The brain map in (**a**) shows the part of the superior frontal gyrus conjointly activated in these two experimental conditions. The timecourse of the neural response in the superior frontal gyrus for the different odor conditions is shown in (**b**): Among conditions without selective attention requirements, the superior frontal gyrus only responded to the hedonically complex jasmine mixture (*orange timecourse*) but not to its individually pleasant or unpleasant components (*green and red timecourses*). This suggested that hedonic complexity in the odor mixture engages a part of the brain involved in attention. (**c**) Across subjects, the magnitude of the activation in the superior frontal gyrus produced by the hedonically complex mixture (i.e. the attentional capture effect) was partly explained by inter-individual differences in subjective hedonic complexity of the mixture, as inferred from ratings. Thus, the more hedonically complex the mixture was (i.e. the more disparate in pleasantness its pleasant and unpleasant components were), the more strongly did the mixture engage the superior frontal gyrus (Adapted with permission from Ref. [9])

is the medial orbitofrontal cortex, where responses to the mixture are larger than to either of its components [10], and where the activations reflect the pleasantness of the stimuli [10, 31, 84, 113]. Indeed, functional connectivity analyses provided an indication that the superior frontal gyrus and orbitofrontal cortex had correlated activity during processing of the hedonically complex mixture.

Thus, part of the efficacy of hedonically complex odor mixtures is that they may operate by attentional capture, which then via top-down effects enhances processing and perhaps reduces habituation in areas such as the orbitofrontal cortex where the pleasantness of the stimuli is represented [10, 18]. This may be an important way in

which hedonically complex odor mixtures that are especially effective in activating brain regions involved in attention and hedonic evaluation [10] can influence value-based choices and behavior.

These investigations are also relevant to the much broader issue of how pleasant and unpleasant stimuli combine to produce what is overall a pleasant experience, and indeed what can sometimes be a more pleasant experience than the pleasant component alone. Our findings suggest that at least part of the affective potency of stimuli with mixed pleasant and unpleasant components is that they become more pleasant by recruiting superior frontal cortical mechanisms involved in attentional capture and enhancement. The finding that the magnitude of the attentional capture effect in the superior frontal gyrus was related to the hedonic complexity of the mixture also indicates that there may be individual differences in the extent to which a hedonically complex stimulus such as an odor mixture captures attention, and this may be related to differences in subjective preferences and value-based choices.

8.6 Conclusions and Future Directions

The orbitofrontal cortex, anterior cingulate cortex and amygdala are principal reward structures of the human brain (Figs. 8.1 and 8.2) [1, 18]. The orbitofrontal cortex receives information from all sensory systems and provides hedonic representations of value and experienced pleasure that are based on the sensory details of rewards. The amygdala is involved in Pavlovian learning processes and allows Pavlovian-learned values and contextual biases to covertly influence affective state, decision-making and behavior. The anterior cingulate cortex represents the reward value and pleasure of many sensory rewards, which it may receive from the orbitofrontal cortex and amygdala, to provide an interface that links these reward representations with output system for emotion and action. Specific operational principles enable these reward systems to provide value representations that are appropriately scaled as inputs for neural decision systems. By providing this "evidence" for value-based decision-making, reward systems may promote a progression through the reward and pleasure space in the environment to find the range of rewards necessary for survival, reproduction and well-being. The ventromedial prefrontal cortex seems to implement a decision processes that transforms these value signals received from the orbitofrontal and anterior cingulate cortices and the amygdala into stimulus choices (Fig. 8.4), thereby guiding action.

Investigations of how the brain's reward and pleasure systems respond to primary rewards have advanced our understanding of some key determinants of reward value and experienced pleasure. The reward value of high-fat foods may be partly explained by the ways in which sensory oral texture signals activate the orbitofrontal cortex, pregenual cingulate cortex and amygdala [5], and produce functional coupling between reward systems and the oral somatosensory cortex [6]. Reward contrast effects, in which the pleasantness of a stimulus is enhanced by a less pleasant stimulus that precedes it, may be linked to the capacity of the orbitofrontal

cortex to represent relative reward value and related value enhancement [31]. Hedonic complexity, the simultaneous presence of pleasant and unpleasant components, is a counter-intuitive property of many natural rewards, for example natural jasmine odor. The potency of such hedonically complex stimuli may be related to special processing in the brain's reward systems which represent the pleasant or aversive components partly independently [10], and to engagement of attentional brain systems [9]. Food labels [8] and attentional cues [169] enhance reward representations in the orbitofrontal cortex and pregenual cingulate cortex to enhance subjective pleasure during food consumption. Food labels can also bias the amygdala's valuation system either to promote processing of food pleasantness or health costs, to influence food preferences as expressed by choices [7].

These advances have implications for applied fields including food design, marketing, and health policy. They may also open up new avenues for a better understanding and treatment of clinical conditions with impairments in reward processing and experienced pleasure, such as anhedonia or eating disorders, as they identify candidate mechanisms for how reward value and pleasure may be computed in the brain. Investigation of these candidate mechanisms in clinical populations could potentially lead to the identification of specific vulnerabilities concerning the different types of reward processing implemented in different brain systems.

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References

1. Grabenhorst F, Rolls ET. Value, pleasure, and choice in the ventral prefrontal cortex. Trends Cogn Sci. 2011;15:56–67.
2. Padoa-Schioppa C. Neurobiology of economic choice: a good-based model. Annu Rev Neurosci. 2011;34:333–59.
3. Glimcher PW. Foundations of neuroeconomic analysis. Oxford: Oxford University Press; 2011.
4. Rangel A, Camerer C, Montague PR. A framework for studying the neurobiology of value-based decision making. Nat Rev Neurosci. 2008;9:545–56.
5. Grabenhorst F, Rolls ET, Parris BA, D'Souza A. How the brain represents the reward value of fat in the mouth. Cereb Cortex. 2010;20:1082–91.
6. Grabenhorst F, Rolls ET. The representation of oral fat texture in the human somatosensory cortex. Hum Brain Mapp. 2013 Sep 3. doi: 10.1002/hbm.22346. [Epub ahead of print].
7. Grabenhorst F, Schulte FP, Maderwald S, Brand M. Food labels promote healthy choices by a decision bias in the amygdala. Neuroimage. 2013;74:152–63.
8. Grabenhorst F, Rolls ET, Bilderbeck A. How cognition modulates affective responses to taste and flavor: top down influences on the orbitofrontal and pregenual cingulate cortices. Cereb Cortex. 2008;18:1549–59.
9. Grabenhorst F, Rolls ET, Margot C. A hedonically complex odor mixture captures the brain's attention. Neuroimage. 2011;55:832–43.

10. Grabenhorst F, Rolls ET, Margot C, da Silva MAAP, Velazco MI. How pleasant and unpleasant stimuli combine in different brain regions: odor mixtures. J Neurosci. 2007;27:13532–40.
11. Gray JA. Elements of a two-process theory of learning. London: Academic; 1975.
12. Millenson JR. Principles of behavioral analysis. New York: MacMillan; 1967.
13. Weiskrantz L. Emotion. In: Weiskrantz L, editor. Analysis of behavioural change. New York/London: Harper and Row; 1968. p. 50–90.
14. Rolls ET. A theory of emotion, and its application to understanding the neural basis of emotion. In: Oomura Y, editor. Emotions. Neural and chemical control. Basel: Karger; 1986. p. 325–44.
15. Rolls ET. A theory of emotion, and its application to understanding the neural basis of emotion. Cogn Emotion. 1990;4:161–90.
16. Rolls ET. The brain and emotion. Oxford: Oxford University Press; 1999.
17. Rolls ET. Emotion explained. Oxford: Oxford University Press; 2005.
18. Rolls ET, Grabenhorst F. The orbitofrontal cortex and beyond: from affect to decision-making. Prog Neurobiol. 2008;86:216–44.
19. Cabanac M. Physiological role of pleasure. Science. 1971;173:1103–7.
20. Rolls ET, Rolls BJ, Rowe EA. Sensory-specific and motivation-specific satiety for the sight and taste of food and water in man. Physiol Behav. 1983;30:185–92.
21. Panksepp J. Affective neuroscience: the foundations of human and animal emotions. New York: Oxford University Press; 1998.
22. Cabanac M. Pleasure: the common currency. J Theor Biol. 1992;155:173–200.
23. Kahneman D, Tversky A. Choices, values, and frames. Am Psychol. 1984;4:341–50.
24. Kahneman D, Wakker PP, Sarin R. Back to Bentham? – Explorations of experienced utility. Q J Econ. 1997;112:375–405.
25. Rolls ET. The affective neuroscience of consciousness: higher order linguistic thoughts, dual routes to emotion and action, and consciousness. In: Zelazo P, Moscovitch M, Thompson E, editors. Cambridge handbook of consciousness. Cambridge: Cambridge University Press; 2007. p. 831–59.
26. Rolls ET. Consciousness, decision-making, and neural computation. In: Cutsuridis V, Hussain A, Taylor JG, editors. Perception-action cycle: models, algorithms and systems. Berlin: Springer; 2011. p. 287–333.
27. Grabenhorst F, Rolls ET, Parris BA. From affective value to decision-making in the prefrontal cortex. Eur J Neurosci. 2008;28:1930–9.
28. Balleine BW, O'Doherty JP. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacology. 2010;35:48–69.
29. Seymour B, Dolan R. Emotion, decision making, and the amygdala. Neuron. 2008;58:662–71.
30. Rolls ET. The orbitofrontal cortex. Philos Trans R Soc Lond B Biol Sci. 1996;351:1433–44.
31. Grabenhorst F, Rolls ET. Different representations of relative and absolute value in the human brain. Neuroimage. 2009;48:258–68.
32. Rolls ET, Grabenhorst F, Parris BA. Warm pleasant feelings in the brain. Neuroimage. 2008;41:1504–13.
33. Rolls ET, O'Doherty J, Kringelbach ML, et al. Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. Cereb Cortex. 2003;13:308–17.
34. Rolls ET, Scott TR. Central taste anatomy and neurophysiology. In: Doty RL, editor. Handbook of olfaction and gustation, vol. chap, 32. 2nd ed. New York: Dekker; 2003. p. 679–705.
35. Rolls ET, Scott TR, Sienkiewicz ZJ, Yaxley S. The responsiveness of neurones in the frontal opercular gustatory cortex of the macaque monkey is independent of hunger. J Physiol. 1988;397:1–12.
36. Scott TR, Yaxley S, Sienkiewicz ZJ, Rolls ET. Satiety does not affect gustatory-evoked activity in the nucleus tractus solitarius or opercular cortex of the alert cynomolgus monkey. Chem Senses. 1985;10:442.

37. Rolls ET. Functions of the primate temporal lobe cortical visual areas in invariant visual object and face recognition. Neuron. 2000;27:205–18.
38. Öngür D, Ferry AT, Price JL. Architectonic division of the human orbital and medial prefrontal cortex. J Comp Neurol. 2003;460:425–49.
39. Wallis JD. Cross-species studies of orbitofrontal cortex and value-based decision-making. Nat Neurosci. 2012;15:13–9.
40. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci. 2005;6:691–702.
41. Kadohisa M, Rolls ET, Verhagen JV. Neuronal representations of stimuli in the mouth: the primate insular taste cortex, orbitofrontal cortex, and amygdala. Chem Senses. 2005;30:401–19.
42. Rolls ET, Baylis LL. Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J Neurosci. 1994;14:5437–52.
43. Rolls ET, Verhagen JV, Kadohisa M. Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness and capsaicin. J Neurophysiol. 2003;90:3711–24.
44. Verhagen JV, Rolls ET, Kadohisa M. Neurons in the primate orbitofrontal cortex respond to fat texture independently of viscosity. J Neurophysiol. 2003;90:1514–25.
45. Rolls ET, Yaxley S, Sienkiewicz ZJ. Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. J Neurophysiol. 1990;64:1055–66.
46. Baylis LL, Rolls ET, Baylis GC. Afferent connections of the orbitofrontal cortex taste area of the primate. Neuroscience. 1995;64:801–12.
47. Critchley HD, Rolls ET. Responses of primate taste cortex neurons to the astringent tastant tannic acid. Chem Senses. 1996;21:135–45.
48. Rolls ET, Critchley H, Wakeman EA, Mason R. Responses of neurons in the primate taste cortex to the glutamate ion and to inosine 5′-monophosphate. Physiol Behav. 1996;59: 991–1000.
49. Pritchard TC, Edwards EM, Smith CA, et al. Gustatory neural responses in the medial orbitofrontal cortex of the old world monkey. J Neurosci. 2005;25:6047–56.
50. Rolls ET. Functions of the orbitofrontal and pregenual cingulate cortex in taste, olfaction, appetite and emotion. Acta Physiol Hung. 2008;95:131–64.
51. Price JL, Carmichael ST, Carnes KM, et al. Olfactory input to the prefrontal cortex. In: Davis JL, Eichenbaum H, editors. Olfaction: a model system for computational neuroscience. Cambridge, MA: MIT Press; 1991. p. 101–20.
52. Morecraft RJ, Geula C, Mesulam M-M. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol. 1992;232:341–58.
53. Barbas H. Organization of cortical afferent input to the orbitofrontal area in the rhesus monkey. Neuroscience. 1993;56:841–64.
54. Carmichael ST, Clugnet M-C, Price JL. Central olfactory connections in the macaque monkey. J Comp Neurol. 1994;346:403–34.
55. Price JL. Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. Ann N Y Acad Sci. 2007;1121:54–71.
56. Seltzer B, Pandya DN. Intrinsic connections and architectonics of the superior temporal sulcus in the rhesus monkey. J Comp Neurol. 1989;290:451–71.
57. Barbas H. Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. Neurosci Biobehav Rev. 1995;19:499–510.
58. Carmichael ST, Price JL. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol. 1995;363:642–64.
59. Rolls ET, Critchley HD, Browning AS, Hernadi A, Lenard L. Responses to the sensory properties of fat of neurons in the primate orbitofrontal cortex. J Neurosci. 1999;19:1532–40.
60. Barbas H. Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. J Comp Neurol. 1988;276:313–42.
61. Öngür D, Price JL. The organisation of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex. 2000;10:206–19.

62. Rolls ET. Memory, attention, and decision-making: a unifying computational neuroscience approach. Oxford: Oxford University Press; 2008.
63. Barbas H. Specialized elements of orbitofrontal cortex in primates. Ann N Y Acad Sci. 2007;1121:10–32.
64. Carmichael ST, Price JL. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol. 1996;371:179–207.
65. Price JL. Connections of orbital cortex. In: Zald DH, Rauch SL, editors. The orbitofrontal cortex. Oxford: Oxford University Press; 2006. p. 39–55.
66. Ferry AT, Ongur D, An X, Price JL. Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. J Comp Neurol. 2000;425:447–70.
67. Kemp JM, Powell TPS. The cortico-striate projections in the monkey. Brain. 1970;93:525–46.
68. Haber SN, Kim KS, Mailly P, Calzavara R. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. J Neurosci. 2006;26:8368–76.
69. Insausti R, Amaral DG, Cowan WM. The entorhinal cortex of the monkey. II. Cortical afferents. J Comp Neurol. 1987;264:356–95.
70. Nauta WJH. Some efferent connections of the prefrontal cortex in the monkey. In: Warren JM, Akert K, editors. The frontal granular cortex and behavior. New York: McGraw Hill; 1964. p. 397–407.
71. Johnson TN, Rosvold HE, Mishkin M. Projections from behaviorally defined sectors of the prefrontal cortex to the basal ganglia, septum and diencephalon of the monkey. Exp Neurol. 1968;21:20–34.
72. Padoa-Schioppa C, Assad JA. Neurons in the orbitofrontal cortex encode economic value. Nature. 2006;441:223–6.
73. Wallis JD. Neuronal mechanisms in prefrontal cortex underlying adaptive choice behavior. Ann N Y Acad Sci. 2007;1121:447–60.
74. Rolls ET, Sienkiewicz ZJ, Yaxley S. Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. Eur J Neurosci. 1989;1:53–60.
75. Mora F, Avrith DB, Phillips AG, Rolls ET. Effects of satiety on self-stimulation of the orbitofrontal cortex in the monkey. Neurosci Lett. 1979;13:141–5.
76. Mora F, Avrith DB, Rolls ET. An electrophysiological and behavioural study of self-stimulation in the orbitofrontal cortex of the rhesus monkey. Brain Res Bull. 1980;5:111–5.
77. Thorpe SJ, Rolls ET, Maddison S. Neuronal activity in the orbitofrontal cortex of the behaving monkey. Exp Brain Res. 1983;49:93–115.
78. Morrison SE, Saez A, Lau B, Salzman CD. Different time courses for learning-related changes in amygdala and orbitofrontal cortex. Neuron. 2011;71:1127–40.
79. Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex. 2003;13:1064–71.
80. Baylis LL, Gaffan D. Amygdalectomy and ventromedial prefrontal ablation produce similar deficits in food choice and in simple object discrimination learning for an unseen reward. Exp Brain Res. 1991;86:617–22.
81. Camille N, Griffiths CA, Vo K, Fellows LK, Kable JW. Ventromedial frontal lobe damage disrupts value maximization in humans. J Neurosci. 2011;31:7527–32.
82. Hornak J, Bramham J, Rolls ET, et al. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. Brain. 2003;126:1691–712.
83. de Araujo IET, Rolls ET, Kringelbach ML, McGlone F, Phillips N. Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur J Neurosci. 2003;18:2059–68.
84. Rolls ET, Kringelbach ML, de Araujo IET. Different representations of pleasant and unpleasant odors in the human brain. Eur J Neurosci. 2003;18:695–703.
85. Tremblay L, Schultz W. Relative reward preference in primate orbitofrontal cortex. Nature. 1999;398:704–8.

86. Padoa-Schioppa C. Range-adapting representation of economic value in the orbitofrontal cortex. J Neurosci. 2009;29:14004–14.
87. Kobayashi S, Pinto de Carvalho O, Schultz W. Adaptation of reward sensitivity in orbitofrontal neurons. J Neurosci. 2010;30:534–44.
88. Kennerley SW, Dahmubed AF, Lara AH, Wallis JD. Neurons in the frontal lobe encode the value of multiple decision variables. J Cogn Neurosci. 2009;21:1162–78.
89. O'Neill M, Schultz W. Coding of reward risk by orbitofrontal neurons is mostly distinct from coding of reward value. Neuron. 2010;68:789–800.
90. Burdach KF. Vom Baue und Leben des Gehirns. Leipzig: Dyk; 1819.
91. Price JL. Comparative aspects of amygdala connectivity. Ann N Y Acad Sci. 2003;985:50–8.
92. Friedman DP, Murray EA, O'Neill JB, Mishkin M. Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. J Comp Neurol. 1986;252:323–47.
93. Aggleton JP, Burton MJ, Passingham RE. Cortical and subcortical afferents to the amygdala in the rhesus monkey (Macaca mulatta). Brain Res. 1980;190:347–68.
94. Baxter MG, Murray EA. The amygdala and reward. Nat Rev Neurosci. 2002;3:563–73.
95. Ghashghaei HT, Barbas H. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. Neuroscience. 2002;115:1261–79.
96. Amaral DG, Price JL. Amygdalo-cortical projections in the monkey (Macaca fascicularis). J Comp Neurol. 1984;230:465–96.
97. Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron. 2005;48:175–87.
98. Pessoa L, Adolphs R. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat Rev Neurosci. 2010;11:773–83.
99. Dolan RJ. The human amygdala and orbital prefrontal cortex in behavioural regulation. Philos Trans R Soc Lond B Biol Sci. 2007;362:787–99.
100. Paton JJ, Belova MA, Morrison SE, Salzman CD. The primate amygdala represents the positive and negative value of visual stimuli during learning. Nature. 2006;439:865–70.
101. Murray EA. The amygdala, reward and emotion. Trends Cogn Sci. 2007;11:489–97.
102. Rolls ET. Neurophysiology and functions of the primate amygdala, and the neural basis of emotion. In: Aggleton JP, editor. The amygdala: a functional analysis. 2nd ed. Oxford: Oxford University Press; 2000. p. 447–78.
103. Bermudez MA, Schultz W. Reward magnitude coding in primate amygdala neurons. J Neurophysiol. 2010;104:3424.
104. Machado CJ, Emery NJ, Mason WA, Amaral DG. Selective changes in foraging behavior following bilateral neurotoxic amygdala lesions in rhesus monkeys. Behav Neurosci. 2010;124:761–72.
105. Rolls ET. Sensory processing in the brain related to the control of food intake. Proc Nutr Soc. 2007;66:96–112.
106. Small DM, Gregory MD, Mak YE, et al. Dissociation of neural representation of intensity and affective valuation in human gustation. Neuron. 2003;39:701–11.
107. Small DM, Gerber JC, Mak YE, Hummel T. Differential neural responses evoked by orthonasal versus retronasal odorant perception in humans. Neuron. 2005;47:593–605.
108. Kadohisa M, Rolls ET, Verhagen JV. The primate amygdala: neuronal representations of the viscosity, fat texture, temperature, grittiness and taste of foods. Neuroscience. 2005;132:33–48.
109. Gottfried JA, O'Doherty J, Dolan RJ. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science. 2003;301:1104–7.
110. Yan J, Scott TR. The effect of satiety on responses of gustatory neurons in the amygdala of alert cynomolgus macaques. Brain Res. 1996;740:193–200.
111. de Araujo IE, Gutierrez R, Oliveira-Maia AJ, et al. Neural ensemble coding of satiety states. Neuron. 2006;51:483–94.
112. Small DM, Veldhuizen MG, Felsted J, Mak YE, McGlone F. Separable substrates for anticipatory and consummatory food chemosensation. Neuron. 2008;57:786–97.

113. Anderson AK, Christoff K, Stappen I, et al. Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci. 2003;6:196–202.
114. Winston JS, Gottfried JA, Kilner JM, Dolan RJ. Integrated neural representations of odor intensity and affective valence in human amygdala. J Neurosci. 2005;25:8903–7.
115. Anderson AK, Phelps EA. Is the human amygdala critical for the subjective experience of emotion? Evidence of intact dispositional affect in patients with amygdala lesions. J Cogn Neurosci. 2002;14:709–20.
116. Feinstein JS, Adolphs R, Damasio A, Tranel D. The human amygdala and the induction and experience of fear. Curr Biol. 2011;21:34–8.
117. Gallagher M, Chiba AA. The amygdala and emotion. Curr Opin Neurobiol. 1996;6:221–7.
118. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155–84.
119. Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry. 2001;6:13–34.
120. Johnsrude IS, Owen AM, White NM, Zhao WV, Bohbot V. Impaired preference conditioning after anterior temporal lobe resection in humans. J Neurosci. 2000;20:2649–56.
121. Balleine BW, Killcross S. Parallel incentive processing: an integrated view of amygdala function. Trends Neurosci. 2006;29:272–9.
122. Prevost C, Liljeholm M, Tyszka JM, O'Doherty JP. Neural correlates of specific and general Pavlovian-to-Instrumental Transfer within human amygdalar subregions: a high-resolution fMRI study. J Neurosci. 2012;32:8383–90.
123. Talmi D, Seymour B, Dayan P, Dolan RJ. Human Pavlovian-instrumental transfer. J Neurosci. 2008;28:360–8.
124. Bechara A, Tranel D, Damasio H, et al. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science. 1995;269: 1115–8.
125. De Martino B, Kumaran D, Seymour B, Dolan RJ. Frames, biases, and rational decision-making in the human brain. Science. 2006;313:684–7.
126. Cardinal N, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev. 2002;26:321–52.
127. Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci. 1999;19: 5473–81.
128. Morris JS, Ohman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. Nature. 1998;393:467–70.
129. Brand M, Grabenhorst F, Starcke K, Vandekerckhove MM, Markowitsch HJ. Role of the amygdala in decisions under ambiguity and decisions under risk: evidence from patients with Urbach-Wiethe disease. Neuropsychologia. 2007;45:1305–17.
130. Schultz W. Behavioral theories and the neurophysiology of reward. Annu Rev Psychol. 2006;57:87–115.
131. Everitt BJ, Cardinal RN, Parkinson JA, Robbins TW. Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. Ann N Y Acad Sci. 2003;985:233–50.
132. Adolphs R, Tranel D, Damasio H, Damasio AR. Fear and the human amygdala. J Neurosci. 1995;15:5879–91.
133. Markowitsch HJ, Staniloiu A. Amygdala in action: relaying biological and social significance to autobiographical memory. Neuropsychologia. 2011;49:718–33.
134. Siebert M, Markowitsch HJ, Bartel P. Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. Brain. 2003;126:2627–37.
135. Grabenhorst F, Hernadi I, Schultz W. Prediction of economic choice by primate amygdala neurons. Proc Natl Acad Sci U S A. 2012;109:18950–5.
136. Morecraft RJ, Tanji J. Cingulofrontal interaction and the cingulate motor areas. In: Vogt BA, editor. Cingulate neurobiology and disease. Oxford: Oxford University Press; 2009. p. 113–44.
137. Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci. 2005;6:533–44.
138. Vogt BA, Pandya DN. Cingulate cortex of the rhesus monkey: II. Cortical afferents. J Comp Neurol. 1987;262:271–89.

139. Van Hoesen GW, Morecraft RJ, Vogt BA. Connections of the monkey cingulate cortex. In: Vogt BA, Gabriel M, editors. The neurobiology of the cingulate cortex and limbic thalamus: a comprehensive handbook. Boston: Birkhauser; 1993. p. 249–84.
140. Öngür D, Price JL. Prefrontal cortical projections to the hypothalamus in macaque monkeys. J Comp Neurol. 1998;401:480–505.
141. de Araujo IET, Rolls ET. The representation in the human brain of food texture and oral fat. J Neurosci. 2004;24:3086–93.
142. McCabe C, Rolls ET. Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. Eur J Neurosci. 2007;25:1855–64.
143. Rolls ET, McCabe C. Enhanced affective brain representations of chocolate in cravers vs. non-cravers. Eur J Neurosci. 2007;26:1067–76.
144. de Araujo IET, Kringelbach ML, Rolls ET, McGlone F. Human cortical responses to water in the mouth, and the effects of thirst. J Neurophysiol. 2003;90:1865–76.
145. Rolls ET. The anterior and midcingulate cortices and reward. In: Vogt BA, editor. Cingulate neurobiology and disease. Oxford: Oxford University Press; 2009. p. 191–206.
146. Rushworth MF, Buckley MJ, Behrens TE, Walton ME, Bannerman DM. Functional organization of the medial frontal cortex. Curr Opin Neurobiol. 2007;17:220–7.
147. Walton ME, Bannerman DM, Alterescu K, Rushworth MF. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J Neurosci. 2003;23:6475–9.
148. Hadland KA, Rushworth MF, Gaffan D, Passingham RE. The anterior cingulate and reward-guided selection of actions. J Neurophysiol. 2003;89:1161–4.
149. Kennerley SW, Walton ME, Behrens TE, Buckley MJ, Rushworth MF. Optimal decision making and the anterior cingulate cortex. Nat Neurosci. 2006;9:940–7.
150. Rudebeck PH, Behrens TE, Kennerley SW, et al. Frontal cortex subregions play distinct roles in choices between actions and stimuli. J Neurosci. 2008;28:13775–85.
151. Walton ME, Devlin JT, Rushworth MF. Interactions between decision making and performance monitoring within prefrontal cortex. Nat Neurosci. 2004;7:1259–65.
152. Luk CH, Wallis JD. Dynamic encoding of responses and outcomes by neurons in medial prefrontal cortex. J Neurosci. 2009;29:7526–39.
153. Matsumoto M, Matsumoto K, Abe H, Tanaka K. Medial prefrontal selectivity signalling prediction errors of action values. Nat Neurosci. 2007;10:647–56.
154. Seo H, Lee D. Temporal filtering of reward signals in the dorsal anterior cingulate cortex during a mixed-strategy game. J Neurosci. 2007;27:8366–77.
155. Cai X, Padoa-Schioppa C. Neuronal encoding of subjective value in dorsal and ventral anterior cingulate cortex. J Neurosci. 2012;32:3791–808.
156. Cole MW, Yeung N, Freiwald WA, Botvinick M. Cingulate cortex: diverging data from humans and monkeys. Trends Neurosci. 2009;32:566–74.
157. Yeung N, Botvinick MM, Cohen JD. The neural basis of error detection: conflict monitoring and the error-related negativity. Psychol Rev. 2004;111:931–59.
158. Hayden BY, Pearson JM, Platt ML. Neuronal basis of sequential foraging decisions in a patchy environment. Nat Neurosci. 2011;14:933–9.
159. Kolling N, Behrens TE, Mars RB, Rushworth MF. Neural mechanisms of foraging. Science. 2012;336:95–8.
160. Grabenhorst F, D'Souza A, Parris BA, Rolls ET, Passingham RE. A common neural scale for the subjective pleasantness of different primary rewards. Neuroimage. 2010;51:1265–74.
161. Barbas H, Pandya DN. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol. 1989;286:353–75.
162. Gabbott PL, Warner TA, Jays PR, Bacon SJ. Areal and synaptic interconnectivity of prelimbic (area 32), infralimbic (area 25) and insular cortices in the rat. Brain Res. 2003;993:59–71.
163. Koski L, Paus T. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. Exp Brain Res. 2000;133:55–65.

164. Johansen-Berg H, Gutman DA, Behrens TE, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. Cereb Cortex. 2008;18:1374–83.
165. Nagai Y, Critchley HD, Featherstone E, Trimble MR, Dolan RJ. Activity in ventromedial prefrontal cortex covaries with sympathetic skin conductance level: a physiological account of a "default mode" of brain function. Neuroimage. 2004;22:243–51.
166. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. Nat Neurosci. 2004;7:189–95.
167. Mayberg HS, Brannan SK, Mahurin RK. Cingulate function in depression: a potential predictor of treatment response. Neuroreport. 1997;8:1057–61.
168. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45:651–60.
169. Grabenhorst F, Rolls ET. Selective attention to affective value alters how the brain processes taste stimuli. Eur J Neurosci. 2008;27:723–9.
170. McCabe C, Rolls ET, Bilderbeck A, McGlone F. Cognitive influences on the affective representation of touch and the sight of touch in the human brain. Soc Cogn Affect Neurosci. 2008;3:97–108.
171. Guest S, Grabenhorst F, Essick G, et al. Human cortical representation of oral temperature. Physiol Behav. 2007;92:975–84.
172. Rolls ET. Brain mechanisms underlying flavour and appetite. Philos Trans R Soc Lond B Biol Sci. 2006;361:1123–36.
173. Bernoulli J. Exposition of a new theory on the measurement of risk. Econometrica. 1738/1954;22:23–36.
174. McFarland DJ, Sibly RM. The behavioural final common path. Philos Trans R Soc Lond B Biol Sci. 1975;270:265–93.
175. Montague PR, Berns GS. Neural economics and the biological substrates of valuation. Neuron. 2002;36:265–84.
176. Deco G, Rolls ET. Decision-making and Weber's Law: a neurophysiological model. Eur J Neurosci. 2006;24:901–16.
177. Wang XJ. Decision making in recurrent neuronal circuits. Neuron. 2008;60:215–34.
178. Deco G, Rolls ET, Romo R. Stochastic dynamics as a principle of brain function. Prog Neurobiol. 2009;88:1–16.
179. Rolls ET, Deco G. The noisy brain: stochastic dynamics as a principle of brain function. Oxford: Oxford University Press; 2010.
180. Padoa-Schioppa C, Assad JA. The representation of economic value in the orbitofrontal cortex is invariant for changes of menu. Nat Neurosci. 2008;11:95–102.
181. Crespi L. Quantitative variation of incentive and performance in the white rat. Am J Psychol. 1942;55:467–517.
182. Mazur JE. Learning and behavior. 4th ed. Upper Saddle River: Prentice Hall; 1998.
183. Kable JW, Glimcher PW. The neurobiology of decision: consensus and controversy. Neuron. 2009;63:733–45.
184. de Araujo IET, Rolls ET, Velazco MI, Margot C, Cayeux I. Cognitive modulation of olfactory processing. Neuron. 2005;46:671–9.
185. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 2002;3:201–15.
186. Hare TA, Camerer CF, Rangel A. Self-control in decision-making involves modulation of the vmPFC valuation system. Science. 2009;324:646–8.
187. Grabenhorst F, Rolls ET. Attentional modulation of affective vs. sensory processing: functional connectivity and a top-down biased activation theory of selective attention. J Neurophysiol. 2010;104:1649–60.
188. Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci. 1995;18:193–222.
189. Deco G, Rolls ET. Neurodynamics of biased competition and co-operation for attention: a model with spiking neurons. J Neurophysiol. 2005;94:295–313.

190. Rolls ET, Grabenhorst F, Deco G. Choice, difficulty, and confidence in the brain. Neuroimage. 2010;53:694–706.
191. Rolls ET, Grabenhorst F, Deco G. Decision-making, errors, and confidence in the brain. J Neurophysiol. 2010;104:2359–74.
192. Petrides M, Pandya DN. Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J Neurosci. 2007;27:11573–86.
193. Goldman-Rakic PS, Leung H-C. Functional architecture of the dorsolateral prefrontal cortex in monkeys and humans. In: Stuss DT, Knight RT, editors. Principles of frontal lobe function. New York: Oxford University Press; 2002. p. 85–95.
194. Heekeren HR, Marrett S, Bandettini PA, Ungerleider LG. A general mechanism for perceptual decision-making in the human brain. Nature. 2004;431:859–62.
195. Watanabe M, Sakagami M. Integration of cognitive and motivational context information in the primate prefrontal cortex. Cereb Cortex. 2007;17 Suppl 1:i101–9.
196. Rangel A, Hare T. Neural computations associated with goal-directed choice. Curr Opin Neurobiol. 2010;20:262–70.
197. Rushworth MF, Behrens TE. Choice, uncertainty and value in prefrontal and cingulate cortex. Nat Neurosci. 2008;11:389–97.
198. Hare TA, O'Doherty J, Camerer CF, Schultz W, Rangel A. Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. J Neurosci. 2008;28:5623–30.
199. Plassmann H, O'Doherty J, Rangel A. Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. J Neurosci. 2007;27:9984–8.
200. Chib VS, Rangel A, Shimojo S, O'Doherty JP. Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. J Neurosci. 2009;29:12315–20.
201. De Martino B, Kumaran D, Holt B, Dolan RJ. The neurobiology of reference-dependent value computation. J Neurosci. 2009;29:3833–42.
202. McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. Science. 2004;306:503–7.
203. Kable JW, Glimcher PW. The neural correlates of subjective value during intertemporal choice. Nat Neurosci. 2007;10:1625–33.
204. Peters J, Buchel C. Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. J Neurosci. 2009;29:15727–34.
205. Levy I, Snell J, Nelson AJ, Rustichini A, Glimcher PW. Neural representation of subjective value under risk and ambiguity. J Neurophysiol. 2010;103:1036–47.
206. FitzGerald TH, Seymour B, Dolan RJ. The role of human orbitofrontal cortex in value comparison for incommensurable objects. J Neurosci. 2009;29:8388–95.
207. Knutson B, Rick S, Wimmer GE, Prelec D, Loewenstein G. Neural predictors of purchases. Neuron. 2007;53:147–56.
208. Behrens TE, Hunt LT, Woolrich MW, Rushworth MF. Associative learning of social value. Nature. 2008;456:245–9.
209. Rolls ET, McCabe C, Redoute J. Expected value, reward outcome, and temporal difference error representations in a probabilistic decision task. Cereb Cortex. 2008;18:652–63.
210. Wang XJ. Probabilistic decision making by slow reverberation in cortical circuits. Neuron. 2002;36:955–68.
211. Kim JN, Shadlen MN. Neural correlates of a decision in the dorsolateral prefrontal cortex of the macaque. Nat Neurosci. 1999;2:176–85.
212. Rolls ET, Grabenhorst F, Parris BA. Neural systems underlying decisions about affective odors. J Cogn Neurosci. 2010;22:1069–82.
213. Rangel A. The computation and comparison of value in goal-directed choice. In: Glimcher PW, Camerer CF, Fehr E, Poldrack RA, editors. Neuroeconomics: decision-making and the brain. London: Academic; 2009. p. 425–40.
214. Rushworth MF, Mars RB, Summerfield C. General mechanisms for making decisions? Curr Opin Neurobiol. 2009;19:75–83.

215. Boorman ED, Behrens TE, Woolrich MW, Rushworth MF. How green is the grass on the other side? Frontopolar cortex and the evidence in favor of alternative courses of action. Neuron. 2009;62:733–43.
216. Wunderlich K, Rangel A, O'Doherty JP. Neural computations underlying action-based decision making in the human brain. Proc Natl Acad Sci U S A. 2009;106:17199–204.
217. Wunderlich K, Rangel A, O'Doherty JP. Economic choices can be made using only stimulus values. Proc Natl Acad Sci U S A. 2010;107:15005–10.
218. Damasio AR. Neuroscience and the emergence of neuroeconomics. In: Glimcher PW, Camerer CF, Fehr E, Poldrack RA, editors. Neuroeconomics: decision-making and the brain. London: Academic; 2009. p. 209–13.
219. Rushworth MF, Behrens TE, Rudebeck PH, Walton ME. Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. Trends Cogn Sci. 2007;11:168–76.
220. Wardle J, Guthrie C, Sanderson S, Birch L, Plomin R. Food and activity preferences in children of lean and obese parents. Int J Obes Relat Metab Disord. 2001;25:971–7.
221. McGloin AF, Livingstone MB, Greene LC, et al. Energy and fat intake in obese and lean children at varying risk of obesity. Int J Obes Relat Metab Disord. 2002;26:200–7.
222. Franken IHA, Muris P. Individual differences in reward sensitivity are related to food craving and relative body weight in healthy women. Appetite. 2005;45:198–201.
223. Hetherington MM. Cues to overeat: psychological factors influencing overconsumption. Proc Nutr Soc. 2007;66:113–23.
224. Drewnowski A. Energy density, palatability, and satiety: implications for weight control. Nutr Rev. 1998;56:347–53.
225. Salbe AD, DelParigi A, Pratley RE, Drewnowski A, Tataranni PA. Taste preferences and body weight changes in an obesity-prone population. Am J Clin Nutr. 2004;79:372–8.
226. Rolls ET. The neural representation of oral texture including fat texture. J Texture Stud. 2011;42:137–56.
227. Verhagen JV, Kadohisa M, Rolls ET. The primate insular/opercular taste cortex: neuronal representations of the viscosity, fat texture, grittiness, temperature and taste of foods. J Neurophysiol. 2004;92:1685–99.
228. Rolls ET. Neural representation of fat texture in the mouth. In: Montmayeur J-P, Coutre J, editors. Fat detection: taste, texture, and postingestive effects. Boca Raton: CRC Press; 2010. p. 197–223.
229. Small DM, Voss J, Mak YE, et al. Experience-dependent neural integration of taste and smell in the human brain. J Neurophysiol. 2004;92:1892–903.
230. Eldeghaidy S, Marciani L, McGlone F, et al. The cortical response to the oral perception of fat emulsions and the effect of taster status. J Neurophysiol. 2011;105:2572–81.
231. Veldhuizen MG, Bender G, Constable RT, Small DM. Trying to detect taste in a tasteless solution: modulation of early gustatory cortex by attention to taste. Chem Senses. 2007;32:569–81.
232. Cerf-Ducastel B, Van de Moortele P-F, MacLeod P, Le Bihan D, Faurion A. Interaction of gustatory and lingual somatosensory perceptions at the cortical level in the human: a functional magnetic resonance imaging study. Chem Senses. 2001;26:371–83.
233. Haase L, Cerf-Ducastel B, Murphy C. Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. Neuroimage. 2009;44:1008–21.
234. Wang GJ, Volkow ND, Felder C, et al. Enhanced resting activity of the oral somatosensory cortex in obese subjects. Neuroreport. 2002;13:1151–5.
235. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J Abnorm Psychol. 2008;117:924–35.
236. Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J Neurosci. 2011;31:4360–6.
237. Kaas JH. The future of mapping sensory cortex in primates: three of many remaining issues. Philos Trans R Soc Lond B Biol Sci. 2005;360:653–64.
238. Kaas JH. Somatosensory system. In: Paxinos G, Mai JK, editors. The human nervous system. 3rd ed. London: Elsevier; 2012. p. 1074–109.

239. Kaas JH, Qi HX, Iyengar S. Cortical network for representing the teeth and tongue in primates. Anat Rec. 2006;288:182–90.
240. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA. 2005;293:1861–7.
241. Krebs JR. The Croonian Lecture 2004. Risk: food, fact and fantasy. Philos Trans R Soc Lond B Biol Sci. 2005;360:1133–44.
242. Schwartz MW, Porte D. Diabetes, obesity, and the brain. Science. 2005;307:375–9.
243. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature. 2006;443:289–95.
244. Rolls ET. Understanding the mechanisms of food intake and obesity. Obes Rev. 2007;8:67–72.
245. Davis C, Patte K, Levitan R, et al. From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. Appetite. 2007;48:12–9.
246. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. Annu Rev Public Health. 2011;32:285–306.
247. Harris JL, Brownell KD, Bargh JA. The food marketing defense model: integrating psychological research to protect youth and inform public policy. Soc Issues Policy Rev. 2009; 3:211–71.
248. Downs JS, Loewenstein G, Wisdom J. Strategies for promoting healthier food choices. Am Econ Rev. 2009;99:159–64.
249. Just DR, Payne CR. Obesity: can behavioral economics help? Ann Behav Med. 2009;38 Suppl 1:S47–55.
250. Kiesel K, McCluskey JJ, Villas-Boas SB. Nutritional labeling and consumer choices. Annu Rev Resour Econ. 2011;3:141–58.
251. Jackendoff R. Foundations of language. Oxford: Oxford University Press; 2002.
252. Berwick RC, Chomsky N. The biolinguistic program: the current state of its development. In: Di Sciullo AM, Boeckx C, editors. The biolinguistic enterprise: new perspectives on the evolution and nature of the human language faculty. Oxford: Oxford University Press; 2011. p. 19–41.
253. Sharot T. The optimism bias. Curr Biol. 2011;21:R941–5.
254. Sharot T, Riccardi AM, Raio CM, Phelps EA. Neural mechanisms mediating optimism bias. Nature. 2007;450:102–5.
255. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. JAMA. 2007;298:2415–7.
256. Thaler RH, Sunstein CR. Nudge: improving decisions about health, wealth and happiness. New Haven: Yale University Press; 2008.
257. McClure SM, Li J, Tomlin D, et al. Neural correlates of behavioral preference for culturally familiar drinks. Neuron. 2004;44:379–87.
258. Yamaguchi S. The synergistic taste effect of monosodium glutamate and disodium 5′-inosinate. J Food Sci. 1967;32:473–8.
259. Rifkin B, Bartoshuk LM. Taste synergism between monosodium glutamate and disodium 5′-guanylate. Physiol Behav. 1980;24:1169–72.
260. Yamaguchi S, Ninomiya K. Umami and food palatability. J Nutr. 2000;130:921S–6.
261. Yaxley S, Rolls ET, Sienkiewicz ZJ. Gustatory responses of single neurons in the insula of the macaque monkey. J Neurophysiol. 1990;63:689–700.
262. Yaxley S, Rolls ET, Sienkiewicz ZJ. The responsiveness of neurons in the insular gustatory cortex of the macaque monkey is independent of hunger. Physiol Behav. 1988;42:223–9.
263. Plassmann H, O'Doherty J, Shiv B, Rangel A. Marketing actions can modulate neural representations of experienced pleasantness. Proc Natl Acad Sci U S A. 2008;105:1050–4.
264. Rolls ET, Grabenhorst F, Margot C, da Silva MAAP, Velazco MI. Selective attention to affective value alters how the brain processes olfactory stimuli. J Cogn Neurosci. 2008;20:1815–26.
265. Hare TA, Malmaud J, Rangel A. Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. J Neurosci. 2011;31:11077–87.
266. Bollinger B, Leslie P, Sorensen A. Calorie posting in chain restaurants. Am Econ J Econ Policy. 2011;3:91–128.

267. Jenison RL, Rangel A, Oya H, Kawasaki H, Howard MA. Value encoding in single neurons in the human amygdala during decision making. J Neurosci. 2011;31:331–8.
268. Phelps EA. Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol. 2006;57:27–53.
269. Mookherjee BD, Trenkle RW, Wilson RA. The chemistry of flowers, fruits and spices: live vs. dead, a new dimension in fragrance research. Pure Appl Chem. 1990;62:1357–64.
270. Ohloff G. Scent and fragrances. Berlin: Springer; 1994.
271. Shepherd GM. Smell images and the flavour system in the human brain. Nature. 2006;444:316–21.
272. Zou Z, Buck LB. Combinatorial effects of odorant mixes in olfactory cortex. Science. 2006;311:1477–81.
273. Wilson DA, Kadohisa M, Fletcher ML. Cortical contributions to olfaction: plasticity and perception. Semin Cell Dev Biol. 2006;17:462–70.
274. Giraudet P, Berthommier F, Chaput M. Mitral cell temporal response patterns evoked by odor mixtures in the rat olfactory bulb. J Neurophysiol. 2002;88:829–38.
275. Kanwisher N, Wojciulik E. Visual attention: insights from brain imaging. Nat Rev Neurosci. 2000;1:91–100.
276. Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci. 2000;3:277–83.
277. Taylor SL, Roberts M. Odor and cognitive alteration of the contingent negative variation. Chem Senses. 1990;15:537–45.
278. Rolls ET, Deco G. Computational neuroscience of vision. Oxford: Oxford University Press; 2002.

Chapter 9
Neurogenetics and Neurobiology of Dopamine in Anhedonia

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Abstract Anhedonia, the inability to feel or experience pleasure, is a major problem for recovering addicts. Anhedonia can persist long after all traces of the offending drug are gone, and it can cause suicidal thinking and behaviors. We believe that anhedonia is not a distinct disorder but is a symptom of hypodopaminergic traits (genetic), epigenetic states, or a combination of the two. The 2011 endorsement of the American Society of Addiction Medicine's new definition of addiction as a brain disorder has caught up with the science. Addiction involves an extended neuro-circuitry of the brain, and anhedonia is a condition that involves some of those same regions, including dopaminergic pathways in the mesocorticolimbic system. Andedonia, commonly reported by addicts in detox centers or early abstinence, may be directly tied to the drug-induced dopaminergic changes. It has been our position for decades that brain dopaminergic deficiencies result in

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reward-circuitry impairments, ultimately leading to *Reward Deficiency Syndrome* (RDS). The prefrontal cortex and cingulate gyrus contribute to drug relapse, and the nucleus accumbens (NAc) is a locus for craving behavior. While dopaminergic activity is very complex and may evoke differential physiological processes as it relates to pain and pleasure mechanisms (e.g., "liking" and "wanting"), anhedonic behavior has at its root a hypodopaminergic phenotype. In this chapter we discuss polymorphisms of reward genes in terms of inducing this hypodopaminergic phenotype (interaction of both genes and environment) and attempt to show their impact on the induction of anhedonia as a symptom of drug-induced withdrawal. Understanding of putative neurogenetic antecedents to RDS behaviors may provide a gene map for accessing the risk of an individual in developing anhedonia, especially following long-term drug abuse. We encourage the scientific community to carry on required studies to test this hypothesis. It is our belief that one mode of treatment to attenuate anhedonia is to provide natural activation of dopaminergic receptors (D2/D3) at the brain sites for craving and relapse in order to increase dopamine sensitivity.

Keywords Anhedonia • Hedonia • Dopamine • Reward deficiency syndrome • Neurogenetics • Neurobiology

Abbreviations

ACh	Acetylcholine
ANKK1	Ankyrin repeat and kinase domain containing 1—a gene that controls the synthesis of dopamine in the brain
COMT	Catechol-O-methyltransferase
CRF	Cortiocotropin-releasing factor
DA	Dopamine
DAT1	Dopamine transporter polymorphism associated with ADHD
D2/D3	Dopamine receptors
DRD2	Dopamine receptor D2
GABA	γ-amino-butyric acid
GTPase	A hydrolase enzyme that can bind and hydrolyze guanosine triphosphate
IFN-a	Interferon-alpha is a pleiotropic cytokine—part of the immune response signaling pathway
NAc	Nucleus accumbens
RAC1	RAS-related C3 botulinum toxin substrate 1
RAS	A family of related proteins belonging to GTPase class and involved in cellular signal transduction
RDS	Reward deficiency syndrome
Taq1A	Polymorphism that can influence DRD2 receptor expression
TREK	Outward rectifying potassium channel

9.1 Introduction

In psychology and psychiatry, **anhedonia** (pron.: /ˌænhiˈdoʊniə// ***AN-hee-DOH-nee-ə***; Greek: **ἀν-** *an-*, "without" + **ἡδονή** *hēdonē*, "pleasure") is defined as the inability to experience pleasure from activities usually found enjoyable, e.g., exercise, hobbies, sexual activities, or social interactions. An extended view beyond pleasurable experience, more recent models have highlighted the need to consider different aspects of enjoyable behavior, such as motivation or desire to engage in an activity ("motivational anhedonia"), as compared to the level of enjoyment of the activity itself ("consummatory anhedonia") [1].

Moreover, anhedonia can be a characteristic of mental disorders including mood disorders, schizoaffective disorder, schizoid personality disorder, schizophrenia, and Reward Deficiency Syndrome (RDS) [2]. For example, people affected with schizophrenia often describe themselves as feeling emotionally empty [3]. Disturbing mood changes also can occur resultant to stressful life events, and they are common during times of physical illness [4]. Anhedonia can be a feature of such mood changes, but they are not mutually inclusive.

While there is much debate regarding the epidemiological basis of anhedonia, scientists theorize that anhedonia may result from the breakdown in the brain reward circuitry, involving the important neurotransmitter dopamine (DA). However, non-dopaminergic mechanisms also may play a role, but this is not currently understood [5]. Interestingly, the reward system may be less responsive in patients displaying anhedonia, especially in depressed patients [6]. Keedwell and Linden [7] using neuroimaging techniques found that the brains of participants who were clinically depressed had to work harder to process rewarding experiences. While earlier research believed DA to be primarily involved in the subjective experience of pleasure, the last 20 years has seen a conceptual shift, such that DA now is believed to underlie various aspects of reward anticipation, learning, and motivation [8–11] (as "wanting" compared to "liking") [12]. Of note, much of the research underlying the newer concepts is based on nonhuman models, and because rewarding experiences in humans are highly complex and may be event dependent, epigenetics of mood [11, 12] must be considered [12]. Moreover, according to Schultz, "many lesion studies report an amazing variety of deficits in behavioral functions that cannot possibly be encoded in great detail by the relatively small number of midbrain dopamine neurons." In terms of DA's function, the speed of observed phasic DA changes varies several thousand-fold, which offers a means to differentiate the behavioral relationships according to their time courses. As such, DA is involved in mediating the reactivity of the organism to the environment (potentially epigenetic) at different time scales, from fast impulse responses related to reward, to slower changes with uncertainty, punishment, and possibly movement to the tonic enabling of postsynaptic motor, cognitive, and motivational systems deficient in reward behaviors like RDS. It is well- known that anhedonia also is a relatively common side effect of antidopaminergic neuroleptics or antipsychotic drugs that block DA binding to post synaptic neuronal loci [13, 14]. Cigarette smoking rates are increased among those

with psychiatric illness, especially those on psychiatric medications [15]. Smoking has been seen as a self-medication for boredom and as an attempt to reverse antipsychotic related anhedonia [16].

It is of clinical interest that utilizing a Chinese version of the Snaith-Hamilton-Pleasure-Scale, a self-reported scale evaluating anhedonia for neuropsychiatric disorders [13], researchers found that patients with depression scored significantly more anhedonia than patients with schizophrenia and healthy controls, and the patients with schizophrenia scored significantly more anhedonia than the healthy controls.

Research with nonhuman animals and human populations is important for conceptualizing the commonality of food and drug addiction. People who take highly reinforcing drugs of abuse have reduced interest in eating, while on the other hand, during drug withdrawal, eating increases [17]. In clinical settings "never get too hungry" is an anti-drug relapse mantra [18]. Anhedonia during withdrawal or due to other causes appears to result from the neurochemical effects of substances such as glucose and opioids during withdrawal states. Human neuroimaging data related to reward circuitry responsivity and weight gain adequately addresses this rhetoric [19, 20]. In nonhungry, nonthirsty rats, the taste sensation associated with the ingestion of sweetened water was clearly more rewarding than the artificial sensations of intravenous cocaine, independent of prior cocaine history, as summarized by Ahmed [21] in the Oxford publication *Food and Addiction*. Moreover, this conclusion was generalized to intravenous heroin; however, heroin was more potent than cocaine in competing with sweet taste, especially in chronic heroin use [22].

9.2 Anhedonia in RDS Behaviors

RDS, first coined by Blum et al. in 1996 [23], has received considerable attention since it inception and represents a conceptual framework for understanding the role of, for example, dopaminergic genetics in not only drug and alcohol abuse, but in behavioral addictions and in severe psychiatric disorders as well [24].

Addictive drugs have in common that they are voluntarily self-administered by laboratory animals, and that they enhance the functioning of the reward circuitry of the brain. The core reward circuitry consists of an in-series circuit linking the ventral tegmental area, NAc, and ventral pallidum via the medial forebrain bundle. As mentioned earlier, although originally believed to simply encode the set point of hedonic tone, these circuits are now believed to be functionally far more complex, also encoding attention, expectancy of reward, disconfirmation of reward expectancy, and incentive motivation. Moreover, hedonic dysregulation or anhedonia, within these circuits may lead to addiction. The second-stage dopaminergic component in this reward circuitry is the crucial addictive-drug-sensitive component [25]. All addictive drugs have in common that they enhance (directly or indirectly or even trans-synaptically) dopaminergic reward synaptic function in the NAc. Drug self-administration is regulated by NAc DA levels, and is done to keep NAc DA within a specific elevated range (to maintain a desired hedonic level).

For some classes of addictive drugs (e.g., opiates), tolerance to the euphoric effects develops with chronic use. Post-use dysphoria then comes to dominate reward circuit hedonic tone, and addicts no longer use drugs to get high, but simply to get back to a new normal ('get straight'). The brain circuits mediating the pleasurable effects of addictive drugs are anatomically, neurophysiologically, and neurochemically different from those mediating physical dependence, and from those mediating craving (NAc) and relapse (prefrontal cortex, cingulate gyrus, and central amygdala).

There are important genetic variations in vulnerability to drug addiction, yet environmental factors such as stress, trauma, exposure during childhood, exposure in utero, and social defeat also alter brain-reward mechanisms in such a manner as to impart vulnerability to addiction (epigenetics). The *bio-psycho-social* model of etiology holds very well for addiction. Addiction to cocaine [26] or other drugs appears to correlate with a hypodopaminergic dysfunctional state within the reward circuitry of the brain as suggested by the RDS model [23]. Neuroimaging studies in humans add credence to this hypothesis. Credible evidence also implicates serotonergic, opioid, endocannabinoid, GABAergic, and glutamatergic mechanisms in addiction. Recent evidence from diffusion tensor magnetic resonance neuroimaging points to the role of polymorphisms of catabolic enzymes like catechol-O-methyl-transferase (COMT) in white matter integrity [27].

According to Gardner [28], drug addiction progresses from occasional recreational use to impulsive use to habitual compulsive use. This correlates with a progression from reward-driven to habit-driven drug-seeking behavior. This behavioral progression correlates with a neuroanatomical progression from ventral striatal (NAc) to dorsal striatal control over drug-seeking behavior. The three classical sets of craving and relapse triggers are (a) re-exposure to addictive drugs, (b) stress, and (c) re-exposure to environmental cues (people, places, things) previously associated with drug-taking behavior. Drug-triggered relapse involves the NAc and the neurotransmitter DA. Stress-triggered relapse involves (a) the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the neurotransmitter corticotrophin-releasing factor, and (b) the lateral tegmental noradrenergic nuclei of the brain stem and the neurotransmitter norepinephrine. Finally, cue-triggered relapse involves the basolateral nucleus of the amygdala, the hippocampus, and the neurotransmitter glutamate. Knowledge of the neuroanatomy, neurophysiology, neurochemistry, neuropharmacology, and neurogenetics of addictive drug action in the brain is currently producing a variety of strategies for pharmacogenomics/nutrigenomics treatment of RDS behaviors [29]. In fact, one interesting natural substance L-acetyl-carnitine, a substance having acetylcholine-like pharmacological activity [30] has been shown to attenuate anhedonia associated with ethanol dependence [31].

9.3 Anhedonia Hypothesis and DA as a Pleasure Molecule

Prior to our concept of RDS, the anhedonia hypothesis of neuroleptic action [32] was, from its inception, a DA hypotheses of reward [33] or reinforcement [34]. Moreover, Dackis and Gold placed significant value on the role of DA depletion in

cocaine seeking behavior and relapse [35]. Of note, DA hypotheses were themselves deviations from an earlier catecholaminergic model, the noradrenergic theory of reward first introduced by Larry Stein [36]. Historically, the anhedonia hypothesis [32]—that brain DA plays a critical role in the subjective pleasure associated with positive rewards—was, according to Wise [37], "intended to draw the attention of psychiatrists to the growing evidence that dopamine plays a critical role in the objective reinforcement and incentive motivation associated with food and water, brain stimulation reward, and psychomotor stimulant and opiate reward."

A number of laboratory studies revealed that neuroleptics, drugs used to treat a human condition involving anhedonia (i.e., schizophrenia), attenuated in non-human animals the positive reinforcement that we normally associate with pleasure [38]. In essence, this seems quite paradoxical, since blocking DA should result in opposite effects. In any case, the hypothesis held only brief interest for psychiatrists, who correctly pointed out that the animal studies reflected acute actions of neuroleptics whereas the treatment of schizophrenia appeared to result from neuroadaptations to chronic neuroleptic administration, and that it was the positive symptoms of schizophrenia that neuroleptics alleviated, rather than the negative symptoms that include anhedonia.

Wise [37] also pointed out that despite its limited heuristic value for the understanding of schizophrenia, the anhedonia hypothesis has had major impact on biological theories of reinforcement, motivation, and addiction and the neurogenetics thereof [39]. Brain DA plays a very important role in reinforcement of response habits, conditioned preferences, and synaptic plasticity in cellular models of learning and memory [40]. The notion that DA plays a dominant role in reinforcement is fundamental to the psychomotor stimulant theory of addiction, to most neuroadaptation theories of addiction, and to current theories of conditioned reinforcement and reward deficiency prediction. Properly understood, it also is fundamental to recent theories of incentive motivation [41].

The notion that DA might be important for pleasure itself came in part from the subjective reports of patients [42] or normal subjects [43, 44] given neuroleptic treatments. The dysphoria caused by neuroleptics is quite consistent with the concept that they attenuate the normal pleasures of life. Consistent with our view [45] and that of others [46], drugs like cocaine and amphetamine and even palatable food—i.e., substances presumed to be addictive at least in part because of the euphoria they cause [47]—increase extracellular DA levels [48–50]. Furthermore, although controversial [51, 52], the neuroleptic pimozide, a competitive antagonist at DA receptors, had been reported to decrease the euphoria induced by intravenous amphetamine in humans [53, 54]. Consistent with the ability of cannabinoids (tetrahydrocannabinol or THC) to increase sucrose palatability is the observation that under THC pretreatment, sucrose acquires the ability to induce a release of DA in the shell of the NAc, and this property undergoes adaptation after repeated exposure to the hedonic taste (habituation) [55].

Finally, Bressan and Crippa [56] reviewed pre-clinical data concerning the role of DA in reward and pleasure behaviors. They utilized a computer-based search of the literature, augmented by extensive bibliography-guided article

reviews, to find basic information on the DA and the reward systems, and symptoms such as dysphoria, anhedonia, and depression. Their results indicated that central dopaminergic neurotransmission is complex, having multiple actions at each level of the mesocorticolimbic reward pathway. Moreover, the role of DA in the reward process and brain reward circuitry, indeed is associated with the ability to experience pleasure, not dismissing a motivational role. The authors highlighted that dysfunction of DA transmission in the reward circuit is associated with symptoms such as anhedonia, apathy, and dysphoria found in several neuropsychiatric disorders, including Parkinson's disease, depression, drug addiction, and neuroleptic-induced dysphoria.

9.4 Reward Genes and Anhedonia: Potential Therapeutic Targets

There are many reward based genes having distinctive effects in terms of mood including anhedonia. Furthermore, these genes and associated polymorphisms in psychiatric disorders have resulted in more than 24,000 listed PubMed articles as of the middle of 2013. A selective sampling is presented in Tables 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, and 9.9

9.4.1 Candidate Reward Genes and RDS: A Sampling

Understanding these gene-environmental interactions may provide important insight for future therapies. As noted earlier, there is mounting evidence that the NAc has an important role in the pathophysiology of anhedonia. As the NAc is a key component in the neural circuitry of reward, it has been hypothesized that anhedonia, a core symptom of depression, might be related to dysfunction of this brain region. Bessa et al. [106] showed that animals displaying anhedonic behavior had a hypertrophy of medium spiny neurons in the NAc. The researchers also showed increased expression of the genes encoding for brain-derived neurotrophic factor, neural cell adhesion molecule, and synaptic protein synapsin 1 (genes associated with dopaminergic regulation). The authors proposed that stress induces anhedonic behavior, and in animals this is associated with specific changes in the neuronal morphology and in the gene-expression of the NAc.

Clinically, the gene expressions that cause stress are effectively reversed after treatment with antidepressants. Furthermore, transcriptional profiling of the NAc for Rho GTPase-related genes, known regulators of synaptic structure, resulted in a sustained reduction in RAS-related C3 botulinum toxin substrate 1 (RAC1) expression after chronic social-defeat stress. Golden et al. [107] found that overexpression of constitutively active RAC1 in the NAc of mice after chronic social-defeat stress reversed anhedonia. Interestingly, another important gene TREK1 is expressed in

Table 9.1 Dopamine D2 receptor gene

Polymorphism(s)	Study findings	References	Comments
SNP rs: 1800497	Taq A1 allele associates with severe alcoholism	Blum et al. (1990) [57]	First study to associate with alcoholism (called reward gene)
ANKKI -p.Glu713Lys	DRD2 Taq1A RFLP is a single nucleotide polymorphism (SNP) that causes an amino acid substitution within the 11th ankyrin repeat of ANKK1	Neville et al. (2004) [58]	The ANKKI gene is a reflection of DRD2 A_1 allele
SNP rs: 1800497	This SNP has been found to predict future RDS behaviors as high as 74 %	Blum et al. (1996) [23]	Using **Bayesian** analysis
SNP rs: 1800497	Presence of the $A1^+$ genotype (A1/A1, A1/A2) compared to the A^- genotype (A2/A2), is associated with reduced density	Noble et al. (1991) [59]	This reduction causes hypodopaminergic functioning in the dopamine reward pathway
SNP rs: 6277 at exon 7	T^+ allele associates with alcohol dependence	Hill et al. (2008) [60]	Associates with drug seeking behavior and other RDS behaviors
SNP rs: 1800497	10 year follow up that carriers of the DRD2 A1 allele have a higher rate of mortality compared to carriers of the A2 allele in alcohol dependent individuals	Dahlgren et al. (2011) [61]	***Taq I*** A1 allele and a substantially increased relapse rate
DRD2-haplotypes I-C-G-A2 and I-C-A-A1	Confirmed the hypothesis that haplotypes, which are supposed to induce a low DRD2 expression, are associated with alcohol dependence	Kraschewski et al. (2009) [62]	High frequency of haplotype was associated with Cloninger Type 2 and family history of alcoholism
SNP rs: 1800497	Genotype analysis showed a significantly higher frequency for the TaqIA polymorphism among the addicts (69.9 %) compared to control subjects (42.6 %)	Teh et al. (2012) [63]	The addicts had higher scores for novelty seeking (NS) and harm avoidance (HA) personality traits

Table 9.2 Dopamine D4 receptor gene

Polymorphism(s)	Study findings	References	Comments
DRD4—The 7 repeat (7R) VNTR	The length of the D4 dopamine receptor (DRD4) exon 3 variable number of tandem repeats (VNTR) affects DRD4 functioning by modulating the expression and efficiency of maturation of the receptor	Van Tol (1998) [64]	The 7 repeat (7R) VNTR requires significantly higher amounts of dopamine to produce a response of the same magnitude as other size VNTRs
120 bp duplication, -616C/G, and -521C/T	Strong finding of -120 bp duplication allele frequencies with schizophrenia ($p=0.008$); -521 C/T polymorphism is associated with heroin addiction	Lai et al. (2010) [65]	This reduced sensitivity or "dopamine resistance" leads to hypodopaminergic functioning. Thus 7R VNTR has been associated with substance –seeking behavior
DRD4 7-repeat allele	A number of putative risk alleles using survival analysis revealed that by 25 years of age 76 % of subjects with a DRD4 7-repeat allele were estimated to have significantly more persistent ADHD compared with 66 % of subjects without the risk allele	Biederman et al. (2009) [66]	Findings suggest that the DRD4 7-repeat allele is associated with a more persistent course of ADHD
7-repeat allele of the dopamine D(4) receptor gene (DRD4)	Although the association between ADHD and DRD4 is small, these results suggest that it is real	Faraone et al. (2001) [67]	For both the case–control and family-based studies, the authors found (1) support for the association between ADHD and DRD4, (2) no evidence that this association was accounted for by any one study, and (3) no evidence for publication bias
Dopamine D4 receptor (DRD4) exon 3 polymorphisms (48 bp VNTR)	Found significant differences in the short alleles (2–5 VNTR) frequencies between controls and patients with a history of delirium tremens and/or alcohol seizures ($p=0.043$)	Grzywacz et al. (2008) [68]	A trend was also observed in the higher frequency of short alleles amongst individuals with an early age of onset of alcoholism ($p=0.063$)
Dopamine D4 receptor (DRD4) -7 repeat allele	Show that the 7-repeat allele is significantly over-represented in the opioid-dependent cohort and confers a relative risk of 2.46	Kotler et al. (1997) [69]	This is the first report of an association between a specific genetic polymorphism and opioid addiction

Table 9.3 Dopamine transporter gene (DAT1)

Polymorphism(s)	Study findings	References	Comments
Localized to chromosome 5p15.3. Moreover, within 3 noncoding region of DAT1 lies a VNTR polymorphism -9 repeat (9R) VNTR	The 9 repeat (9R) VNTR has been shown to influence gene expression and to augment transcription of the dopamine transporter protein	Byerley et al. (1993) [70]	Having this variant results in an enhanced clearance of synaptic dopamine, yielding reduced levels of dopamine to activate postsynaptic neurons
9 repeat (9R) VNTR	DAT1, genotype 9/9 was associated with early opiate addiction	Galeeva et al. (2002) [71]	The combination of SERT genotype 10/10 with DAT1 genotype 10/10 was shown to be a risk factor of opiate abuse less than 16 years of age
Exon 15 rs27072 and VNTR (DAT), promoter VNTR and rs25531	The haplogenotypes 6-A-10/6-G-10 and 5-G-9/5-G-9 were more often present in type 2 alcoholics as compared with type 1 alcoholics [odds ratio (OR): 2.8], and controls (OR: 5.8), respectively	Reese et al. (2010) [72]	In a typology proposed by Cloninger on the basis of adoption studies, a subgroup has been classified as type 2 with patients having high genetic loading for alcoholism, an early onset of alcoholism, a severe course, and coexisting psychiatric problems consisting of aggressive tendencies or criminality
VNTR polymorphism at the dopamine transporter locus (DAT1) 480-bp DAT1 allele	Using the haplotype-based haplotype relative risk (HHRR) method revealed significant association between ADHD/UADD and the 480-bp DAT1 allele (χ^2 7.51, 1 df, P= .006)	Cook et al. (1995) [73]	While there have been some inconsistencies associated with the earlier results the evidence is mounting in favor of the view that the 10R allele of DAT is associated with high risk for ADHD in children and in adults alike
Dopamine transporter (DAT1) variable number tandem repeats (VNTR), genotypes- both 9 and 10-repeat alleles	The non-additive association for the 10-repeat allele was significant for hyperactivity-impulsivity (HI) symptoms. However, consistent with other studies, exploratory analyses of the non-additive association of the 9-repeat allele of DAT1 with HI and oppositional defiant disorder (ODD) symptoms also were significant	Lee et al. (2007) [74]	The inconsistent association between DAT1 and child behavior problems in this and other samples may reflect joint influence of the 10-repeat and 9-repeat alleles

Table 9.4 Catechol-o-methyl-transferase (COMT)

Polymorphism(s)	Study findings	References	Comments
COMT Val158Met and DRD2 Taq1A genotypes	COMT Val158Met and DRD2 Taq1A may affect the intermediate phenotype of central dopamine receptor sensitivity	Schellekens et al. (2012) [75]	COMT Val158Met and DRD2 Taq1A may confer their risk of alcohol dependence through reduced dopamine receptor sensitivity in the prefrontal cortex and hindbrain, respectively
The functional polymorphism (COMT Val108/158Met) affects COMT activity, with the valine (Val) variant associated with higher and the methionine (Met) variant with lower COMT activity	Male alcoholic suicide attempters, compared to male non-attempters, had the higher frequency of Met/Met genotype or Met allele, and significantly (Kruskal-Wallis ANOVA on ranks and Mann–Whitney test) higher aggression and depression scores	Nedic et al. (2011) [76]	These results confirmed the associations between Met allele and aggressive behavior or violent suicide attempts in various psychiatric diagnoses, and suggested that Met allele of the COMT Val108/158 Met might be used as an independent biomarker of suicidal behavior across different psychopathologies
COMT Val(15) Met variation	Both controls and opiate users with Met/Met genotypes showed higher NS scores compared to those with the Val allele	Demetrovis et al. (2010) [77]	Association of the COMT polymorphism and NS temperament scale has been shown for heroin-dependent patients and controls regardless of group status
A functional polymorphism (COMT Val158Met) resulting in increased enzyme activity has been associated with polysubstance abuse and addiction to heroin and meth-amphetamine	These results suggest a significant association between COMT Val158Met polymorphism and susceptibility to cannabis dependence	Baranse et al. (2008) [78]	Cannabis stimulates dopamine release and activates dopaminergic reward neurons in central pathways that lead to enhanced dependence. Catechol-O-methyl transferase (COMT) inactivates amplified extraneuronally released dopamine

Table 9.5 Serotonin transporter gene

Polymorphism(s)	Study findings	References	Comments
Serotonin transporter promoter polymorphism [5-HT transporter gene-linked polymorphic region (5-HTTLPR)]	5-HTTLPR had age-dependent effects on alcohol, tobacco and drug use: substance use did not differ by genotype at age 9, but at age 15, the participants with the short (s)/s genotype had higher tobacco use, and at age 18, they were more active alcohol, drug and tobacco users	Merenäkk et al. (2011) [79]	Results reveal that expression of genetic vulnerability for substance use in children and adolescents may depend on age, gender, interaction of genes, and type of substance
The short (s), low activity allele of a polymorphism (5-HTTLPR) in the serotonin transporter gene (SLC6A4) has been related to alcohol dependence	The 5-HTTLPR short allele predicted adolescent's growth (slope) in alcohol use over time. Adolescents with the 5-HTTLPR short allele showed larger increase in alcohol consumption than those without the 5-HTTLPR short allele	van der Zwaluw et al. (2010) [80]	5-HTTLPR genotype was not related to the initial level (intercept) of alcohol consumption
Triallelic 5-HTTLPR genotype : SA/SA and SA/LG compared to LA/LA	Triallelic 5-HTTLPR genotype : SA/SA and SA/LG compared to LA/LA	Kosek et al. (2009) [81]	Previously, the 5-HTTLPR s-allele had been associated with higher risk of developing chronic pain conditions, but in this study we show that the genotype coding for low 5-HTT expression is associated with a better analgesic effect of an opioid. The s-allele has been associated with down regulation of 5-HT1 receptors and we suggest that individuals with a desensitization of 5-HT1 receptors have an increased analgesic response to opioids during acute pain stimuli, but may still be at increased risk of developing chronic pain conditions

Table 9.6 Mu opiate receptor (MOR)

Polymorphism(s)	Study findings	References	Comments
A single nucleotide polymorphism (SNP) in the human MOR gene (OPRM1 A118G) has been shown to alter receptor protein level in preclinical models and smoking behavior in humans	Independent of session, smokers homozygous for the wild-type OPRM1 A allele exhibited significantly higher levels of MOR BP (ND) than smokers carrying the G allele in bilateral amygdala, left thalamus, and left anterior cingulate cortex	Ray et al. (2011) [82]	Among G allele carriers, the extent of subjective reward difference (de-nicotinized versus nicotine cigarette) was associated significantly with MOR BP(ND) difference in right amygdala, caudate, anterior cingulate cortex, and thalamus
Polymorphism in A118G in exon 1 and C1031G in intron 2 of the MOR gene	Results showed a significant association for both A118G and C1031G polymorphisms and opioid dependence. The G allele is more common in the heroin-dependent group (39.5 and 30.8 % for A118G and C1031G polymorphisms, respectively) when compared to the controls (29.4 and 21.1 % for A118G and C1031G polymorphisms, respectively)	Szeto et al. (2001) [83]	This study suggests that the variant G allele of both A118G and C1031G polymorphisms may contribute to the vulnerability to heroin dependence
A118G single-nucleotide polymorphism (SNP) in exon 1 of the MOR gene (OPRM1), which encodes an amino-acid substitution, is functional and receptors encoded by the variant 118G allele bind the endogenous opioid peptide beta-endorphin with threefold greater affinity than prototype receptors. Other groups subsequently reported that this variant alters stress-responsivity in normal volunteers and also increases the therapeutic response to naltrexone (a mu-preferring opioid antagonist) in the treatment of alcohol dependence	There was a significant overall association between genotypes with an 118G allele and alcohol dependence ($p=0.0074$). The attributable risk for alcohol dependence in subjects with an 118G allele was 11.1 %	Bart et al. (2005) [84]	There was no difference in A118G genotype between type 1 and type 2 alcoholics. In central Sweden, the functional variant 118G allele in exon 1 of OPRM1 is associated with an increased attributable risk for alcohol dependence

(continued)

Table 9.6 (continued)

Polymorphism(s)	Study findings	References	Comments
MOR gene knockout (KO) were examined in wild-type (+/+), heterozygote MOR KO (+/–) and homozygote MOR KO (–/–) mice on voluntary ethanol consumption	Heterozygous and homozygous MOR KO mice consumed less ethanol than wild-type mice. These effects appeared to be greater in female KO mice than in male KO mice. MOR KO mice, especially females, exhibited less ethanol reward in a conditioned place preference paradigm	Hall et al. (2001) [85]	These data fit with the reported therapeutic efficacy of MOR antagonists in the treatment of human alcoholism. Allelic variants that confer differing levels of MOR expression could provide different degrees of risk for alcoholism

Table 9.7 GABA beta subunit 3

Polymorphism(s)	Study findings	References	Comments
GABA A receptor beta 3 subunit gene (GABRB3)	The G1- alleles of the GABRB3 in COAs were significantly higher than non COAs	Namkoong et al. (2008) [86]	In the same study the frequency of the A1+ allele at DRD2 in the COAs was significantly higher than non COAs
Beta 3 subunit m RNAs	The levels of the beta 2 and beta 3 subunit mRNAs remain elevated at 24 h withdrawal from chronic ethanol. Chronic ethanol treatment increased the levels of both of these polypeptides in cerebral cortex	Mhatre and Ticku (1994) [87]	Chronic ethanol administration produced an up-regulation of the beta-subunit mRNA and the polypeptide expression of these subunits in rat cerebral cortex
A1+ (A1A1 and A1A2 genotypes) and A1- (A2A2 genotype) alleles of the DRD2 and G1+ (G1G1 and G1 non-G1 genotypes) and G1- (non-G1 non-G1 genotype) alleles of the GABRB3 gene, Study involved Mood-related alcohol expectancy (AE) and drinking refusal self-efficacy (DRSE) were assessed using the Drinking Expectancy Profile	Patients with the DRD2 A1+ allele, compared with those with the DRD2 A1- allele, reported significantly lower DRSE in situations of social pressure. Similarly, lower DRSE was reported under social pressure by patients with the GABRB3 G1+ allele when compared to those with the GABRB3 G1- alleles. Patients with the GABRB3 G1+ allele also revealed reduced DRSE in situations characterized by negative affect than those with the GABRB3 G1- alleles. Patients carrying the GABRB3 G1+ allele showed stronger AE relating to negative affective change (for example, increased depression) than their GABRB3 G1- counterparts	Young et al. (2004) [88]	Molecular genetics research has identified promising markers of alcohol dependence, including alleles of the D2 dopamine receptor (DRD2) and the GABAA receptor beta 3 subunit (GABRB3) genes

(continued)

Table 9.7 (continued)

Polymorphism(s)	Study findings	References	Comments
Dinucleotide repeat polymorphisms of the GABA(A) receptor beta 3 subunit gene were compared to scores on the General Health Questionnaire-28 (GHQ)	Analysis of GHQ subscale scores showed that heterozygotes compared to the combined homozygotes had higher scores on the somatic symptoms (P=0.006), anxiety/insomnia (P=0.003), social dysfunction (P=0.054) and depression (P=0.004) subscales	Feusner et al. (2001) [89]	The present study indicates that in a population of PTSD patients, heterozygosity of the GABRB3 major (G1) allele confers higher levels of somatic symptoms, anxiety/insomnia, social dysfunction and depression than found in homozygosity
GABRB3 major (G1) allele & DRD@ A1 allele	A significant progressive increase was observed in DRD2 A1 allelic prevalence (P=3.1×10(−6)) and frequency (P=2.7×10(−6)) in the order of non-alcoholics, less severe and severe alcoholics. In severe alcoholics, compared to non-alcoholics, a significant decrease was found in the prevalence (P=4.5×10(−3)) and frequency (P=2.7×10(−2)) of the GABRB3 major (G1) allele. Furthermore, a significant progressive decrease was noted in G1 allelic prevalence (P=2.4×10(−3)) and frequency (P=1.9×10(−2)) in non-alcoholics, less severe and severe alcoholics, respectively	Noble et al. (1988) [90]	In sum, in the same population of non-alcoholics and alcoholics studied, variants of both the DRD2 and GABRB3 genes independently contribute to the risk for alcoholism, with the DRD2 variants revealing a stronger effect than the GABRB3 variants. However, when the DRD2 and the GABRB3 variants are combined, the risk for alcoholism is more robust than when these variants are considered separately

Table 9.8 MOA-A

Polymorphism(s)	Study findings	References	Comments
MAOA genotype	Significant three-way interactions, MAOA genotype by abuse by sex, predicted dysthymic symptoms. Low-activity MAOA genotype buffered against symptoms of dysthymia in physically abused and multiply-maltreated women. Significant three-way interactions, MAOA genotype by sexual abuse by race, predicted all outcomes. Low-activity MAOA genotype buffered against symptoms of dysthymia, major depressive disorder, and alcohol abuse for sexually abused white participants. The high-activity genotype was protective in the nonwhite sexually abused group	Nikulina et al. (2012) [91]	This prospective study provides evidence that MAOA interacts with child maltreatment to predict mental health outcomes
Low-repeat MAOA allele	Individuals with CUD had reductions in GMV in the orbitofrontal, dorsolateral prefrontal, and temporal cortex and the hippocampus compared with controls. (2) The orbitofrontal cortex reductions were uniquely driven by CUD with low- MAOA genotype and by lifetime cocaine use	Alia-Klein et al. (2011) [92]	Long-term cocaine users with the low-repeat MAOA allele have enhanced sensitivity to gray matter loss, specifically in the orbitofrontal cortex, indicating that this genotype may exacerbate the deleterious effects of cocaine in the brain
MAOA u-VNTR	Girls, carrying the long MAOA u-VNTR variant showed a higher risk of being high alcohol consumers, whereas among boys, the short allele was related to higher alcohol consumption	Nilsson et al. (2011) [93]	The present study supports the hypothesis that there is a relation between MAOA u-VNTR and alcohol consumption and that this relation is modulated by environmental factors

(continued)

Table 9.8 (continued)

Polymorphism(s)	Study findings	References	Comments
30-bp repeat in the promoter region of the monoamine oxidase-A gene (MAO-A)	Significant associations between cold pain tolerance and DAT-1 ($p=0.008$) and MAO-A ($p=0.024$) polymorphisms were found. Specifically, tolerance was shorter for carriers of allele 10 and the rarer allele 11, as compared to homozygous for allele 9, and for carriers of allele 4 (MOA) as compared to homozygous for allele 3, respectively	Treister et al. (2009) [94]	These results, together with the known function of the investigated candidate gene polymorphisms, suggest that low dopaminergic activity can be associated with high pain sensitivity and vice versa
The Revised Psychopathy Checklist (PCL-R) has shown a moderate association with violence and as such studied with MAOA genotyped alcoholic offenders	The PCL-R total score predicts impulsive reconvictions among high-activity MAOA offenders (6.8 % risk increase for every one-point increase in PCL-R total score, $P=0.015$), but not among low-activity MAOA offenders, whereas antisocial behavior and attitudes predicted reconvictions in both genotypes (17 % risk increase among high-activity MAOA offenders and 12.8 % increase among low-activity MAOA offenders for every one-point increase in factor 2 score)	Tikkanen et al. (2011) [95]	Results suggest that the efficacy of PCL-R is altered by MAOA genotype, alcohol exposure, and age, which seems important to note when PCL-R is used for risk assessments that will have legal or costly preventive work consequences

Genotyping of two functional polymorphisms in the promoter region of the serotonin transporter and monoamine oxidase-A, respectively, (5-HTT-LPR and MAOA-VNTR), was performed in a group of women with severe alcohol addiction	Within the group of alcoholics, when the patients with known co-morbid psychiatric disorders were excluded, aggressive anti-social behavior was significantly linked to the presence of the high activity MAOA allele	Gokturk et al. (2008) [96]	The pattern of associations between genotypes of 5-HTT-LPR and MAOA-VNTR in women with severe alcoholism differs from most corresponding studies on males
The MAOA gene presents several polymorphisms, including a 30-bp VNTR in the promoter region (MAOA-uVNTR). Alleles with 3.5 and 4 repeats are 2–10 times more efficient than the 3-repeat allele	The results suggest that the 3-repeat allele is associated to: (1) alcohol dependence ($P<0.05$); (2) an earlier onset of alcoholism ($P<0.01$); (3) comorbid drug abuse among alcoholics ($P<0.05$); and (4) a higher number of antisocial symptoms ($P<0.02$)	Contini et al. (2006) [97]	Results confirmed previous reports showing an association of the low activity 3-repeat allele of MAOA-uVNTR polymorphism with substance dependence and impulsive/antisocial behaviors. These findings in a different culture further support the influence of the MAOA-uVNTR in psychiatric disorders

Table 9.9 Dopamine D3

Polymorphism(s)	Study findings	References	Comments
The genotypes of the BDNF Val66Met and DRD3 Ser9Gly polymorphisms. BDNF regulates expression of D3	Logistic regression analysis showed a significant main effect for the Val/Val genotype of the BDNF Val66Met polymorphism (P = 0.020), which predicted bipolar-II patients. Significant interaction effects for the BDNF Val66Met Val/Val genotype and both DRD3 Ser9Gly Ser/Ser and Ser/Gly genotypes were found only in bipolar-II patients (P = 0.027 and 0.006, respectively)	Lee et al. (2012) [98]	Evidence that the BDNF Val66Met and DRD3 Ser9Gly genotypes interact only in bipolar-II disorder (hypomania) and that bipolar-I (Mania) and bipolar-II may be genetically distinct
D3R KO mice	The possible interaction between morphine-induced tolerance and D3 receptors has not been investigated. Compared with wild-type (WT) mice, the dopamine D3 receptor knockout (D3R KO) mice showed pronounced hypoalgesia. The D3R KO mice clearly developed lower morphine-induced tolerance and showed attenuated withdrawal signs compared with the WT mice	Li et al. (2012) [99]	These results suggest that D3 receptors regulate basal nociception and are involved in the development of morphine-induced tolerance and withdrawal
DNA microarrays of two different alcohol-preferring rat lines (HAD and P) and D3 receptors	Data revealed an up-regulation of the dopamine D3 receptor (D3R) after 1 year of voluntary alcohol consumption in the striatum of alcohol preferring rats that was confirmed by qRT-polymerase chain reaction	Vengeliene et al. (2006) [100]	Long-term alcohol consumption leads to an up-regulation of the dopamine D3R that may contribute to alcohol-seeking and relapse. We therefore suggest that selective antagonists of this pharmacological target provide a specific treatment approach to reduce alcohol craving and relapse behavior

Gly9 homozygotes in comparison to Ser9 carriers of D3 receptor gene	Investigated 124 unrelated healthy subjects of German descent and have found diminished parietal and increased frontal P300 amplitudes in Gly9 homozygotes in comparison to Ser9 carriers. Further studies should address the direct role of the DRD3 Ser9Gly polymorphism in attenuated P300 amplitudes in psychiatric disorders like schizophrenia or alcoholism	Mulert et al. (2006) [101]	An important reason for the interest in P300 event-related potentials are findings in patients with psychiatric disorders like schizophrenia or alcoholism in which attenuations of the P300 amplitude are common findings
Dopamine receptor D3 gene BalI polymorphism	Patients above the median value for cognitive impulsiveness (one of the three dimensions of the Barratt scale) were more frequently heterozygous than both alcohol-dependent patients with lower impulsiveness (OR = 2.51, P = 0.019) and than 71 healthy controls (OR = 2.32, P = 0.025)	Limosin et al. (2005) [102]	The D3 Receptor gene has been associated with addictive behaviors especially impulsiveness
Bal I polymorphism at the DRD3 gene	Patients with a sensation-seeking score above 24 were more frequently homozygotes for both alleles than patients with a sensation-seeking score under 24 (P = 0.038) or controls (P = 0.034)	Duaux et al. (1998) [103]	These results suggest that the DRD3 gene may have a role in drug dependence susceptibility in individuals with high sensation-seeking scores
mRNA of both DRD2 and DRD3 gene expression	After a chronic schedule of intermittent bingeing on a sucrose solution, mRNA levels for the D2 dopamine receptor, and the preproenkephalin and preprotachykinin genes were decreased in dopamine-receptive regions of the forebrain, while D3 dopamine receptor mRNA was increased. The effects of sugar on mRNA levels were of greater magnitude in the nucleus accumbens than in the caudate-putamen	Spangler et al. (2004) [104]	Striatal regions of sugar-dependent rats show alterations in dopamine and opioid mRNA levels similar to morphine-dependent rats

Blum et al. [105] with permission

reward-related basal ganglia regions. TREK1 genetic variation may be associated with anhedonic symptoms of depression. Dillon et al. [108] found that the total number of "protective" TREK1 alleles was associated with stronger responses to monetary incentive gains in several other reward-related regions, including the dorsal anterior cingulate cortex, orbitofrontal cortex, and mesial prefrontal cortex. The authors concluded that future studies in depressed samples should evaluate whether variation in neural responses to rewards could contribute to the association between TREK1 and antidepressant response in humans.

Law et al. [109] found that in mood disorders, early stressors such as parental separation are vulnerability factors which affected hippocampal gene expressions. They concluded that early deprivation in nonhuman primates, in the absence of subsequent stressors, has a long-term effect on the hippocampal expression of genes implicated in synaptic function and plasticity. The reductions in GAP-43 and serotonin 1A receptor expressions are comparable with findings in mood disorder, supporting the possibility that the latter reflect an early developmental contribution to anhedonia vulnerability. It is well established that drugs of abuse alter expression of AMPA-type glutamate receptor subunits (GluRs) in the NAc. Todtenkopf et al. [110] found that elevated GluR1 in NAc shell increased intracranial self-stimulation thresholds, an effect similar to that caused by treatments that cause anhedonia and dysphoria (pro-depressive effects) in rats and humans (e.g., drug withdrawal, kappa-opioid agonists). On the other hand, elevated GluR2 decreased intracranial self-stimulation thresholds, an effect similar to that caused by rewarding treatments (e.g., drugs of abuse).

Neuroimaging studies in humans have demonstrated that inflammatory cytokines target basal ganglia function and presynaptic DA, leading to symptoms of anhedonia. Felger et al. [111] found that *in vivo* microdialysis demonstrated decreased release of DA in nonhuman primates after 4 weeks of interferon-alpha (IFN-α) administration compared to saline. Positron emission tomography also showed decreased DA release after 4 weeks of IFN-α as evidenced by reduced displacement of [^{11}C] raclopride following amphetamine administration. Additionally, 4 weeks of IFN-α associated with decreased D2R binding but no change in the DA transporter. Importantly, sucrose consumption was attenuated during IFN-α administration and was correlated with decreased DA release at 4 weeks as measured by *in vivo* microdialysis. The authors concluded that these findings indicated that chronic peripheral IFN-α exposure reduced striatal DA release in association with anhedonia-like behavior in nonhuman primates.

Cocaine often is proposed as the extreme but ideal model for all addictions. Cocaine stimulates its own taking to the point of death in nonhuman animal studies, and withdrawal from psychostimulants like cocaine or amphetamines are used as animal models in screening for antidepressants in humans [112]. Post cocaine or amphetamine addiction leads to a burn-out that looks very much like naturally occurring psychomotorically retarded depressions. However, once that passes, the post addict reports hyperphagia and hypersexuality associated with an important feature of cocaine addiction in humans, the development of a negative affect (e.g., dysphoria, irritability, anhedonia). Such anhedonia is an important factor in craving

and relapse. The DSM-V recognizes that social, occupational, and/or recreational activities decrease as a consequence of repeated drug use, where previously rewarding experiences (e.g., food, job, family) become devalued as the dependent person continues to seek and use drugs despite serious negative consequences.

Recent findings by Carelli and West [113] revealed that cocaine-conditioned cues elicited a "cocaine-need state" that was aversive and was encoded by a distinct subset of NAc neurons and rapid DA release (signaling), and induced cocaine-seeking behavior. Other experiments [114] revealed that bidirectional control (inhibition or excitation) of specified midbrain DA neurons immediately and bidirectionally modulated (induced or relieved) multiple independent depression symptoms such as anhedonia caused by chronic stress. Additionally, optogenetic recruitment of these DA neurons potently altered the neural encoding of anhedonia in the downstream NAc of freely moving rodents. This work suggests that processes affecting anhedonia may involve alterations in the neural encoding of action in limbic circuitry. Accordingly, similar to drugs of abuse, even high fat diets induce reduced DA signaling with an increase in anhedonia-associated behaviors in rodents [115]. This further suggests that agonistic dopaminergic functioning may induce anti-anhedonia.

The role of chronic stress in rodents suggests an effect on DA D1 receptor excitation of melanocortin 4 receptor, which is responsible in part of inducing anhedonia. Lim et al. [116] found that stress-elicited increases in behavioral measurements of anhedonia, but not increases in measurements of behavioral despair, were prevented by blocking these melanocortin 4 receptor-mediated synaptic changes *in vivo*. Further involvement of dopaminergic activity has been shown to be reduced in an animal model whereby chronic social-defeat stress was induced experimentally [117]. This work suggests that chronic social-defeat stress-induced anhedonia might be linked to specific alteration of dopaminergic pathways involved in rewarding processes. Additionally, it was found in the social-defeat model of depression in rats, dynorphin and orexin both were diminished in the hypothalamus; this is noteworthy since nearly all hypothalamic orexin cells co-express dynorphin. Accordingly, these observations suggested that orexin and dynorphin function may be imbalanced between the hypothalamus and mesocortical dopaminergic brain regions in anhedonia [118].

Certainly, the role of serotonin and DA have been studied and elucidated in terms of stress induction and influence on corticosterone activity. Zoratto et al. [119] have shown that in adult tryptophane-depleted and high corticosterone-induced rats, offspring showed significantly increased anhedonia-related behaviors, reduced striatal, and increased hypothalamic brain-derived neurotrophic factor and reduced DA and serotonin in the prefrontal cortex and their turnover in the hippocampus. Zoratto et al. [119] proposed that neonatal variations in the functionality of the serotonergic system and of the hypothalamic-pituitary-adrenal axis may contribute to inducing anhedonia in adulthood.

It is well established that the NAc Shell has been implicated in controlling stress responses through corticotrophin-releasing factor (CRF). In addition to studies indicating that CRF in the NAc Shell increases appetitive motivation, there is indirect

evidence indicating that NAc Shell CRF also may cause aversive responses and that these behaviors (e.g., anhedonia) may be mediated through local DA and acetylcholine (ACh) systems [120]. Chen et al. [120] found that NAc Shell CRF can induce a variety of aversive behaviors, including swim depression, anhedonia, and anxiety, in addition to approach behavior. They proposed that these behaviors, through enhanced activation of ACh and DA in the NAc Shell, support a role for this brain area in mediating the effects of stress and anhedonia and involvement of multi-neurotransmitter deficits [121, 122].

9.5 Conclusions

The study of drug self-administration, abstinence, and post abstinence in laboratory animals and humans has emphasized the importance of DA, pleasure, and anhedonia [123]. Understanding of putative neurogenetic antecedents to RDS behaviors may provide a gene map for accessing the risk of an individual in developing anhedonia, especially following long-term drug abuse. It is quite possible that anhedonia reflects drug induced mini-withdrawal, but due to genetic antecedents, any one individual may be at a higher than normal risk especially in depression. It is our belief that one mode of treatment to attenuate anhedonia is to provide natural activation of dopaminergic receptors (D2/D3) at brain sites for craving and relapse in order to increase DA sensitivity. Additional studies are necessary. In the meantime, diet and exercise and other approaches to stimulate patients' return to their healthy hedonic levels and homeostatic DA states make sense.

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References

1. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55.
2. Blum K, Oscar-Berman M, Giordano J, et al. Neurogenetic impairments of brain reward circuitry links to Reward Deficiency Syndrome (RDS): potential nutrigenomic induced dopaminergic activation. J Genet Syndr Gene Ther. 2012;3:131.
3. Hales R, Yudofsky S, Talbott J. Textbook of psychiatry. 3rd ed. Washington, DC: The American Psychiatric Press; 1999.
4. Gelder MG, Mayou R, Geddes J. Psychiatry. In: Geddes J, editor. Psychiatry, vol. 2. 3rd ed. New York/London: Oxford University Press; 2005. p. 99.
5. Ritsner MS, Miodownik C, Ratner Y, et al. L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study. J Clin Psychiatry. 2011;72:34–42.

6. Surguladze SA. Neural systems underlying affective disorders. Adv Psychiatric Treat. 2003;9:446–55.
7. Keedwell PA, Linden DE. Integrative neuroimaging in mood disorders. Curr Opin Psychiatry. 2013;26:27–32.
8. Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl). 2007;191:391–431.
9. Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology (Berl). 2007;191:461–82.
10. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron. 2012;76:470–85.
11. Schultz W. Multiple dopamine functions at different time courses. Annu Rev Neurosci. 2007;30:259–88.
12. Blum K, Gardner E, Oscar-Berman M, Gold M. "Liking" and "wanting" linked to Reward Deficiency Syndrome (RDS): hypothesizing differential responsivity in brain reward circuitry. Curr Pharm Des. 2012;18:113–8.
13. Liu WH, Wang LZ, Zhu YH, Li MH, Chan RC. Clinical utility of the Snaith-Hamilton-Pleasure scale in the Chinese settings. BMC Psychiatry. 2012;12:184.
14. Lambert M, Schimmelmann BG, Karow A, Naber D. Subjective well-being and initial dysphoric reaction under antipsychotic drugs – concepts, measurement and clinical relevance. Pharmacopsychiatry. 2003;36 Suppl 3:S181–90.
15. Gold MS. Drugs of abuse: a comprehensive series for clinicians. Vol. IV. Tobacco. New York/London: Plenum Medical Book Company; 1995.
16. Miller NS, Gold MS. Comorbid cigarette and addiction: epidemiology and treatment. In: Gold MS, editor. Smoking and illicit drug use. New York: Haworth Medical Press; 1998.
17. Edge PJ, Gold MS. Drug withdrawal and hyperphagia: lessons from tobacco and other drugs. Curr Pharm Des. 2011;17:1173–9.
18. Gold MS, Herkov MJ. Tobacco smoking and nicotine dependence: biological basis for pharmacotherapy from nicotine to treatments that prevent relapse. J Addict Dis. 1998;17:7–21.
19. Avena NM, Gearhardt AN, Gold MS, Wang GJ, Potenza MN. Tossing the baby out with the bathwater after a brief rinse? The potential downside of dismissing food addiction based on limited data. Nat Rev Neurosci. 2012;13:514; author reply.
20. Stice E, Yokum S, Blum K, Bohon C. Weight gain is associated with reduced striatal response to palatable food. J Neurosci. 2010;30:13105–9.
21. Ahmed SH. Is sugar as addictive as cocaine? In: Brownell KD, Gold MS, editors. Food and addiction. Oxford/New York: Oxford University Press; 2012. p. 231–7.
22. Ahmed SH. Imbalance between drug and non-drug reward availability: a major risk factor for addiction. Eur J Pharmacol. 2005;526:9–20.
23. Blum K, Sheridan PJ, Wood RC, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med. 1996;89:396–400.
24. Green AI, Zimmet SV, Strous RD, Schildkraut JJ. Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiatry. 1999;6:287–96.
25. Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction. 2000;95 Suppl 2:S91–117.
26. Gold MS, Miller NS. Cocaine (and crack): neurobiology. In: Lowinson J, Ruiz P, Millman R, editors. Substance abuse: a comprehensive textbook. 3rd ed. New York: Williams and Wilkins; 1997. p. 181–99.
27. Zhang X, Lee MR, Salmeron BJ, et al. Prefrontal white matter impairment in substance users depends upon the catechol-o-methyl transferase (COMT) val158met polymorphism. Neuroimage. 2013;69:62–9.
28. Gardner EL. Addiction and brain reward and antireward pathways. Adv Psychosom Med. 2011;30:22–60.
29. Blum K, Chen AL, Giordano J, et al. The addictive brain: all roads lead to dopamine. J Psychoactive Drugs. 2012;44:134–43.

30. Blum K, Seifter E, Seifter J. The pharmacology of d- and l-carnitine and d- and l-acetylcarnitine. Comparison with choline and acetylcholine. J Pharmacol Exp Ther. 1971;178:331–8.
31. Martinotti G, Andreoli S, Reina D, et al. Acetyl-l-carnitine in the treatment of anhedonia, melancholic and negative symptoms in alcohol dependent subjects. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:953–8.
32. Wise RA. Neuroleptics and operant behavior: the anhedonia hypothesis. Behav Brain Sci. 1982;5:39–87.
33. Wise RA. Catecholamine theories of reward: a critical review. Brain Res. 1978;152:215–47.
34. Fibiger HC. Drugs and reinforcement mechanisms: a critical review of the catecholamine theory. Annu Rev Pharmacol Toxicol. 1978;18:37–56.
35. Dackis CA, Gold MS. New concepts in cocaine addiction: the dopamine depletion hypothesis. Neurosci Biobehav Rev. 1985;9:469–77.
36. Stein L. Chemistry of reward and punishment. In: Efron DH, editor. Proceedings of the American College of NeuroPsychoPharmacology. Washington, DC: U. S. Government Printing Office; 1968. p. 105–23.
37. Wise RA. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox Res. 2008;14:169–83.
38. Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav Brain Res. 2002;137:75–114.
39. Archer T, Oscar-Berman M, Blum K, Gold M. Neurogenetics and epigenetics in impulsive behaviour: impact on reward circuitry. J Genet Syndr Gene Ther. 2012;3:1000115.
40. Bowirrat A, Chen TJ, Oscar-Berman M, et al. Neuropsychopharmacology and neurogenetic aspects of executive functioning: should reward gene polymorphisms constitute a diagnostic tool to identify individuals at risk for impaired judgment? Mol Neurobiol. 2012;45:298–313.
41. Robinson S, Sandstrom SM, Denenberg VH, Palmiter RD. Distinguishing whether dopamine regulates liking, wanting, and/or learning about rewards. Behav Neurosci. 2005;119:5–15.
42. Healy D. Neuroleptics and psychic indifference: a review. J R Soc Med. 1989;82:615–9.
43. Hollister LE, Eikenberry DT, Raffel S. Chlorpromazine in nonpsychotic patients with pulmonary tuberculosis. Am Rev Respir Dis. 1960;81:562–6.
44. Belmaker RH, Wald D. Haloperidol in normals. Br J Psychiatry. 1977;131:222–3.
45. Blum K, Liu Y, Shriner R, Gold MS. Reward circuitry dopaminergic activation regulates food and drug craving behavior. Curr Pharm Des. 2011;17:1158–67.
46. Tomasi D, Volkow ND. Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. Crit Rev Biochem Mol Biol. 2013;48:1–19.
47. Bijerot N. Addiction to pleasure: a biological and social-psychological theory of addiction. In: Lettieri DJ, Sayersand M, Pearson HW, editors. Theories on drug abuse: selected contemporary perspectives. Rockville: National Institute on Drug Abuse; 1980. p. 246–55.
48. van Rossum J, van der Schoot J, Hurkmans JA. Mechanism of action of cocaine and amphetamine in the brain. Experientia. 1962;18:229–31.
49. Axelrod J. Amphetamine: metabolism, physiological disposition, and its effects on catecholamine storage. In: Costa E, Garattini S, editors. Amphetamines and related compounds. New York: Raven; 1970. p. 207–16.
50. Carlsson A. Amphetamine and brain catecholamines. In: Costa E, Garattini S, editors. Amphetamines and related compounds. New York: Raven; 1970. p. 289–300.
51. Grace AA. The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. Addiction. 2000;95 Suppl 2:S119–28.
52. Volkow ND, Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. Am J Psychiatry. 2003;160:1909–18.
53. Jonsson LE, Anggard E, Gunne LM. Blockade of intravenous amphetamine euphoria in man. Clin Pharmacol Ther. 1971;12:889–96.
54. Gunne LM, Anggard E, Jonsson LE. Clinical trials with amphetamine-blocking drugs. Psychiatr Neurol Neurochir. 1972;75:225–6.
55. De Luca MA, Solinas M, Bimpisidis Z, Goldberg SR, Di Chiara G. Cannabinoid facilitation of behavioral and biochemical hedonic taste responses. Neuropharmacology. 2012;63:161–8.

56. Bressan RA, Crippa JA. The role of dopamine in reward and pleasure behaviour – review of data from preclinical research. Acta Psychiatr Scand Suppl. 2005;427:14–21.
57. Blum K, Noble EP, Sheridan PJ, et al. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA. 1990;263:2055–60.
58. Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat. 2004;23:540–5.
59. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch Gen Psychiatry. 1991;48:648–54.
60. Hill SY, Hoffman EK, Zezza N, et al. Dopaminergic mutations: within-family association and linkage in multiplex alcohol dependence families. Am J Med Genet B Neuropsychiatr Genet. 2008;147B:517–26.
61. Dahlgren A, Wargelius HL, Berglund KJ, et al. Do alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? a pilot study. Alcohol Alcohol. 2011;46:509–13.
62. Kraschewski A, Reese J, Anghelescu I, et al. Association of the dopamine D2 receptor gene with alcohol dependence: haplotypes and subgroups of alcoholics as key factors for understanding receptor function. Pharmacogenet Genomics. 2009;19:513–27.
63. Teh LK, Izuddin AF, Fazleen HMH, Zakaria ZA, Salleh MZ. Tridimensional personalities and polymorphism of dopamine D2 receptor among heroin addicts. Biol Res Nurs. 2012;14:188–96.
64. Van Tol HH. Structural and functional characteristics of the dopamine D4 receptor. Adv Pharmacol. 1998;42:486–90.
65. Lai JH, Zhu YS, Huo ZH, et al. Association study of polymorphisms in the promoter region of DRD4 with schizophrenia, depression, and heroin addiction. Brain Res. 2010;1359:227–32.
66. Biederman J, Petty CR, Ten Haagen KS, et al. Effect of candidate gene polymorphisms on the course of attention deficit hyperactivity disorder. Psychiatry Res. 2009;170:199–203.
67. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. Am J Psychiatry. 2001;158:1052–7.
68. Grzywacz A, Kucharska-Mazur J, Samochowiec J. Association studies of dopamine D4 receptor gene exon 3 in patients with alcohol dependence. Psychiatr Pol. 2008;42:453–61.
69. Kotler M, Cohen H, Segman R, et al. Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. Mol Psychiatry. 1997;2:251–4.
70. Byerley W, Hoff M, Holik J, Caron MG, Giros B. VNTR polymorphism for the human dopamine transporter gene (DAT1). Hum Mol Genet. 1993;2:335.
71. Galeeva AR, Gareeva AE, Iur'ev EB, Khusnutdinova EK. VNTR polymorphisms of the serotonin transporter and dopamine transporter genes in male opiate addicts. Mol Biol (Mosk). 2002;36:593–8.
72. Reese J, Kraschewski A, Anghelescu I, et al. Haplotypes of dopamine and serotonin transporter genes are associated with antisocial personality disorder in alcoholics. Psychiatr Genet. 2010;20:140–52.
73. Cook Jr EH, Stein MA, Krasowski MD, et al. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet. 1995;56:993–8.
74. Lee SS, Lahey BB, Waldman I, et al. Association of dopamine transporter genotype with disruptive behavior disorders in an eight-year longitudinal study of children and adolescents. Am J Med Genet B Neuropsychiatr Genet. 2007;144B:310–7.
75. Schellekens AF, Franke B, Ellenbroek B, et al. Reduced dopamine receptor sensitivity as an intermediate phenotype in alcohol dependence and the role of the COMT Val158Met and DRD2 Taq1A genotypes. Arch Gen Psychiatry. 2012;69:339–48.
76. Nedic G, Nikolac M, Sviglin KN, Muck-Seler D, Borovecki F, Pivac N. Association study of a functional catechol-O-methyltransferase (COMT) Val108/158Met polymorphism and suicide attempts in patients with alcohol dependence. Int J Neuropsychopharmacol. 2011;14:377–88.

77. Demetrovics Z, Varga G, Szekely A, et al. Association between novelty seeking of opiate-dependent patients and the catechol-O-methyltransferase Val(158)Met polymorphism. Compr Psychiatry. 2010;51:510–5.
78. Baransel Isir AB, Oguzkan S, Nacak M, Gorucu S, Dulger HE, Arslan A. The catechol-O-methyl transferase Val158Met polymorphism and susceptibility to cannabis dependence. Am J Forensic Med Pathol. 2008;29:320–2.
79. Merenakk L, Maestu J, Nordquist N, et al. Effects of the serotonin transporter (5-HTTLPR) and alpha2A-adrenoceptor (C-1291G) genotypes on substance use in children and adolescents: a longitudinal study. Psychopharmacology (Berl). 2011;215:13–22.
80. van der Zwaluw CS, Engels RC, Vermulst AA, et al. A serotonin transporter polymorphism (5-HTTLPR) predicts the development of adolescent alcohol use. Drug Alcohol Depend. 2010;112:134–9.
81. Kosek E, Jensen KB, Lonsdorf TB, Schalling M, Ingvar M. Genetic variation in the serotonin transporter gene (5-HTTLPR, rs25531) influences the analgesic response to the short acting opioid remifentanil in humans. Mol Pain. 2009;5:37.
82. Ray R, Ruparel K, Newberg A, et al. Human Mu Opioid Receptor (OPRM1 A118G) polymorphism is associated with brain mu-opioid receptor binding potential in smokers. Proc Natl Acad Sci U S A. 2011;108:9268–73.
83. Szeto CY, Tang NL, Lee DT, Stadlin A. Association between mu opioid receptor gene polymorphisms and Chinese heroin addicts. Neuroreport. 2001;12:1103–6.
84. Bart G, Kreek MJ, Ott J, et al. Increased attributable risk related to a functional mu-opioid receptor gene polymorphism in association with alcohol dependence in central Sweden. Neuropsychopharmacology. 2005;30:417–22.
85. Hall FS, Sora I, Uhl GR. Ethanol consumption and reward are decreased in mu-opiate receptor knockout mice. Psychopharmacology (Berl). 2001;154:43–9.
86. Namkoong K, Cheon KA, Kim JW, Jun JY, Lee JY. Association study of dopamine D2, D4 receptor gene, GABAA receptor beta subunit gene, serotonin transporter gene polymorphism with children of alcoholics in Korea: a preliminary study. Alcohol. 2008;42:77–81.
87. Mhatre M, Ticku MK. Chronic ethanol treatment upregulates the GABA receptor beta subunit expression. Brain Res Mol Brain Res. 1994;23:246–52.
88. Young RM, Lawford BR, Feeney GF, Ritchie T, Noble EP. Alcohol-related expectancies are associated with the D2 dopamine receptor and GABAA receptor beta 3 subunit genes. Psychiatry Res. 2004;127:171–83.
89. Feusner J, Ritchie T, Lawford B, Young RM, Kann B, Noble EP. GABA(A) receptor beta 3 subunit gene and psychiatric morbidity in a post-traumatic stress disorder population. Psychiatry Res. 2001;104:109–17.
90. Noble EP. The D2 dopamine receptor gene: a review of association studies in alcoholism and phenotypes. Alcohol. 1998;16:33–45.
91. Nikulina V, Widom CS, Brzustowicz LM. Child abuse and neglect, MAOA, and mental health outcomes: a prospective examination. Biol Psychiatry. 2012;71:350–7.
92. Alia-Klein N, Parvaz MA, Woicik PA, et al. Gene x disease interaction on orbitofrontal gray matter in cocaine addiction. Arch Gen Psychiatry. 2011;68:283–94.
93. Nilsson KW, Comasco E, Aslund C, Nordquist N, Leppert J, Oreland L. MAOA genotype, family relations and sexual abuse in relation to adolescent alcohol consumption. Addict Biol. 2011;16:347–55.
94. Treister R, Pud D, Ebstein RP, et al. Associations between polymorphisms in dopamine neurotransmitter pathway genes and pain response in healthy humans. Pain. 2009;147:187–93.
95. Tikkanen R, Auvinen-Lintunen L, Ducci F, et al. Psychopathy, PCL-R, and MAOA genotype as predictors of violent reconvictions. Psychiatry Res. 2011;185:382–6.
96. Gokturk C, Schultze S, Nilsson KW, von Knorring L, Oreland L, Hallman J. Serotonin transporter (5-HTTLPR) and monoamine oxidase (MAOA) promoter polymorphisms in women with severe alcoholism. Arch Womens Ment Health. 2008;11:347–55.
97. Contini V, Marques FZ, Garcia CE, Hutz MH, Bau CH. MAOA-uVNTR polymorphism in a Brazilian sample: further support for the association with impulsive behaviors and alcohol dependence. Am J Med Genet B Neuropsychiatr Genet. 2006;141B:305–8.

98. Lee SY, Chen SL, Chen SH, et al. Interaction of the DRD3 and BDNF gene variants in subtyped bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39:382–7.
99. Li T, Hou Y, Cao W, Yan CX, Chen T, Li SB. Role of dopamine D3 receptors in basal nociception regulation and in morphine-induced tolerance and withdrawal. Brain Res. 2012;1433:80–4.
100. Vengeliene V, Leonardi-Essmann F, Perreau-Lenz S, et al. The dopamine D3 receptor plays an essential role in alcohol-seeking and relapse. Faseb J. 2006;20:2223–33.
101. Mulert C, Juckel G, Giegling I, et al. A Ser9Gly polymorphism in the dopamine D3 receptor gene (DRD3) and event-related P300 potentials. Neuropsychopharmacology. 2006;31:1335–44.
102. Limosin F, Romo L, Batel P, Ades J, Boni C, Gorwood P. Association between dopamine receptor D3 gene BalI polymorphism and cognitive impulsiveness in alcohol-dependent men. Eur Psychiatry. 2005;20:304–6.
103. Duaux E, Gorwood P, Griffon N, et al. Homozygosity at the dopamine D3 receptor gene is associated with opiate dependence. Mol Psychiatry. 1998;3:333–6.
104. Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. Brain Res Mol Brain Res. 2004;124:134–42.
105. Blum K, Oscar-Berman M, Barh D, Giordano J, Gold M. Dopamine genetics and function in food and substance abuse. J Genet Syndr Gene Ther. 2013;10(4):121.
106. Bessa JM, Morais M, Marques F, et al. Stress-induced anhedonia is associated with hypertrophy of medium spiny neurons of the nucleus accumbens. Transl Psychiatry. 2013;3:e266.
107. Golden SA, Christoffel DJ, Heshmati M, et al. Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression. Nat Med. 2013;19:337–44.
108. Dillon DG, Bogdan R, Fagerness J, Holmes AJ, Perlis RH, Pizzagalli DA. Variation in TREK1 gene linked to depression-resistant phenotype is associated with potentiated neural responses to rewards in humans. Hum Brain Mapp. 2010;31:210–21.
109. Law AJ, Pei Q, Walker M, et al. Early parental deprivation in the marmoset monkey produces long-term changes in hippocampal expression of genes involved in synaptic plasticity and implicated in mood disorder. Neuropsychopharmacology. 2009;34:1381–94.
110. Todtenkopf MS, Parsegian A, Naydenov A, Neve RL, Konradi C, Carlezon Jr WA. Brain reward regulated by AMPA receptor subunits in nucleus accumbens shell. J Neurosci. 2006;26:11665–9.
111. Felger JC, Mun J, Kimmel HL, et al. Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates. Neuropsychopharmacology. 2013;38(11):2179–87.
112. Gold MS. Dopamine depletion hypothesis for acute cocaine abstinence clinical observations, prolactin elevations, and persistent anhedonia/dysphoria. Neuro Endocrinol Lett. 1993;15:271.
113. Carelli RM, West EA. When a good taste turns bad: Neural mechanisms underlying the emergence of negative affect and associated natural reward devaluation by cocaine. Neuropharmacology. 2014;76:360–369. doi: 10.1016/j.neuropharm.2013.04.025.
114. Tye KM, Mirzabekov JJ, Warden MR, et al. Dopamine neurons modulate neural encoding and expression of depression-related behaviour. Nature. 2013;493:537–41.
115. Sharma S, Fernandes MF, Fulton S. Adaptations in brain reward circuitry underlie palatable food cravings and anxiety induced by high-fat diet withdrawal. Int J Obes (Lond) 2013;37(9):1183–91. doi: 10.1038/ijo.2012.197.
116. Lim BK, Huang KW, Grueter BA, Rothwell PE, Malenka RC. Anhedonia requires MC4R-mediated synaptic adaptations in nucleus accumbens. Nature. 2012;487:183–9.
117. Venzala E, Garcia-Garcia AL, Elizalde N, Tordera RM. Social vs. environmental stress models of depression from a behavioural and neurochemical approach. Eur Neuropsychopharmacol. 2013;23:697–708.
118. Nocjar C, Zhang J, Feng P, Panksepp J. The social defeat animal model of depression shows diminished levels of orexin in mesocortical regions of the dopamine system, and of dynorphin and orexin in the hypothalamus. Neuroscience. 2012;218:138–53.

119. Zoratto F, Fiore M, Ali SF, Laviola G, Macri S. Neonatal tryptophan depletion and corticosterone supplementation modify emotional responses in adult male mice. Psychoneuroendocrinology. 2013;38:24–39.
120. Chen YW, Rada PV, Butzler BP, Leibowitz SF, Hoebel BG. Corticotropin-releasing factor in the nucleus accumbens shell induces swim depression, anxiety, and anhedonia along with changes in local dopamine/acetylcholine balance. Neuroscience. 2012;206:155–66.
121. Vrieze E, Ceccarini J, Pizzagalli DA, et al. Measuring extrastriatal dopamine release during a reward learning task. Hum Brain Mapp. 2013;34:575–86.
122. Lin Y, Sarfraz Y, Jensen A, Dunn AJ, Stone EA. Participation of brainstem monoaminergic nuclei in behavioral depression. Pharmacol Biochem Behav. 2011;100:330–9.
123. Gold MS, Avena NM. Animal models lead the way to further understanding food addiction as well as providing evidence that drugs used successfully in addictions can be successful in treating overeating. Biol Psychiatry. 2013;74(7):11. doi: 10.1016/j.biopsych.2013.04.022.

Chapter 10
The Neuroendocrinology of Anhedonia

George T. Taylor, Omar Cabrera, and Jessica Hoffman

Abstract One of the more fascinating developments in neuroscience is the recognition of endocrine influences on brain regions unrelated to reproductive and basic homeostatic functions. It is now clear that hormones impact both normal function and dysfunction, including the experience of pleasure and the anhedonia accompanying a number of psychiatric disorders, most notably depression. Brain regions contributing to these functions are rich in receptors for the peptides and steroids of the hypothalamic – pituitary – gonadal (HPG) and hypothalamic – pituitary – adrenal (HPA) axes. Indeed, the brain has evolved new functions for ancient hormones. Examples include the brain adaptive uses of steroid precursors and metabolites for non-reproductive functions and the brain co-opting or "hijacking" peptides of the two axes to serve as neuromodulators and neurotransmitters. The result is that HPA and HPG hormones and their interactions have profound influences on opioids and monoamines, especially dopamine and serotonin. These are the same neurotransmitter pathways underlying activation of the brain reward pathway stretching from midbrain to the prefrontal cortex.

Our ultimate goal is to fulfill the promise of the title, an evaluation of neuroendocrine – anhedonia relations. This requires, first, an overview of the endocrine system, and their steroids and peptides. There, we also provide a brief review of the interaction of the HPA and HPG axes in depression. Before embarking on an evaluation of hormones and anhedonia, we will examine normal neuroendocrine influences on pleasure from natural experiences such as food and sex but also from psychoactive drugs. Logic suggests examining data on pleasure before addressing loss of pleasure. The emphasis throughout will be on animal models with a liberal sprinkling of human findings, mostly psychiatric patients.

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This journey will take us through endocrine basics (Sect. 10.1), and the influence of hormones on brain systems underlying the experience of pleasure (Sect. 10.2). In Sect. 10.3, the modest literature on the neuroendocrinology of anhedonia in depression will be reviewed. Finally, future research and directions (Sect. 10.4) will provide ideas on filling in the gaps in our understanding of endocrine – anhedonia relations.

Keywords Endocrine system • Stress • HPA axis • HPG axis • Corticosteroid • Testosterone • Estrogen • Dopamine • Mesocorticolimbic pathway • Brain reward system • Chronic mild stress

Abbreviations

5HT	Serotonin
ACTH	Adrenocorticotropin hormone
ALLO	Allopregnanolone
AVP	Arginine vasopressin
BNST	Bed nucleus of the stria terminalis
BRS	Brain reward system
CMS	Chronic mild stress
CORT	Corticosteroid
CRH	Corticotropin-releasing hormone
CSF	Cerebrospinal fluid
DA	Dopamine
DHEA	Dehydroepiandrosterone
DOPAC	3, 4-Dihydroxyphenlacetic acid
E2	Estradiol
EPI	Epinephrine
FST	Forced swim test
GABA	Gamma-Aminobutyric acid
GnRH	Gonadotropin releasing hormone
GR	Glucocorticoid receptor
HPA	Hypothalamic-pituitary-adrenal
HPG	Hypothalamic-pituitary-gonadal
HVA	Homovanillic acid
ICSS	Intracranial self-stimulation
LH	Luteinizing hormone
MDD	Major Depressive Disorder
MFB	Medial forebrain bundle
MR	Mineralocorticoid receptor
NAcc	Nucleus accumbens
NE	Norepinephrine
OVX	Ovariectomy

PFC	Prefrontal cortex
POMC	Proopiomelanocortin
PROG	Progesterone
PVN	Paraventricular nucleus of the hypothalamus
SAM	Sympathetic adrenal medullary system
SSRI	Selective serotonin reuptake inhibitors
TH	Tyrosine hydroxylase
TS	Testosterone
VTA	Ventral tegmental area

10.1 Endocrine Basics

Hormones have profound effects on structures and functions of the body, including brain and behavior. The metaphor of a river, the Mississippi or Rhine, for the endocrine system is apt because it is the body's way to send hormones produced locally in glands to nearby and far away destinations. The result is integrating and coordinating disparate functions in multiple tissues.

Endocrine products begin their influences during early fetal life and continue to exert influences through childhood, adolescence, and adulthood. Yet, the importance of the endocrine system in pathological behaviors is often underappreciated, if not ignored altogether, by journal and book editors. Happily, this editor and book are exceptions.

Because endocrinology is not well known by many researchers of psychiatric conditions, we will provide an introduction to a few of the most important endocrine principles. This overview will use stress as related to depression as the exemplar condition.

10.1.1 Endocrinology of Stress

As the reader of this volume will have recognized by now, anhedonia is part of the symptomology of a number of psychopathologies. Nonetheless, anhedonia is a hallmark symptom of major depressive disorder (MDD). And, there is a rich literature on depression and stress-related endocrinology.

Early life adversity has shown a clear link to the development of depressive-like symptoms in laboratory animals [1] and to MDD in humans [2]. Moreover, exposure to chronic stress at any ontogenetic stage is one of the few generally accepted antecedents of depression in susceptible individuals [3]. Susceptibility is derived presumably from genotype and its epigenetic activation from the environment and individual experiences [4, 5]. The neuroendocrine mechanisms for stress responses are found in two complementary physiological systems. When activated by stressful conditions, the hypothalamus – pituitary – adrenal (HPA) axis and sympathetic adrenal medullary (SAM) system release a sequence of hormones [6].

10.1.1.1 HPA Axis

There are three primary HPA hormones, corticosteroid (CORT), adrenocorticotropin hormone (ACTH), and corticotropin-releasing hormone (CRH). CORT and ACTH can be detected and easily measured in the peripheral bloodstream whereas CRH is mainly in the brain, making its measurement much more difficult. Still, the workings of the HPA axis are well known [7].

Most familiar to non-endocrinologists is CORT because of its widespread use as a medication. Also known as glucocorticoid, glucocorticosteroid, corticosterone (in rodents) or cortisol (in humans), CORT carries a heavy load in medicine from the topical treatment of skin rashes with cortisone to a variety of more serious conditions. The analogs of cortisone, prednisone for instance, are widely prescribed for emphysema and asthma [8].

CORT is the endpoint hormone of the HPA axis. The term axis describes a cascade of events with activation of endocrine products. Under the influence of the hippocampus and other upstream brain regions, CRH is one of several "releasing hormones," so named because they induce the pituitary to release its hormones. Synthesized in CRH neurons originating in the paraventricular nucleus (PVN) of the hypothalamus, CRH is deposited from the median eminence into the hypothalamus – pituitary portal system, a small, one-way blood canal leading into the anterior pituitary. There, CRH binds receptors located on corticotropes that release ACTH into general blood circulation. An interesting factoid is that ACTH is "cleaved" from a larger protein proopiomelanocortin (POMC). Cleaving a different section of POMC yields endorphin and the other endogenous opioids that serve as neurotransmitters and neuromodulators. This is further evidence of the close relation between endocrine and central nervous systems.

Once in the bloodstream, ACTH is carried to the distant adrenal glands embedded in fat above the kidneys. ACTH binds adrenocortical receptors located in the outer, cortical layer of the adrenals. These bindings induce CORT to be released into the bloodstream to increase energy available to cells and other metabolic functions in the periphery.

As the bloodstream circulates throughout the body, CORT makes its passage to the pituitary, the hypothalamus and other brain regions. At all points, CORT binds receptors with one result being decrease in the release of ACTH and CRH. This cascade describes the negative feedback processes of an endocrine axis.

But CORT is not done. CORT binds its two receptors, mineralocorticoid (MR) and glucocorticoid (GR), in the brain, particularly in the hippocampus. Presence of MR and GR provide the hippocampus with a mechanism to regulate the HPA axis. Experiments using lesions or electrical stimulation reveal the hippocampus inhibits HPA activity [6]. Interestingly, CORT has a higher affinity for the MR and binds the GR only after the MR are occupied [9]. Thus, chronically high levels of CORT appear to be required, along with CRH activation, to modify hippocampal function [10].

The far reach of HPA hormones includes CRH. CRH neurons are found throughout the limbic system, in the interneurons of the hippocampus and in the locus coeruleus of the midbrain from which norepinephrine cells arise. The

neuropeptide is central to the experience of stress and a major player in the pathology induced by chronic HPA activation [11].

10.1.1.2 The Sympathetic Adrenal Medullary (SAM) System

The two SAM agents are epinephrine (EPI) and norepinephrine (NE). EPI is well known outside of neuroendocrinology by its alternate name, adrenaline. NE in the brain is a neurotransmitter closely related to its monoamine cousins, dopamine and serotonin.

EPI is synthesized in the same adrenal glands that synthesize CORT, but in the middle segment known as the adrenal medulla. Upon confrontation with a stressful stimulus, peripheral EPI is released into general circulation and NE neurons alert the subcortex and cortex. Together, the SAM system activates the sympathetic segment of the autonomic nervous system.

The most notable feature of the SAM system is its speed. While the HPA axis requires 15–30 min to be fully activated, SAM activation is achieved within seconds [12]. Although often ignored in reviews of stress, SAM is responsible for the immediate physiological reactions to stressful stimuli including increased heart rate, sweating, and pupillary dilation. These are the hallmark features we describe when discussing our stress response to a near accident [13, 14].

Nevertheless, HPA hormones are the focus of most studies of stress, and of its relation to depression. Indeed, elevated CORT levels remain the gold standard for confirming that an individual is exhibiting a stress response [15].

10.1.2 Reproductive Steroids

Along with corticosteroid, there is another set of familiar hormones, the sex steroids. Estrogens, androgens and progestins are reproductive steroids, although they serve many functions besides reproduction [16]. Although they are often grouped according to gender, all three sex steroids are found in both males and females, albeit in different amounts. The plurals for the sex steroids suggest there are more than one estrogen, androgen and progestin, and there are. Nonetheless, the most biologically active are the familiar estradiol (E2), testosterone (TS) and progesterone (PROG). These are the gonadal hormones that represent the end product of the *other* major endocrine axis, the hypothalamus – pituitary – gonadal (HPG) axis.

Workings of the HPG axis bear close similarity to the HPA axis. The HPG has a hypothalamic hormone (gonadotropin releasing hormone, GnRH), a pituitary hormone (luteinizing hormone, LH), and a distant hormone synthesizing structure (ovaries or testes). The sequential release and negative feedback are also similar to the HPA axis. Indeed, the similarity with TS to CORT in males is notable. That there are two ovarian steroids, along with separate cycles for each, makes the female HPG system more complicated.

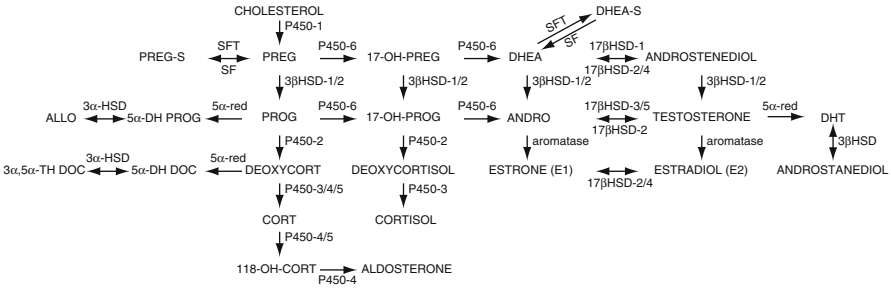

Fig. 10.1 Metabolic cascade for steroids in the brain. Steroid acronyms are: PREG = pregnanolone, PREG-S = pregnanolone sulfate, PROG = progesterone, 5α DH PROG = 5α DH progesterone, ALLO = allopregnanolone (also known as 3α,5α tetrahydroprogesterone or 3α,5α TH PROG), DEOXYCORT = 11-deoxycorticosterone, 5α TH DOC = 5α dihydroxydeoxycorticosterone, 3α,5α TH DOC = allotetrahydrodeoxycorticosterone, CORT = corticosterone, and 18-OH-CORT = 18-OH-corticosterone. Further steroid acronyms are: 17-OH-PREG = 17-OH-pregnanolone, DHEA-S = dehydroxyepiandrosterone sulfate, DHEA = dehydroxyepiandrosterone, 17-OH-PROG = 17-OH-progesterone, and ANDRO = androstenedione. Enzyme acronyms are: P450-1 through 6 = six different forms of P450, SFT = sulfatransferase, SF = sulfatase, 3β HSD 1/2 = 3β hydroxysteroid dehydrogenase form 1 or 2, 5α-red = 5α-reductase, 3α HSD = 3α hydroxysteroid dehydrogenase, and 17β HSD through 6 = different forms of 17β hydroxysteroid dehydrogenase

The term "steroids" is heard often in everyday discussions, although the reference is used to describe different substances, e.g., synthetic drug treatments (corticosteroids) or illicit use by athletes of performance enhancing drugs (androgens). Steroids are a large group of related biochemical compounds. Figure 10.1 depicts the metabolic cascade for the multiple branches yielding the many familiar, and unfamiliar, steroids.

First feature to note in the figure is cholesterol as the common origin of the steroids. The lipid backbone of the steroids gives them the capacity to cross with ease the blood-brain barrier and enter the brain. Peptides have a more difficult path into the brain from the periphery, if they get there at all. Second feature to note is that E2 is a metabolite of testosterone. This fact has led to countless experiments and journal articles, particularly after the realization that TS may act as an androgen or, after conversion to E2, as an estrogen. Third, not all steroids in the figure are hormones. Among other requirements to earn the label, hormones must have defined receptors. At this time, two estrogen receptors, ER-α and ER-β, and a single androgen receptor, AR have been identified. There are two isoforms for PROG, PR-A and PR-B [17].

Finally, even though steroids in the cascade may not be elevated to hormonal status, a number of the products in the figure have gained acceptance as having important influences on brain function and behavior. Examples include dehydroepiandrosterone (DHEA) and allopregnanolone (ALLO). DHEA is a precursor of TS that is of such importance to neural functions that the brain synthesizes its own DHEA, earning its designation as a "neurosteroid" [18]. Another important

neurosteroid is ALLO, a metabolite of progesterone [19], that appears to modify CORT and CRH releases to stress [20].

10.1.3 HPA, HPG & Depression

There is a rich literature revealing both endocrine axes as prominent factors in mood disorders, including major depressive disorder (MDD). Recognition of the involvement of HPG hormones comes, first, from epidemiological findings of a dramatic sex difference in MDD incidence. Compared to men, women have 2–3 times the likelihood of being diagnosed with clinical depression sometime during their lifetimes [21]. Further epidemiological evidence for the involvement of the hypothalamic – pituitary – ovarian axis is that depressive episodes in women closely follow major HPG lifetime events. Puberty, the ebb and flow of hormones during the menstrual cycle, and periparturition and menopausal stages are all related to MDD.

Of surprise to many people, depression can develop in children. The gender ratio in younger children is even. The female bias ratio begins in the peripubertal stage. Incidence of depression increases progressively and the female bias ratio increases with the surge of sex hormones with oncoming puberty and incidences continue to rise into young adulthood [22]. The rise and fall of circulating sex hormones during the menstrual cycle track depression symptomology. Women of reproductive age report fewer symptoms during the follicular stage than other phases of their cycles [23]. Finally, depressive episodes are notorious during the post-partum period, and menopause can signal relief for previously depressed women [24, 25].

MDD patients overwhelmingly report chronic stress as antecedent to a depressive episode. Clinical and pre-clinical data support their observations [26]. In an animal model of depression, chronic stress in the form of daily restraint reduces spontaneous locomotor activity and induces weight loss [27], both markers of depression in humans. Cumulative stress exposure in life is a risk factor for the development of a number of psychiatric illnesses, including clinical depression and substance use. It is of interest that both of these disorders often are comorbid and are characterized by anhedonia [28].

Early childhood experiences of parental abuse or neglect seem to be a particularly sensitive period, confirmed in animal models. Repeated separation of neonatal rat pups from their mother result in persistent alterations in biology and behavior mimicking those in human depression [29]. The animals also experience elevated CORT during adulthood, another clue for the importance of the HPA axis in depression.

Basal levels of CORT often are elevated during depressive episodes [30], and return to normal baseline levels upon successful anti-depressive drug treatments [31, 32]. Results of a study in MDD patients and healthy controls indicated increased activity of the intracellular cortisol-deactivating enzymes 5α-reductase and 11β-HSD2 in the depressed individuals. These metabolic changes increase CORT bioavailability within tissues [33].

Other evidence supporting a link between the HPA and MDD is the behavioral similarities in symptomology of the endocrine disorder Cushing's disease and depressive diseases [34]. Elevated CORT is a distinguishing feature of Cushing's disease, and many patients have a history of depression. Also, exogenous corticosteroids administered as medicines may have the same effect on mood and the hippocampus [35].

CRH also plays a central role. High densities of CRH receptors have been observed in brain regions important in MDD, including the neocortex, the central nucleus of the amygdala, the bed nucleus of the stria terminalis, the hippocampus, the nucleus accumbens and the hypothalamus [36]. Chronic stress can elevate CRH receptor numbers in rats [37]. Moreover, the effects of CRH are amplified in the rodent pituitary by arginine vasopressin (AVP). Levels of AVP also increase after prolonged stress, magnifying further the functional activity of CRH [38]. These results confirm characterization of activation of the HPA axis by stress as "sluggish but long lasting" [6].

These effects have been observed also in humans. CRH and AVP actions in the hypothalamus of patients are sensitized and their adrenals are enlarged. Depressed patients often fail to reveal the normal negative feedback suppression of cortisol to administration of dexamethasone, a synthetic CORT [39, 40]. Failure to show suppression to a sudden increase in CORT points to HPA axis dysregulation in MDD. It is not clear if dysregulation is a cause or an effect. The former is suggested, however, by the observation that chronic elevation of HPA hormones is an antecedent to the development of MDD. Hyper-reactivity of the HPA axis was detected in people at high genetic risk for developing MDD prior to the onset of clinical symptoms [26].

Structural changes in the brain after exposure to stress have been confirmed in animal research. Chronic stress in rodents produces numerous morphological and physiological changes in a variety of limbic brain regions. Dendritic tree branches are reduced and neurotransmitter responses are less predictable with subsequent stress. Daily restraint modulates GR concentrations in the PFC, hypothalamus and, of particular note, in the hippocampus of rats [27, 41].

The hippocampus is a target for both CORT and CRH and is the single most studied brain region for stress – depression interactions [42]. The most dramatic neural consequence to chronic HPA hyperactivity is atrophy of the hippocampus. As much as 20 % of hippocampal volume is lost in long-term depressed people [43]. Volumetric loss is significantly correlated with total lifetime duration of depression. This suggests that repeated stress during recurrent depressive episodes may result in cumulative hippocampal injury as reflected in volume loss [44]. Moreover, atrophy increases with longer durations of depression and persists up to decades after depression has been resolved.

Neuronal loss is the most likely source for atrophy. The mechanism appears to be an indirect influence of CORT on the excitatory neurotransmitter glutamate. Glutamate is notorious for excitotoxicity when overly activated [45]. Chronically high CORT enhances amounts of glutamate released. The results are neuronal death and reduced neurogenesis in the vulnerable hippocampus [43]. There is evidence

that exogenous CORT administered as medicines may have the same effects on the hippocampus [35].

A final note is the participation of DHEA in HPA endocrinology. Released by the adrenal medulla, DHEA can serve to reduce the impact of elevated CORT in experimental animals [46, 47]. In the rat brain, DHEA has anti-glucocorticoid effects and is protective against the neurotoxic effects of CORT both *in vivo* and *in vitro* [48]. A prediction from those data is of reduced DHEA in patients and, indeed, there is evidence of low serum DHEA levels in both adolescents and adults diagnosed with MDD [49].

Here, we see the seeds of an intimate interaction between stress hormones and reproductive hormones because DHEA is a precursor of both testosterone and estrogen (Fig. 10.1).

10.1.4 HPA-HPG Interactions & Depression

The HPA axes of males and females are different and their responses to acute and chronic stress are different. The differences are clearer in laboratory animals than in humans [50]. In humans, physiological and neurological measures are more limited. For example, most endocrine measures are from collection of saliva. Only the unbound, "free" CORT can be detected in saliva, thus failing to consider the bound CORT that can be quickly converted to the unbound form [51].

Relying mostly on animal models, the data point to a sexual dimorphic HPG response to stress. The CORT findings reliably identify greater HPA activity in females. Female rats have higher resting levels of CORT, a greater CORT sensitivity to acute stress [52], and a more persistent CORT response to stressful conditions [53]. Although recovery may be delayed in males exposed to physical stressors, such as restraint, return of CORT to baseline following social stress is longer in female rats [54]. Similarly, women have a greater and longer lasting CORT response when submitted to social rejection challenges, which may contribute to their greater vulnerability to depression [55].

However, there are mitigating factors for findings in both rats and humans. One is stage of the estrous cycles of rodents or menstrual cycles of women. Females have higher CORT during the late follicular phase when circulating estradiol is high, decreasing in the other phases when progesterone is high or both hormones are low [56, 57]. Excising the ovaries (ovariectomy or OVX) reduces plasma levels of CORT and restoration with estrogen therapy restores the levels to pre-OVX levels [54]. Males show the opposite pattern as testosterone appears to suppresses the HPA axis. Castrated male rats tend to have a greater stress response compared to intact males or TS-treated castrates [58].

Pregnancy features dramatic increases in E2, PROG and CORT. In women, the hormonal increases reach a peak in the third trimester and, with birth, the levels fall quickly to markedly low levels, setting the stage for post-partum depression [59]. There are conflicting data on whether there are increased or decreased incidences of

depression during pregnancy. It is likely that a key factor is whether or not a woman had a history of MDD prior to pregnancy [60].

Effectiveness of modern anti-depressant drugs is well established. That there are sex differences in drug effectiveness is suggested by clinical and pre-clinical studies. Overall, anti-depressants seem to be more effective in young women than men [61]. Moreover, there is a sexually dimorphic response to the different classes of drugs. Depressed women respond better to selective serotonin receptor inhibitors (SSRI) than to the tricyclic anti-depressants while men responded equally well to both [62] or better to the tricyclics than women [63]. Yet, hypoestrogenic women, as with menopause and its accompanying rapid loss of circulating ovarian hormones, show less sensitivity to SSRIs [64].

Although various steroids and peptides are likely involved, estrogen is the one hormone most often believed to be responsible for the relation of the HPG axis to stress and to depression [65]. Findings cited earlier on cycling hormones point to high physiological levels of estrogen having the most favorable response to stress and HPA activation. Depressed women show various HPG deficits, for example lower circulating estrogen, than healthy women [66]. Women who underwent bilateral removal of ovaries (oophorectomy) before the onset of menopause had an increased risk of depressive symptoms [67]. Women with a history of MDD but in remission had lower serum E2 levels but higher PROG at mid-cycle of menstrual cycle than controls [68]. Finally, molecular biology studies have suggested the beneficial effects of estrogens on mood are most likely due to estrogen receptor activation. E2 binding of ERs attenuate the glucocorticoid responses to stress, suggesting that estrogens improve mood by suppressing CORT hyperactivity [69].

The general conclusion is that estrogen protects females from the adverse effects of stress. This points to a paradox. That women suffer MDD at higher rates than men stands in stark contrast to the notion of E2 as a protective agent. The answer to the paradox is that we do not know the answer.

A prominent hypothesis centers on the cyclical nature of ovarian steroids [64, 70]. The rise and fall of the hormones is thought to promote conditions for development of mood disorders in susceptible women. Depression itself may contribute to neuroendocrine dysregulation. Depression suppresses E2 levels that are then normalized with antidepressant treatments [24].

Other hormones surely have involvement in MDD. Depressed women have been reported to have higher baseline serum levels of both TS [71] and PROG [72] than healthy women. The suggestion is that the release of TS and PROG may have effects in opposite directions to those of E2.

More recently, the emphasis has switched to non-gonadal endocrine steroids and peptides influencing the two axes and the development of depression. A prime candidate is the progesterone metabolite ALLO, a neurosteroid that is an agonist of the amino acid neurotransmitter gamma aminobutyric acid (GABA) [73]. Cerebrospinal fluid (CSF) levels of ALLO are decreased in people diagnosed with major depression. This decrease is corrected in patients by SSRIs in doses that improve depressive symptoms [74]. DHEA interacts with the other major amino acid neurotransmitter, glutamate, and influences the response to stress. Ultimately, both

precursors and metabolites of steroid hormones affect the biological activity of dopamine. We will now see these are the neurotransmitters that will play prominently in hedonia and, likely, anhedonia.

10.2 The Neurobiology of Pleasure

10.2.1 Pleasure

Pleasure is recognized as a basic feature of humans and, likely, most other vertebrates. Seeking pleasurable experiences probably has been recognized as a fundamental force in humans since the very beginnings of Homo sapiens and long before someone characterized it as "wine, women and song." Loss of the capacity to experience pleasure is sure to have a significant impact on one's psychological wellbeing. Anhedonia accompanying depression and other psychiatric conditions is, indeed, a fundamental loss.

One logical approach to understanding the neuroendocrine underpinnings of anhedonia is to examine hedonia [75, 76]. The concept of pleasure has been a central topic of interest in psychology, and only slightly less so in philosophy and biology, the two precursors of modern psychology.

Evolutionary principles placed hedonism as a key factor in adaptation. Nature (natural selection) regularly ensured that pleasure was highly correlated with the most critical activities required of the animal. Reproduction would generate the most pleasure with food and avoiding pain not far behind. A familiar example is the energy contained in different foods. If it tastes good, it is almost surely to be highly caloric.

The status of hedonism in the form of reward and punishment was elevated to a basic principle in psychology by the early behaviorists such as E.L. Thorndike and B.F. Skinner. Skinner [77] expanded rewards to define it behaviorally as the now-familiar term, reinforcement. A positive reinforcement is anything that led to an animal repeating a response to gain the stimulus, for instance a treat for a dog for obeying a command. A negative reinforcement is anything the animal would respond to remove, a thorn in the dog's paw for instance. Note that both positive and negative reinforcers are ultimately based on pleasure. Punishment that led to a decrease in responding was not an important concept for Skinner and, even today, is seldom the focus of a research project in psychology.

Pleasure is a subjective experience. Yet, as with all other subjective states, there are brain regions and circuits responsible for the experience. Neuroscience research has pointed to dopamine pathways and the limbic system as likely candidates. Nonetheless, the underlying mechanisms have proven complex and fundamental questions remain unanswered [78].

Our working assumption is that pleasure and anhedonia are opposite side of the same coin [28]. This suggests it is worthwhile to take a cursory look at the workings

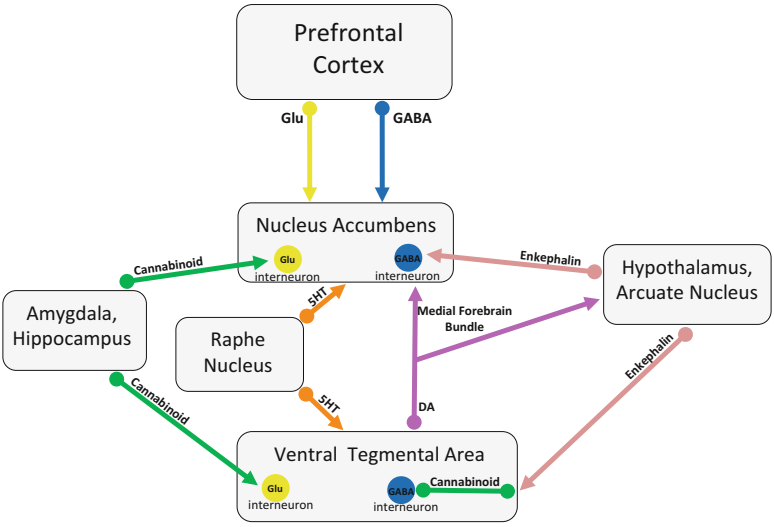

Fig. 10.2 A schematic of the dopamine mesocorticolimbic pathway. Included are the various brain regional and neurotransmitter inputs that are thought by many to serve as the brain's reward system

of the processing of rewards in the brain and, then, the relation of the reward circuitry to sex and stress hormones.

10.2.2 Brain Reward System (BRS)

10.2.2.1 Neuroanatomy

The primary neuroanatomical regions involved in rewards are found in the midbrain and forebrain. The ventral tegmental area (VTA) is located deep in the ancient brain and communicates with the subcortex through a bundle of neuronal axes, known as the medial forebrain bundle (MFB). Serotonin and norepinephrine neurons leave the MFB as it passes near the hypothalamus to make connections with hypothalamic nuclei. Dopamine (DA) neurons in the MFB continue and terminate in the nucleus accumbens (NAcc).

The NAcc is strategically located nearby other subcortical nuclei that subserve limbic activation. Reciprocal connections of the NAcc with the amygdala, hippocampus and, most notably, the prefrontal cortex (PFC) ensure a top-down influence on the NAcc and VTA. Collectively, this route has been dubbed the brain reward system or BRS. Figure 10.2 offers a schematic of the BRS.

The figure also highlights NAcc connections to other brain regions via an array of neurotransmitters [79, 80]. Most of the neurotransmitters thought to be involved

in psychopathology are found somewhere along the tract from midbrain VTA to the cortex. Found in the VTA along with DA are serotonin (5HT), acetylcholine, enkephalin, glutamate and GABA. The PFC receives dopaminergic input and sends projections toward the NAcc via glutamate and GABAergic neurons. The amygdala contributes cannabinoid transmitters to both the VTA and PFC [81]. Still, it is DA that holds the spotlight in the BRS.

10.2.2.2 Focus on Dopamine

The origins of DA neurons are cell bodies located in the substantia nigra and the ventral tegmental area (VTA). The former projects to the striatum of the basal ganglia, thus the term nigrostriatal dopamine pathway. The VTA is the origin of the second DA pathway known as the mesocorticolimbic dopamine system. The VTA originated system often is described in its two segments, mesolimbic or mesocortical. The mesolimbic system sends DA axons into the MFB that terminate in the NAcc. There, the mesocortical pathway makes connections with upstream subcortical structures and continuing onward into the PFC. That processing of rewards depends on an intact mesocorticolimbic DA pathway is well established [75, 82]. Examples are bountiful.

With microdialysis and related technology, neurotransmitter release can be quantified in real time. DA increased in the NAcc and in the medial PFC in rats upon being fed a highly palatable food [83]. DA levels were high in the NAcc prior to and during copulation, followed by increased levels of the DA metabolites, suggesting increased DA turnover [84]. Castrating male rats results in loss of copulatory ability over days that correlates with the loss of DA release to an estrous female. Restoration of copulation with exogenous TS revealed the reemergence of the DA response [85, 86].

There are high concentrations of DA neurons and their receptors in the caudate nucleus of the striatum and in the nearby NAcc, as well as in the central nucleus of the amygdala and several regions of the frontal cortex [87]. Neurophysiological evidence includes increasing firing rates of dopamine neurons in the MFB in the presence of food or a receptive sex partner. Learning plays an important role as there is similar increased neuronal activity in environments in which the animal had previously eaten or copulated [88]. Neuroimaging studies have suggested a similar pattern of activation in humans exposed to pleasurable stimuli [89, 90].

NAcc activation in animal models has been observed to aversive stimuli, which may be a consequence of the rewarding effects of their termination [91]. This "relief" bears notable similarity to Skinner's negative reinforcement [77].

Additional evidence for the role of the dopamine BRS is found in the drug abuse literature. Cocaine, methamphetamine and many other stimulant drugs target the catecholamines, NE and DA. Other commonly abused drugs, nicotine, marijuana and heroin, also indirectly activate DA neurons in the NAcc [81, 92].

It should be noted before moving on from this section that not everyone is convinced that DA is the pleasure neurotransmitter. The critics cite puzzling and

contradictory data. For example, single cell recordings of DA neurons in the VTA indicated DA activation to novel and unexpected rewards and less so to expected ones [93]. Also, depletion of DA in the NAcc failed to interfere with food consumption or effort to obtain food in rats [94]. Finally, because the thalamus receives projections from the NAcc, thalamic neural activity was monitored in rats receiving sucrose rewards. When sucrose access was delayed, thalamic firing rates increased progressively over the delay period. The peak was before the delivery of the reward and firing decreased dramatically during consumption of the sucrose. The same conclusion was suggested in a study of humans [95] using money and social approval as rewards.

The suggestion is that the increase in DA in NAcc and other parts of the BRS is to predict reward, and perhaps not the neurophysiological agent underlying pleasure. In this model, DA is responsible for attention and information processing of salient cues predicting reward that contribute to motivation to obtain the reward [96]. Its role is more questionable in mediating the experience of pleasure [97, 98].

This is not an insignificant semantic debate. Therapies for drug abuse are built on the notion that the mesocorticolimbic DA systems chiefly mediate the intense pleasure of addictive drugs and of anhedonia during drug withdrawal [99].

To better understand the distinction, it is helpful to contrast anticipatory behaviors and consummatory responses [95]. Sexual behavior in male rats can be used as an example. Anticipatory behaviors of the male include increased activity when motivated by cues, e.g., smells of a receptive female or even environmental stimuli from previous learning, indicating a reward awaits the male. Consummation with the acts of copulating and ejaculating is a separate component of the sexual encounter involving separate brain regions [100]. Other researchers have cast this into more familiar language, the difference between "wanting" and "liking" [82, 101].

The critical role played by DA is unquestioned in anticipatory behaviors. The role of DA in consummatory behaviors is less certain. One result is that the search for the ultimate source of pleasure has shifted to the endogenous opiates. Opioid receptors are highly expressed in brain areas of the BRS, including VTA, NAcc, amygdala and PFC. Animal studies demonstrate facilitation of DA release by endogenous opiates binding the opioid receptors. These data have led back to dopamine, and the hypothesis that the mediation of pleasure by endogenous opioids may be secondary to DA release [102].

The most likely opioid candidate (see Fig. 10.2) is enkephalin as it interacts with DA in the NAcc, thus modifying the upstream BRS activity in other limbic areas and into the cortex. The conclusion is that DA and enkephalin are interconnected in the motivation-pleasure cascade [92]. Moreover, these data demonstrate the complexities of brain reward circuitry, and that we do not know yet all the pieces that create the experience of pleasure [78].

Although it may not be the sole contributor, DA is clearly involved in seeking a pleasurable stimulus and, likely, in the experiencing of pleasure. Next, we will examine the interaction of HPA and HPG hormones with the BRS and dopamine.

10.2.3 Hormones and the Brain Reward System

10.2.3.1 HPA & the DA BRS

A principle common to both acute and chronic stress is that a hyperactive HPA axis can change DA release and metabolism and, thus, function of the mesocorticolimbic pathway.

Two areas of research have led to that conclusion. Most direct are the studies of changes in DA integrity along the BRS pathways to acute and chronic stress. Second, studies of humans and animal models suggest a close relation between stress hormones and DA-related drugs that have high abuse potential.

A well-functioning HPA axis complements well-functioning DA pathways. The normal synthesis, release and metabolism of DA in the medial forebrain bundle [103] and the NAcc [104] are dependent upon CORT. CORT regulates tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis [105]. Also, CORT is essential for maintaining normal DA metabolism and function of the PFC [106]. Changing CORT levels with stress or administration of psychostimulant drugs can modify those processes.

The bulk of the findings demonstrate that acute stress enhances dopamine BRS activity. Exposure to a brief stressor increases DA activity throughout the BRS. Acute stress activates DA neurons in the VTA [107]. DA activation in the NAcc, measured by increases in DA metabolites, was increased in mice exposed to a single 2 h restraint [108] or a social defeat [109]. Acute tail pressure stress to rats increased DA dialyses in the PFC [110].

The influence of chronic stress on the dopamine BRS is more complicated. Whereas DA activity is increased by acute stress, effects of longer periods of stress on DA are different in mesolimbic and mesocortical segments. With chronic stress the VTA – NAcc segment habituates while the NAcc – cortex segment continues to respond with higher DA activity [111]. One implication is that a sensitized PFC with chronic stress is involved in reward dysfunction and its normalization with anti-depressant drugs [112].

The literature on stress and drug use and abuse has a special connection to the dopamine BRS. An often-stated behavioral model for drug use and abuse recalls the positive – negative reinforcement distinction made by Skinner and others [113]. The model suggests drug use is driven by the good feelings induced by most psychoactive drugs. With continued use and the onset of "addiction," self-administration of the drug is driven by relief from the unpleasant withdrawal symptoms.

The BRS fits comfortably within the model because all drugs of abuse ultimately increase release of DA in the NAcc. HPA hormones do not have as natural of a fit in this model, yet stress has an important place in drug abuse. Studies in lab animals indicate a variety of stressors accelerate the acquisition of drug self-administration. Moreover, once established, self-administration of cocaine increases to acute or chronic stress. One possible result is the triggering of relapse of drug-seeking even after a period of abstinence [114].

Indications of CORT involvement are the findings that exogenous CORT increased cravings in cocaine dependent people and in an animal model of cravings [115]. Indeed, CORT antagonists decreased cravings for the drug [116].

Research also has focused on genetics and early experiences [117]. The rewarding effects in adulthood to amphetamine, for instance, are increased by neonatal stress in rats [118]. Behavioral reactivity to a stressor may be related to self-administration of abused drugs [119]. Individual rats or humans who are highly reactive to novelty are more prone to drug self-administration. High reactive rats reveal an elevated and prolonged CORT response to acute stress. They also have a lower density of dopamine D2 receptors in the NAcc, but a higher elevation of mesolimbic DA release than those found in low reactive rats [120, 121]. Notably, the high reactive animals also had greater concentrations of dopamine in the NAcc to self-administered cocaine [122].

These data suggested the hypothesis that HPA hormones can enhance the incentive value of cocaine. That is to say stress enhances the reward value of drugs of abuse [123]. However, there is no agreement on the mechanism(s) underlying the hypothesized increased "liking" of a drug with current or previous stressors.

10.2.3.2 HPG & the Dopamine BRS

Pre-clinical evidence indicates that HPG hormones also are involved in dopamine pathways [124]. Rodent studies have documented sex differences in the depletion, turnover, and extracellular accumulation of dopamine in the striatal pathway following methamphetamine administration [125]. Sex hormones influence the mesocorticolimbic pathways, as well. Concentrations of DA and its metabolite, dihydroxyphenylacetic acid (DOPAC), in the NAcc decreased after castration. Both DA and DOPAC were restored with exogenous TS or, interestingly, with exogenous E2 [126].

The few relevant studies of humans suggest a similar conclusion. Supraphysiological levels of androgens produced by self-administration of anabolic steroids by athletes elicit electrophysiological responses that are similar to the responses to amphetamine. A primary mechanism of action for Cocaine and amphetamine is increases in synaptic DA in the mesocorticolimbic pathway [127]. There is some question about the receptor responsible for these very high dosages of TS. Because the aromatase enzyme that metabolizes TS to E2 is highly concentrated in limbic structures, hippocampus and cortex [128], it may be the hedonic effects are actually from after TS is converted to E2 and the latter binds ERs [129].

Interactions between E2 and DA can be observed at all levels of the dopamine BRS pathways [130]. Reports of decreased DA and 5HT in the VTA of OVX rats indicate activity in both neurotransmitters can be restored by exogenous E2 [131].

Much of the focus in this research area has been on subcortical structures. Other brain regions along the mesolimbic DA segment also reveal sensitivity to estrogenic input. Acute or chronic exposure of OVX rats to E2 enhanced the release of DA in the NAcc to amphetamine or cocaine [129, 132]. Levels of 5-HT and DA in the

amygdala were significantly reduced by OVX in rats [133]. OVX rats administered E2 increased DA turnover in both striatum and NAcc. Notably, the increase coincided with peak circulating E2 concentrations [134].

The NAcc is closely linked to the striatum with reciprocal projections between the two structures. DA receptor density in the striatum increased significantly in juvenile rats at puberty. It is interesting that the male juveniles showed a much higher increase in DA receptors than their female counterparts [135]. In adulthood, no such sex differences are observed in DA receptor activity in the striatum, measured by density of DA reuptake sites, is significantly higher in gonadally intact female rats than in OVX, intact and castrated male rats. DA reuptake density sites also fluctuated during the female estrous cycle with a peak occurring in the morning of proestrus when estradiol is elevated [136].

The relation of E2 to the mesocortical segment of the dopamine BRS is more complicated. One example is that phases of the estrous cycle in which there are high levels of E2 can lead to DA and PFC dysregulation [137]. Another study reported that basal DA concentrations in the PFC varied during the estrous cycle, with DA being lowest in proestrus when endogenous E2 levels are highest [138]. On the other hand, administration of an ER-β agonist in OVX rats was reported to increase levels of DA turnover by 100 % in the PFC [139].

DA turnover was elevated in the medial PFC with E2 treatments. These data are notable in that the subjects were castrated male rats [140]. Moreover, the opposite effect, inhibition of DA turnover in the medial PFC, was observed in another group of castrates who were administered dihydrotestosterone (DHT), an androgen that cannot be aromatized into E2.

In summary, E2 has potent influences on DA [141]. Indeed, estrogen has been observed repeatedly to have a larger role in brain functions than the other HPG hormones and, perhaps, any other hormone. A potential reason is found in studies of molecular evolution. The estrogen receptor is reported to be the original member of the steroid receptor family. Moreover, it is probably not a coincidence that E2 is the final product to be synthesized in the metabolic pathway of steroids [142]. One result of its ancient status would be that the brain had a longer evolutionary time to co-opt E2 and its receptors for a diversity of influences on different tissues.

10.3 Hormones and Anhedonia

Clinical observation, patient comments and various psychological test batteries are used to assess anhedonia in MDD [143]. Animal models of anhedonia are based on reducing MDD symptomology into component parts and then designing a paradigm to induce and assess the depressive-like symptom [144]. Prominent among the animal models of depression is the forced swim test (FST) that is designed to mimic learned helplessness in MDD. The FST, however, does not reliably produce anhedonia [145].

A few animal models marginally related to depression have been proposed to assess anhedonia. Intracranial self-stimulation (ICSS) is based on the propensity of rats to bar press to deliver electrical stimulation to locations in the medial forebrain bundle or related areas. ICSS has been used to assess reward sensitivity with concomitant drug administration and then upon drug withdrawal. Notably, drug withdrawal has been proposed as a model of changes in the dopamine BRS that may underlie anhedonia. The logic is based on the high rates of co-morbidity between drug abuse and depression, suggesting a shared neurobiology. Both conditions can modify dopamine BRS circuitry underlying anhedonia [28].

A typical experiment in ICSS literature is to establish bar pressing for cocaine, followed by disabling the bar or changing the response requirements for self-administration and observing changes in the animal's behaviors. Findings include reductions in bar pressing for ICSS, increases in the current required to maintain ICSS or shorter time to the "break point" at which the animal stops bar pressing [146, 147]. All three are believed to be indicators of an anhedonia based on a lowered of sensitivity to rewards [118].

Exposure to social defeat in aggressive encounters is a type of chronic stress that can lead to reductions in subsequent social interactions [148]. This outcome is said to model the loss of interest in social interactions accompanying depression, an outcome that could be considered a form of anhedonia. However, the other markers of anhedonia seem less dependent on the complex of factors that can modify the experience of defeat and subsequent social interactions [149, 150]. Because avoidance of social contact could result from a fear induced catatonic-like state, social defeat may better simulate the social withdrawal common in schizophrenia [151].

A surgical paradigm also has been used to model anhedonia and other symptoms of depression. Olfactory bulbs are removed and the animal is tested in several behavioral paradigms. Results indicate bulbectomized rats show greater startle to a loud noise, elevated serum levels of CORT and reductions in sexual behaviors and a suppressed preference for sucrose [145]. On the other hand, anosmic animals are hyperactive in both familiar and unfamiliar locations, which is uncharacteristic of MDD patients.

A final paradigm, chronic mild stress (CMS), also uses the natural attraction to sucrose as its primary measure. Indeed, CMS is the dominant animal paradigm for the study of anhedonia [152, 153]. The CMS paradigm has the virtues of reliably inducing anhedonia in most laboratories and of face validity. Daily exposure to nuisance events mimics the stressful events of everyday human life. That the animals show a progressive loss of attraction to a formerly pleasurable stimulus over time is a form of anhedonia with which many of us older scientists can identify.

Unpredictable stressors are applied daily over weeks, each typically for 12–24 h duration, to an individually housed rodent. Mild stressor can be a manipulation of home cage, e.g., wet bedding or cage tilted 45°, or of the animal room environment, e.g., a strobe light or a low decibel noise. Quantifying anhedonia is accomplished by measuring once every 5 or 7 days quantities of sweet water in which regular tap water freely available. Some researchers use a relative measure, i.e., sweet vs. tap water percentages, and others use total amount of sweet water consumed. Regardless,

the typical findings are the original preference for the sweet solution decreases over several weeks of exposure to the mild stressors.

Clearly, the extensive CMS literature provides a fine segue to this third section. Here, we review the CMS findings related to the main topics presented in Sects. 10.1 and 10.2. First, we examine the CMS literature related to DA and the BRS, and then the CMS findings related to the HPA and HPG axes. Included in the latter are unpublished data from our laboratory on androgenic influences on anhedonia with a CMS paradigm.

10.3.1 CMS & Dopamine

Given the central role proposed for DA in the neurobiology of rewards, there is a surprisingly small literature measuring DA parameters in the CMS paradigm. One reason may be that the paradigms using severe stressors are not conducive to measurements of consummatory behaviors. Also, as presented in Sect. 10.2, acute stressors such as restraint induce stark increases in HPA activity and DA hyperactivity while chronic stress can suppress DA activity.

Nonetheless, much of the relevant DA research with the chronic mild stress procedure has been directed at brain regions either directly in the mesocorticolimbic pathway or regions closely associated with the pathway [152]. At its simplest, the working hypothesis is that induction of anhedonia with CMS predicts reduced DA activity in this brain reward system.

Although there are notable exceptions, the data support the prediction of reduced DA in the brains of CMS animals [154]. CMS was found to be associated with a reduction in DA and its metabolites or reduced DA turnover in the PFC [155]. There also is evidence of CMS interfering with dopaminergic activity in the NAcc [83], although others report no differences in the NAcc of CMS and no stress controls [152].

A couple of CMS experiments have included assessment of the midbrain and reported decreased DA receptor expression in the VTA [112]. Of particular interest is that the cleanest evidence of DA activity decreasing with CMS is in the hippocampus [152].

Finally, CMS appears to have long-term effects on DA neurotransmission. After CMS has been terminated, an additional acute stressor increased DA release in both PFC and NAcc [83]. The suggestion is of CMS sensitizing the dopamine BRS to a subsequent, more intense stressor.

In summary, a prediction from the hypothesis that the experience of pleasure and anhedonia are opposite sides of the same coin is that the loss of sucrose preference would be associated with DA dysfunction in BRS pathways. Modest empirical support for an hypodopaminergic state comes from examination of dopamine BRS structures. The evidence is clearer for the PFC and hippocampus than for the NAcc. This is consistent with the conclusion in Sect. 10.2 that the mesocortical segment is more sensitive to chronic stress than is the mesolimbic segment of the BRS.

Of course, there remains the data on hyper-activity in DA responses to the more severe stressors standing in opposition to the DA hypo-activation with CMS. One conclusion is validation that the CMS paradigm is markedly different from the paradigms employed in the traditional animal studies with intense stressors. That anhedonia is commonly observed in both CMS rats and MDD patients recommends the paradigm for research on depression.

10.3.2 CMS & HPA Hormones

The relation of chronic mild stressors to the HPA system is less predictable than the endocrine response to restraint and other more severe stressors. Evidence of a relation of CMS – HPA activity comes from measuring CRH receptors in structures of the DA mesocorticolimbic pathway. An increase in receptor concentrations is predicted by dysregulation of the HPA, and there are reports of upregulation of CRH receptors with CMS in frontal cortex, hippocampus and, especially, hypothalamus [37, 156]. The mesolimbic segment has been less well studied and results are equivocal.

Elevated CORT levels have been reported for most, but not all, studies measuring sucrose preference and endocrine variables. For example, Grippo and colleagues [157, 158] reported on several experiments in which rats were subjected to CMS that induced anhedonia. In male rats exposed, CORT levels increased in male rats relative to controls [157]. In a subsequent study, there was a statistically non-significant trend toward elevated CORT [158]. Still, the overall pattern was a 30 % increase in CORT with CMS which is a much lesser rise compared to more severe chronic stressors [159]. The CMS findings of modest increases in CORT have been replicated in other laboratories [160].

It is to be noted that in the above experiments and most others in the literature [161], blood samples for hormone assays were collected at necropsy, i.e., after the animals had been in the CMS for weeks. More problematic for this discussion is interpretation of the studies that measured CORT, but only after exposure to an intense stressor that followed the weeks of CMS [83, 162, 163].

The absence of a dramatic elevation in CORT after weeks of stress is not surprising. The endocrine system shows partial adaptation with repeated exposure even to severe stressors [159]. A modest elevation of CORT above threshold values after weeks of CMS is consistent with mild stress and adaptation to chronic exposure.

On the other hand, consistent with chronically higher titers of CORT during the earlier weeks of CMS are reports of downregulation of CORT receptors at the end of CMS. The reductions in GR and MR expression have been found primarily in the hippocampus [152]. No one, to our knowledge, has measured CORT or CRH receptors in the PFC, nucleus accumbens or other areas in the mesocorticolimbic pathway after CMS.

Of greater interest is the relation of anhedonia to CORT levels. That is, does HPA activation closely correlate with the loss of sucrose preference, suggesting HPA

may contribute to anhedonia. Indirect evidence is that the sweet preference often recovers spontaneously over several weeks without the stressors [164]. Also, administration of anti-depressants that moderate hippocampal and HPA activity speeds the recovery [165, 166] Anti-depressants administered at the start of CMS exposure may prevent the development of anhedonia [167].

An experiment using a social defeat paradigm rather than CMS measured sucrose preference along with CORT levels [150]. Results were that the sucrose preference decreased while CORT increased in defeated rats soon after the experiences. However, 2 weeks later the elevated CORT returned to baseline values along with the recovery of the sucrose preference. The suggestion is of an inverse relation of sucrose preference and CORT in socially defeated, stressed animals.

The relation of anhedonia and CORT also has been examined in humans. In an interesting study, different psychological scales were used to identify MDD patients exhibiting different degrees of severity of symptoms accompanying depression [30]. Results were clearest for individuals with predominantly anhedonia symptoms, i.e., higher anhedonia was associated with higher CORT levels measured upon awakening in the morning. Although CORT was not measured, an acute but moderately intense stressor that normally activates the HPA axis was applied to healthy young women. The women revealed a reduced sensitivity to a reward that was especially evident in individuals with existing anhedonic tendencies [168].

Collectively, the data, mainly from animal models, support the hypothesis that HPA hormones are involved in the development and reversal of anhedonia. However, that conclusion is limited by the paucity of studies of receptors in the mesocorticolimbic pathway and the absence of CORT monitored during the weeks of CMS.

10.3.3 CMS & HPG Hormones

10.3.3.1 Sex Differences

Several studies of gender differences in MDD patients have included assessments of anhedonia. Psychological scales of multiple symptoms of depression were used. Contrary to the female bias for other symptoms of depression, the findings were either of no sex differences [169] or an unexpected higher incidence of anhedonia in depressed men [170].

Research with animal models has helped clarify the picture, but only somewhat. Comparing male and female animals has been the focus on studies to evaluate sex differences in behavioral and endocrine outcomes with chronic mild stress. Some also have included sucrose preferences as a measure of anhedonia.

The answer to the question of whether CMS is more stressful to one sex over the other in lab animals seems to depend upon which of the various measures of the stress response is used. Loss of body weight is one measure of stress, and the overall results suggest greater relative loss of body weight with CMS in male rats than in females [161, 171]. Males also were affected more by CMS than females when

subsequently observed in the FST. Using an ICSS paradigm to assess anhedonia, Bielajaw and colleagues [171] found no differences between males and females in their rates or thresholds of bar press responses.

Recalling the gold standard for determining HPA activation, assays of circulating CORT reveals a female bias. Female rats are reliably. Female rats are reliably found to have elevated CORT levels in the CMS paradigm [161]. Surprisingly, males may not show a CORT response at all to CMS exposure [160].

Results are more nuanced for relative sucrose consumption in the experiments using both males and females. In an early study [172], both males and females showed a decrease in sucrose preference with CMS exposure. However, there were no sex differences in consumption by the rats. Similar findings of no sex differences in preference with CMS were reported for intact or for gonadectomized male and female rats [173, 174].

Evidence for greater anhedonic response in females has also been reported. Male and female rats from two strains were subjected to a CMS procedure. Overall, females tended to show a gradual reduction of sucrose consumption; males did not [160]. Other findings have indicated sucrose reductions as being greater in males than females in the CMS paradigm [175]. Of interest are other findings that sucrose suppression over weeks of CMS was observed in both genders, but the reductions occurred much earlier in male rats than in the females [157]. For example, Dalla and colleagues [161] measured several neurochemical and behavioral parameters in male and female rats in the CMS paradigm. Although the experimental design was incomplete, sucrose consumption was observed as early as the 1st week of CMS in the males while the females required exposure for several weeks longer to reveal sucrose suppression.

These latter data suggest an explanation for the inconsistent findings on sex differences of sucrose preferences. Males may experience stress in the CMS paradigm earlier than females and, thus, are more habituated to the stressors by the end of stress exposure. In that scenario, males would reveal CORT elevation and anhedonia earlier than females. The males could have habituated and returned to baseline levels of sucrose consumption by the end of the 6 week of CMS.

10.3.3.2 Testosterone and Anhedonia

As reviewed in the previous section, there is a notable influence of HPG hormones, especially ovarian hormones, on dopaminergic activity in the BRS. Those data would suggest considerable research interest in manipulating hormone levels of animals in the CMS paradigm. That has not been the case.

There is a small literature on androgenic effects on anhedonia. A sensitive marker of testicular function is sexual behavior, and exposure to CMS increased latency both to intromission and ejaculation in male rats after 4 week of CMS [176]. That sucrose preference also progressively decreased in those males suggested development of anhedonia coinciding with the reduced HPG function. In a series of experiments [177], gonadally intact middle-aged male rats were given TS supplements to

match the circulating TS levels of young males. Animals were subjected to CMS either before or after TS supplementation began. Findings were that TS blocked the onset of anhedonia. However, if the loss of sucrose preference was established before TS supplementation, TS could not reverse the anhedonia.

Evidence supporting that conclusion came from a study of castrated males in another anhedonia paradigm [178]. Although CMS was not used, castrated rats were administered either TS or vehicle only and sucrose preference was measured with daily FST exposures. The vehicle control animals developed anhedonia while the males restored with TS maintained their normal preferences for sucrose. Because hormone metabolism was also manipulated, the authors concluded the estrogen receptor was responsible, that is, TS maintained sucrose preferences in male rats only after being metabolized to estrogen [178]. Finally, there is a report that CMS was associated with elevations of circulating TS in male rats relative to untreated controls. However, this was serum obtained after only a brief, 10 day exposure to CMS [179].

Dehydroepiandrosterone (DHEA) appears to be a good candidate for androgens blocking the development of anhedonia. In a report of middle-aged depressed patients administered DHEA for 6 week, depressive symptoms, and prominently anhedonia, improved in 60 % of the DHEA group compared to a 20 % improvement in placebo controls [180].

An unpublished experiment from our lab attempted to examine the role of DHEA in depression in an animal model. We used a CMS paradigm similar to our earlier, published study in which our goal was assessing the capacity of a kappa opioid agonist to promote a faster recovery of anhedonia after CMS had ended [181]. Gonadally intact rats were exposed to CMS over 3 weeks and, as expected, revealed progressive reductions in percent preference of sucrose water over tap water. Beginning in the 4th week, with CMS halted, half the animals received daily SC injections of DHEA (800 μg/kg body weight). Results are depicted in Fig. 10.3. DHEA induced a more complete recovery of sucrose preference than the control animals without DHEA treatments.

10.3.3.3 Estrogen and Anhedonia

A few experiments in the animal literature included direct manipulation of E2 in females. In one experiment, young adult and middle-aged rats were ovariectomized and exposed over 7 weeks to CMS. Beginning in the second week and continuing until the end of CMS exposure, the females were administered E2 alone or E2 plus a SSRI antidepressant. Both ages of OVX rats receiving E2 + SSRI increased their relative sucrose preferences. E2 alone failed to significantly influence sucrose consumption in either age group [182]. Of note, the middle-aged females showed earlier recovery from CMS-induced anhedonia than the young adult females. However, the conclusion that E2 alone is unable to influence anhedonia can be questioned. The low dosage of hormone used (2.5 μg) was unlikely to restore the animals to normal circulating E2 levels and are certainly unable to simulate proestrus [183].

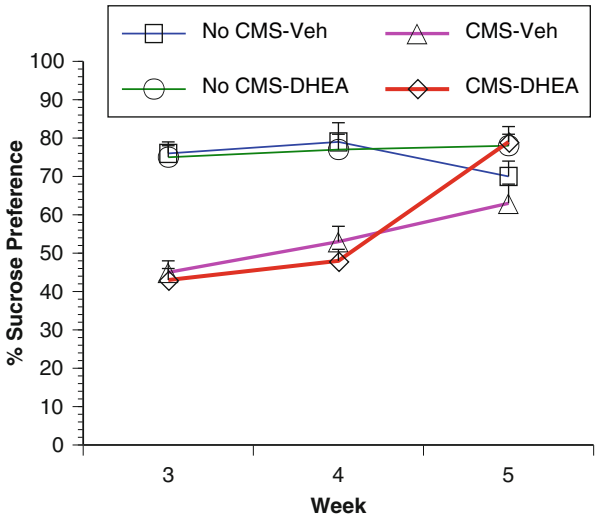

Fig. 10.3 Results of an unpublished experiment by the authors on recovery from anhedonia in male rats. Groups of rats were either exposed or not exposed to chronic mild stress for 3 weeks. Beginning in the 4th week, groups from CMS exposed and non-CMS exposure were SC administered daily either saline vehicle or dehydroepiandrosterone (DHEA) at a dosage of 800 μg/kg body weight

In another experiment, E2 (1 mg or 2 mg) was administered as a single bolus to OVX middle-aged females after the first of 3 weeks of CMS exposure. No significant differences in sucrose preferences were observed between hormone-treated and untreated controls [184]. It appears, however, that the hormone may have been effective in inhibiting development of anhedonia during the early weeks with the lower of the two dosages. However, the E2 dosages, 1–2 mg, would have produced dramatically supraphysiological levels of hormone [183]. Thus the two direct tests of the hypothesis that E2 could prevent or relieve anhedonia could be questioned on their choices of restoration dosages of hormone.

Less direct tests of the hypothesis have yielded data suggesting a more profound estrogenic influence on CMS females. Although intact animals were not included for comparison, female rats ovariectomized a month before introduction of CMS showed an unusually rapid development of anhedonia. By the second week of CMS, the OVX animals were drinking less sucrose water than non-CMS OVX rats [173].

In a recent ICSS experiment [185], OVX rats had higher sensitivity thresholds, indicative of anhedonia, than gonadally intact females. With E2 restoration therapy, the stimulation threshold was restored to the levels of the intact animals. Studies of the reward value of drugs of abuse also have pointed to E2 being capable of inhibiting anhedonic behaviors [186]. For example, Galankin and colleagues [187] used stimulation thresholds in a ICSS paradigm and found that E2 to OVX female rats enhanced the hedonic value of cocaine.

OVX decreased reward value of cocaine in females while castrating male rats had no effect [131]. OVX also decreased DA and 5HT in the VTA. The authors interpreted the findings as gonadal hormones influencing reward differently in males and females with the primary mechanism being E2 altering monoamine neurotransmitter systems.

Finally, circulating progesterone was elevated in female rats after a shortened 10 day exposure to CMS that produced anhedonia. Their E2 levels were no different than untreated control females [179]. In a review of ovarian hormonal influences on drug-seeking behavior, the authors [186] concluded that both PROG and its metabolite ALLO reduce drug seeking, a form of anhedonia. Indeed, PROG often is found to oppose the effects of estrogen. For example, PROG counteracts the enhanced effects of estrogen on cocaine self-administration and psychomotor activation [131, 188].

Our own conclusion is a hypothesis of inhibition of anhedonia from estrogenic binding of the ER in brain regions of the DA mesocorticolimbic pathways. This influence on the dopamine BRS can be direct of E2 can be directly from circulating estrogens from the periphery or indirectly from metabolic conversion of DHEA to TS and then to E2 in the brain.

10.4 Conclusions and Future Directions

The doggedly persistent reader who makes it to this section is acutely aware of the glaring gaps in our knowledge of neuroendocrine influences on anhedonia. Here we cite a few questions awaiting answers from future research efforts. Researchers working with either humans or other animal species can find rich fodder for projects from the list.

- **What are the common endocrine elements with other psychiatric conditions that often include anhedonia?**

Schizophrenia and MDD appear to be distinct diseases but share anhedonia symptomology [143]. It is entirely possible that anhedonia arises from distinct processes "with only an apparent resemblance of (anhedonia) expression in the two groups of patients" [189]. We know there are sex differences in incidence, timing, and/or severity in both diseases. Examination of circulating HPG hormones and degree of anhedonia in patient groups would be a first start.

Usefulness of animal models of psychiatric conditions is also suggested. One approach would be to manipulate fetal and perinatal HPA and HPG hormones. Subsequently, the animals would be evaluated as an adult with one of the several measures of anhedonia.

Another approach would be to systematically administer E2 and TS to gonadectomized animals before, during and after exposure to the CMS paradigm. The same approach could be used in an animal model of schizophrenia [190]. Finally, DHEA is the most plentiful circulating sex steroid in humans that begins a

steady, predictable decline in the 30's with rates of decline faster in men than women [191]. Studies are sorely needed on the influence of DHEA on the mesocorticolimbic system.

- **What are the systematic changes in anhedonia symptomology with therapy?**

We know that medications used to treat psychiatric disorders such as MDD and schizophrenia are effective, more or less, in relieving symptoms the diseases. However, there is surprisingly little study of the time courses of relief from the various symptoms. For example, anhedonia symptoms may resolve faster, or slower, than the other symptoms of MDD under the different SSRI drugs [192]. Although there is some work already done with SSRIs in the CMS paradigm [112, 182], we recommend more systematic comparisons of established and new psychiatric medications with lab animals.

- **Is anhedonia at base a disorder of the dopamine brain reward system?**

An initial goal for both animal and human researchers would be to better understand the neural basis of anhedonia. Modern neuroimaging techniques can be used to search for blunted responses to reward signals in the dopamine BRS in clinically depressed people [75]. Gender differences should always be an independent variable in these studies, along with awareness of current oral contraceptive use and stage of the menstrual cycle of women participants.

Animal models offer a wider range of options to examine dopamine BRS function using behavioral indicators of hedonia and anhedonia. Of particular interest would be the interaction of the HPA and HPG axis in such experiments. There are often surprising influences of one axis on the other [193]. Researchers should take care, however, to ensure physiological dosages of replacement hormones and to include gonadally intact animals as comparison groups.

- **Do understudied groups differing in endocrine status show differences in development and recovery from anhedonia?**

Not only are there endocrine differences depending on stage of the menstrual cycle in women, there are many other natural lifetime phases in which humans and lab animals have markedly different endocrine states. Juvenile rats and adolescent humans provide opportunities for researchers to examine the relation of anhedonia with the onset and suddenly high levels of HPG hormones. Pregnancy is characterized by remarkably high levels of steroidal hormones with the highest levels observed during the third trimester in women and 18–21 days of the rodent gestation period [194]. Their dramatic drop with parturition and ensuing mood changes in women are legendary [195]. Yet, we found no studies in the literature of anhedonia in teenagers or depressed pregnant women or in their animal models in the CMS paradigm.

- **Are there simple experiments without necessity of sophisticated technology that will help us to better understand the neuroendocrinology of anhedonia?**

The short answer is a resounding yes. A few examples include obtaining blood samples from rats every week of CMS to assay for circulating CORT that likely

change over time and changes differently in males and females. Also the SAM system is a critical part of the stress response. It would be easy to examine epinephrine (adrenaline) in the periphery or to use another marker of SAM activation in patients with anhedonia exposed to an acute stressor or in animals exposed vs. not exposed to CMS. Evaluating pregnancy – anhedonia relations would be straightforward with a sample of women in different trimesters using one of the psychological batteries that probe for anhedonia. Similarly, pregnant rats exposed to CMS could be examined for sucrose preference and recovery, with special attention paid to the last days of their 21 days gestation period.

There surely are many other experiments wanting for empirical study by more clever researchers. We hope the long journey through this chapter will inspire them.

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References

1. Ruedi-Bettschen D, Zhang W, Russig H, et al. Early deprivation leads to altered behavioural, autonomic and endocrine responses to environmental challenge in adult Fischer rats. Eur J Neurosci. 2006;24:2879–93.
2. Frodl T, Reinhold E, Koutsouleris N, et al. Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. J Psychiatr Res. 2010;44:799–807.
3. McEwen BS, Eiland L, Hunter RG, et al. Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology. 2012;62:3–12.
4. Heim C, Owens MJ, Plotsky PM, et al. Persistent changes in corticotropin-releasing factor systems due to early life stress: relationship to the pathophysiology of major depression and post-traumatic stress disorder. Psychopharmacol Bull. 1997;33:185–92.
5. Pohl J, Olmstead MC, Wynne-Edwards KE, et al. Repeated exposure to stress across the childhood–adolescent period alters rats' anxiety- and depression-like behaviors in adulthood: the importance of stressor type and gender. Behav Neurosci. 2007;121:462–74.
6. de Kloet ER. Brain corticosteroid receptor balance in health and disease. Endocr Rev. 1998;19:269–300.
7. Charmandari E, Kino T, Chrousos GP. Glucocorticoids and their actions an introduction. Ann N Y Acad Sci. 2004;1024:1–8.
8. Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. Ann N Y Acad Sci. 2009;1179:41–55.
9. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6:463–76.
10. Rodrigues SM, LeDoux JE, Sapolsky RM. The influence of stress hormones on fear circuitry. Annu Rev Neurosci. 2009;32:289–313.
11. Stern CM. Corticotropin-releasing factor in the hippocampus: eustress or distress? J Neurosci. 2011;31:1935–6.
12. Sgoifo A, DeBoer SF, Haller J, et al. Individual differences in plasma catecholamine and corticosterone stress responses of wild-type rats: relationship with aggression. Physiol Behav. 1996;60:1403–7.

13. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol. 2005;67:259–84.
14. Sapolsky RM. Stress, the aging brain, and the mechanisms of neuronal death. Cambridge, MA: The M.I.T. Press; 1992.
15. Taylor G, Bardgett M, Csernansky J, et al. Male rat reproductive systems under chronic fluoxetine or trimipramine treatment. Physiol Behav. 1996;59:479–85.
16. Taylor GT, Weiss J, Zimmermann F. Animal models of sex differences in nonreproductive brain function. In: Tatlisumak T, Fisher M, editors. Handbook of experimental neurology: methods and techniques in animal research. New York: Cambridge University Press; 2006. p. 239–56.
17. Conneely OM, Mulac-Jericevic B, DeMayo F, et al. Reproductive functions of progesterone receptors. Recent Prog Horm Res. 2002;57:339–55.
18. Baulieu EE. Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog Horm Res. 1997;52:1–32.
19. Engin E, Treit D. The anxiolytic-like effects of allopregnanolone vary as a function of intracerebral microinfusion site: the amygdala, medial prefrontal cortex, or hippocampus. Behav Pharmacol. 2007;18:461–70.
20. Brunton PJ, Russell JA. Allopregnanolone and suppressed hypothalamo-pituitary-adrenal axis stress responses in late pregnancy in the rat. Stress. 2011;14:6–12.
21. Kessler RC. Gender differences in major depression: epidemiologlcal findings. In: Frank E, editor. Gender and its effects on psychopathology. Washington, DC: American Psychiatric Press; 2000. p. 61–84.
22. Taylor GT, Boggiano J, Cabrera O, et al. Steroidal influences on anxiety disorders in childhood and their animal models. Curr Top Steroid Res. 2011;8:47–64.
23. Gonda X, Telek T, Juhasz G, et al. Patterns of mood changes throughout the reproductive cycle in healthy women without premenstrual dysphoric disorders. Prog Neuro-Psychopharmacol Biol Psychiatry. 2008;32:1782–8.
24. Bloch M, Daly RC, Rubinov DR. Endocrine factors in the etiology of postpartum depression. Compr Psychiatry. 2003;44:234–46.
25. Meltzer-Brody S. Understanding and treating mood disorders across the reproductive years. Sex Reprod Menopause. 2010;8:12–8.
26. Holsboer F, Ising M. Stress hormone regulation: biological role and translation into therapy. Annu Rev Psychol. 2010;61:81–109.
27. Chiba S, Numakawa T, Ninomiya M, et al. Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. Prog Neuro-Psychopharmacol Biol Psychiatry. 2012;39:112–9.
28. Paterson NE, Markou A. Animal models and treatments for addiction and depression comorbidity. Neurotox Res. 2007;11:1–32.
29. Post RM, Weiss SR, Li H, et al. Neural plasticity and emotional memory. Dev Psychopathol. 1998;10:829–55.
30. Wardenaar KJ, Vreeburg SA, van Veen T, et al. Dimensions of depression and anxiety and the hypothalamo-pituitary-adrenal axis. Biol Psychiatry. 2011;69:366–73.
31. Barden N. Implication of the hypothalamic – pituitary – adrenal axis in the physiopathology of depression. J Psychiatry Neurosci. 2004;29:185–93.
32. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology. 2000;23:477–501.
33. Romer B, Lewicka S, Kopf D, et al. Cortisol metabolism in depressed patients and healthy controls. Neuroendocrinology. 2009;90:301–6.
34. Wolkowitz OM, Burke H, Epel ES, et al. Mood, memory, and mechanisms. Ann N Y Acad Sci. 2009;1179:19–40.
35. Hoschl C, Hajek T. Hippocampal damage mediated by corticosteroids–a neuropsychiatric research challenge. Eur Arch Psychiatry Clin Neurosci. 2001;251 Suppl 2:II81–8.
36. DeSouza EB. Corticotropin-releasing factor receptors: physiology, pharmacology, biochemistry and role in central nervous system and immune disorders. Psychoneuroendocrinology. 1995;20:789–819.

37. Duncko R, Kiss A, Skultetyova I, et al. Corticotropin-releasing hormone mRNA levels in response to chronic mild stress rise in male but not in female rats while tyrosine hydroxylase mRNA levels decrease in both sexes. Psychoneuroendocrinology. 2001;26:77–89.
38. Muller MB, Keck ME. Genetically engineered mice for studies of stress-related clinical conditions. J Psychiatr Res. 2002;36:53–76.
39. Murphy BE. Steroids and depression. J Steroid Biochem Mol Biol. 1991;38:537–58.
40. Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. Horm Behav. 2003;43:60–6.
41. Krugers HJ, Lucassen PJ, Karst H, et al. Chronic stress effects on hippocampal structure and synaptic function: relevance for depression and normalization by anti-glucocorticoid treatment. Front Synaptic Neurosci. 2010;2:24.
42. Kubera M, Obuchowicz E, Goehler L, et al. In animal models, psychosocial stress-induced (neuro)inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35:744–59.
43. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry. 2000;48:755–65.
44. Sheline YI, Sanghav M, Mintun M, et al. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci. 1999;19:5034–43.
45. Olney JW. Excitotoxic amino acids and neuropsychiatric disorders. Annu Rev Pharmacol Toxicol. 1990;30:47–71.
46. Kaminska M, Harris J, Gijsbers K, et al. Dehydroepiandrosterone sulfate (DHEAS) counteracts decremental effects of corticosterone on dentate gyrus LTP: implications for depression. Brain Res Bull. 2000;52:229–34.
47. Naert G, Maurice T, Tapia-Arancibia L, et al. Neuroactive steroids modulate HPA axis activity and cerebral brain derived neurotrophic factor (BDNF) protein levels in adult male rats. Psychoneuroendocrinology. 2007;32:1062–78.
48. Maninger N, Wolkowitz OM, Reus VI, et al. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Endocrinol. 2009;30:65–91.
49. Herbert J. Neurosteroids, brain damage, and mental illness. Exp Gerontol. 1998;33:713–27.
50. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: a review. Biol Psychol. 2005;69:113–32.
51. Matsumoto AM, Bremner WJ. Serum testosterone assays–accuracy matters. J Clin Endocrinol Metab. 2004;89:520–4.
52. Becker JB, Monteggia LM, Perrot-Sinal TS, et al. Stress and disease: is being female a predisposing factor? J Neurosci. 2007;27:11851–5.
53. Viau V, Meaney MJ. The inhibitory effect of testosterone on hypothalamic-pituitary-adrenal responses to stress is mediated by the medial preoptic area. J Neurosci. 1996;16:1866–76.
54. McCormick CM, Mathews IZ. HPA function in adolescence: role of sex hormones in its regulation and the enduring consequences of exposure to stressors. Pharmacol Biochem Behav. 2007;86:220–33.
55. Stroud LR, Salovey P, Epel ES. Sex differences in stress responses: social rejection versus achievement stress. Biol Psychiatry. 2002;52:318–27.
56. Altemus M. Sex differences in depression and anxiety disorders: potential biological determinants. Horm Behav. 2006;50:534–8.
57. Atkinson HC, Waddell BJ. Circadian variation in basal plasma corticosterone and adrenocorticotropin in the rat: sexual dimorphism and changes across the estrous cycle. Endocrinology. 1997;138:3842–8.
58. McCormick CM, Linkroum W, Sallinen BJ, et al. Peripheral and central sex steroids have differential effects on the HPA axis of male and female rats. Stress. 2002;5:235–47.
59. Brummelte S, Galea LA. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. Prog Neuro-Psychopharmacol Biol Psychiatry. 2010;34:766–76.
60. Young EA, Altemus M. Puberty, ovarian steroids, and stress. Ann N Y Acad Sci. 2004;1021:124–33.

61. Yang S-J, Kim S-Y, Stewart RB, et al. Gender differences in 12-week antidepressant treatment outcomes for a naturalistic secondary care cohort: the CRESCEND study. Psychiatry Res. 2011;189:82–90.
62. Baca E, Garcia-Garcia M, Porras-Chavarinoc A. Gender differences in treatment response to sertraline versus imipramine in patients with nonmelancholic depressive disorders. Prog Neuro-Psychopharmacol Biol Psychiatry. 2004;28:57–65.
63. Kornstein SG, Sloan DME, Thase ME. Gender-specific differences in depression and treatment response. Psychopharmacol Bull. 2002;36 Suppl 3:99–112.
64. Osterlund MK. Underlying mechanisms mediating the antidepressant effects of estrogens. Biochim Biophys Acta. 2010;1800:1136–44.
65. Osterlund MK, Keller E, Hurd YL. The human forebrain has discrete estrogen receptor α messenger RNA expression: high levels in the amygdaloid complex. Neuroscience. 2000;95:333–42.
66. Young EA, Midgley AR, Carlson NE, et al. Alteration in the hypothalamic-pituitary-ovarian axis in depressed women. Arch Gen Psychiatry. 2000;57:1157–62.
67. Rocca WA, Grossardt BR, Geda YE, et al. Long-term risk of depressive and anxiety symptoms after early bilateral oophorectomy. Menopause. 2008;15:1050–9.
68. Holsen LM, Spaeth SB, Lee JH, et al. Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. J Affect Disord. 2011;131:379–87.
69. Solomon MB, Herman JP. Sex differences in psychopathology: of gonads, adrenals and mental illness. Physiol Behav. 2009;97:250–8.
70. Steiner M, Dunn E, Born L. Hormones and mood: from menarche to menopause and beyond. J Affect Disord. 2003;74:67–83.
71. Baischer W, Koinig G, Hartmann B, et al. Hypothalamic–pituitary–gonadal axis in depressed premenopausal women: elevated blood testosterone concentrations compared to normal controls. Psychoneuroendocrinology. 1995;20:553–9.
72. Hardoy MC, Serra M, Carta MG, et al. Increased neuroactive steroid concentrations in women with bipolar disorder or major depressive disorder. J Clin Psychopharmacol. 2006;26:379–84.
73. Nin MS, Martinez LA, Pibiri F, et al. Neurosteroids reduce social isolation-induced behavioral deficits: a proposed link with neurosteroid-mediated upregulation of BDNF expression. Front Endocrinol. 2011;2:73. doi:10.3389/fendo.2011.00073.
74. Pinna G, Costa E, Guidotti A. SSRIs act as selective brain steroidogenic stimulants (SBSSs) at low doses that are inactive on 5-HT reuptake. Curr Opin Pharmacol. 2009;9:24–30.
75. Martin-Soelch C. Is depression associated with dysfunction of the central reward system? Biochem Soc Trans. 2009;37:313–7.
76. Nestler EJ, Carlezon JWA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006;59:1151–9.
77. Skinner BF. The behavior of organisms. New York: Appleton; 1938.
78. Esch T, Stefano GB. The neurobiology of pleasure, reward processes, addiction and their health implications. Neuro Endocrinol Lett. 2004;25:235–51.
79. Picciotto MR, Corrigall WA. Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. J Neurosci. 2002;22:3338–41.
80. Russell VA. Dopamine hypofunction possibly results from a defect in glutamate-stimulated release of dopamine in the nucleus accumbens shell of a rat model for attention deficit hyperactivity disorder–the spontaneously hypertensive rat. Neurosci Biobehav Rev. 2003;27:671–82.
81. Parolaro D, Realini N, Vigano D, et al. The endocannabinoid system and psychiatric disorders. Exp Neurol. 2010;224:3–14.
82. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci. 2002;22:3306–11.
83. DiChiara G, Loddo P, Tanda G. Reciprocal changes in prefrontal and limbic dopamine responsiveness to aversive and rewarding stimuli after chronic mild stress: implications for the psychobiology of depression. Biol Psychiatry. 1999;46:1624–33.

84. Pfaus JG, Damsma G, Wenkstern D, et al. Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats. Brain Res. 1995;693:21–30.
85. Putnam SK, Sato S, Hull EM. Effects of testosterone metabolites on copulation and medial preoptic dopamine release in castrated male rats. Horm Behav. 2003;44:419–28.
86. Putnam SK, Sato S, Riolo JV, et al. Effects of testosterone metabolites on copulation, medial preoptic dopamine, and NOS-immunoreactivity in castrated male rats. Horm Behav. 2005;47:513–22.
87. Elhwuegi AS. Central monoamines and their role in major depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2004;28:435–51.
88. Schultz W. Behavioral theories and the neurophysiology of reward. Annu Rev Psychol. 2006;57:87–115.
89. Andersen ML, Sawyer EK, Howell LL. Contributions of neuroimaging to understanding sex differences in cocaine abuse. Exp Clin Psychopharmacol. 2012;20:2–15.
90. Aron A, Fisher HE, Mashek D, et al. Reward, motivation, and emotion systems associated with early-stage intense romantic love. J Neurophysiol. 2005;94:327–37.
91. Levita L, Hare TA, Voss HU, et al. The bivalent side of the nucleus accumbens. Neuroimage. 2009;44:1178–87.
92. Kornetsky C. Brain-stimulation reward, morphine-induced oral stereotypy, and sensitization: implications for abuse. Neurosci Biobehav Rev. 2004;27:777–86.
93. Schultz W. Behavioral dopamine signals. Trends Neurosci. 2007;30:303–10.
94. Salamone J, Cousins M, Snyder B. Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. Neurosci Biobehav Rev. 1997;21:341–59.
95. Rademacher L, Krach S, Kohls G, et al. Dissociation of neural networks for anticipation and consumption of monetary and social rewards. Neuroimage. 2010;49:3276–85.
96. Bromberg-Martin ES, Hikosaka O. Midbrain dopamine neurons signal preference for advance information about upcoming rewards. Neuron. 2009;63:119–26.
97. Becker JB, Rudick CN, Jenkins WJ. The role of dopamine in the nucleus accumbens and striatum during sexual behavior in the female rat. J Neurosci. 2001;21:3236–41.
98. Becker JB. Sexual differentiation of motivation: a novel mechanism? Horm Behav. 2009;55:646–54.
99. Volkow ND, Wang G-J, Fischman MW, et al. Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature. 1997;386:827–30.
100. Everitt BJ. Sexual motivation: a neural and behavioral analysis of the mechanisms underlying appetitive and copulatory responses in male rats. Neurosci Biobehav Rev. 1990;14:217–32.
101. Berridge KC. Motivation concepts in behavioral neuroscience. Physiol Behav. 2004;81:179–209.
102. Colasanti A, Searle GE, Long CJ, et al. Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. Biol Psychiatry. 2012;72:371–7.
103. Nakahara D, Nakamura M, Oki Y, et al. Lack of glucocorticoids attenuates the self-stimulation-induced increase in the in vivo synthesis rate of dopamine but not serotonin in the rat nucleus accumbens. Eur J Neurosci. 2000;12:1495–500.
104. Barrot M, Marinelli M, Abrous DN, et al. The dopaminergic hyper-responsiveness of the shell of the nucleus accumbens is hormone-dependent. Eur J Neurosci. 2000;12:973–80.
105. Lindley SE, Tasha G, Bengoechea TG, et al. Glucocorticoid effects on mesotelencephalic dopamine neurotransmission. Neuropsychopharmacology. 1999;21:399–407.
106. Mizoguchi K, Ishige A, Takeda S, et al. Endogenous glucocorticoids are essential for maintaining prefrontal cortical cognitive function. J Neurosci. 2004;24:5492–9.
107. Chocyk A, Dudys D, Przyborowska A, et al. Maternal separation affects the number, proliferation and apoptosis of glia cells in the substantia nigra and ventral tegmental area of juvenile rats. Neuroscience. 2011;173:1–18.
108. Cabib S, Puglisi-Allegra S, Damato F. Effects of postnatal stress on dopamine mesolimbic system responses to aversive experiences in adult life. Brain Res. 1993;604:232–9.

109. Cabib S, D'Amato FR, Puglisi-Allegra S, et al. Behavioral and mesocorticolimbic dopamine responses to non aggressive social interactions depend on previous social experiences and on the opponent's sex. Behav Brain Res. 2000;112:13–22.
110. Finlay JM, Zigmond MJ, Abercrombie ED. Increased dopamine and norepinephrine release in medial prefrontal cortex induced by acute and chronic stress: effects of diazepam. Neuroscience. 1995;64:619–28.
111. Cabib S, Puglisi-Allegra S. Different effects of repeated stress on mesocortical and mesolimbic dopamine metabolism. Neuroscience. 1996;73:375–80.
112. Dziedzicka-Wasylewska M, Willner P, Papp M. Changes in dopamine receptor mRNA expression following chronic mild stress and chronic antidepressant treatment. Behav Pharmacol. 1997;8:607–18.
113. Koob GF, Caine SB, Parsons L, et al. Opponent process model and psychostimulant addiction. Pharmacol Biochem Behav. 1997;57:513–21.
114. Boutrel B. A neuropeptide-centric view of psychostimulant addiction. Br J Pharmacol. 2008;154:343–57.
115. Elman I, Lukas SE, Karlsgodt KH, et al. Acute cortisol administration triggers craving in individuals with cocaine dependence. Psychopharmacol Bull. 2003;37:84–9.
116. Marinelli M, Piazza PV. Interaction between glucocorticoid hormones, stress and psychostimulant drugs. Eur J Neurosci. 2002;16:387–94.
117. Goodman A. Neurobiology of addition: an integrative review. Biochem Pharmacol. 2008;75:266–322.
118. Der-Avakian A, Markou A. Neonatal maternal separation exacerbates the reward-enhancing effect of acute amphetamine administration and the anhedonic effect of repeated social defeat in adult rats. Neuroscience. 2010;170:1189–98.
119. Tidey JW, Miczek KA. Acquisition of cocaine self-administration after social stress: role of accumbens dopamine. Psychopharmacology. 1997;130:203–12.
120. Dellu F, Mayo W, Vallee M, et al. Behavioral reactivity to novelty during youth as a predictive factor of stress-induced corticosterone secretion in the elderly – a life-span study of rats. Psychoneuroendocrinology. 1996;21:441–53.
121. Kabbaj M, Devine DP, Savage VR, Akil H. Neurobiological correlates of individual differences in novelty-seeking behavior in the rat: differential expression of stress-related molecules. J Neurosci. 2000;20:6983–8.
122. Hooks MS, Jones GH, Smith AD, et al. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse. 1991;9:121–8.
123. Piazza P, Le Moal M. The role of stress in drug self-administration. Trends Pharmacol Sci. 1998;19:67–74.
124. Dluzen DE, Salvaterra TJ. Sex differences in methamphetamine-evoked striatal dopamine output are abolished following gonadectomy: comparisons with potassium-evoked output and responses in prepubertal mice. Neuroendocrinology. 2005;82:78–86.
125. Xiao L, Becker JB. Quantitative microdialysis determination of extracellular striatal dopamine concentration in male and female rats: effects of estrous cycle and gonadectomy. Neurosci Lett. 1994;180:155–8.
126. Mitchell JB, Stewart J. Effects of castration, steroid replacement, and sexual experience on mesolimbic dopamine and sexual behaviors in the male rat. Brain Res. 1989;491:116–27.
127. Frye CA. Some rewarding effects of androgens may be mediated by actions of its 5alpha-reduced metabolite 3alpha-androstanediol. Pharmacol Biochem Behav. 2007;86:354–67.
128. Yague JG, Wang AC, Janssen WG, et al. Aromatase distribution in the monkey temporal neocortex and hippocampus. Brain Res. 2008;1209:115–27.
129. Shieh KR, Yang SC. Effects of estradiol on the stimulation of dopamine turnover in mesolimbic and nigrostriatal systems by cocaine- and amphetamine-regulated transcript peptide in female rats. Neuroscience. 2008;154:1589–97.
130. McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev. 1999;20:279–307.

131. Russo SJ, Festa ED, Fabian SJ, et al. Gonadal hormones differentially modulate cocaine-induced conditioned place preference in male and female rats. Neuroscience. 2003;120:523–33.
132. Becker JB, Molenda H, Hummer DL. Gender differences in the behavioral responses to cocaine and amphetamine: implications for mechanisms mediating gender differences in drug abuse. Ann N Y Acad Sci. 2001;937:173–87.
133. Izumo N, Ishibashi Y, Ohba M, et al. Decreased voluntary activity and amygdala levels of serotonin and dopamine in ovariectomized rats. Behav Brain Res. 2012;227:1–6.
134. DiPaolo T, Rouillard C, Bedard P. 17B-Estradiol at a physiological dose acutely increases dopamine turnover in rat brain. Eur J Pharmacol. 1985;117:197–203.
135. Andersen SL, Teicher MH. Sex differences in dopamine receptors and their relevance to ADHD. Neurosci Biobehav Rev. 2000;24:137–41.
136. Morris ME, Lee HJ, Predko LM. Gender differences in the membrane transport of endogenous and exogenous compounds. Pharmacol Rev. 2003;55:220–40.
137. Shansky RM, Glavis-Bloom C, Lerman D, et al. Estrogen mediates sex differences in stress-induced prefrontal cortex dysfunction. Mol Psychiatry. 2004;9:531–8.
138. Dazzi L, Seu E, Cherchi G, et al. Estrous cycle-dependent changes in basal and ethanol-induced activity of cortical dopaminergic neurons in the rat. Neuropsychopharmacology. 2007;32:892–901.
139. Jacome LF, Gautreaux C, Inagaki T, et al. Estradiol and ERbeta agonists enhance recognition memory, and DPN, an ERbeta agonist, alters brain monoamines. Neurobiol Learn Mem. 2010;94:488–98.
140. Kritzer MF. Long-term gonadectomy affects the density of tyrosine hydroxylase- but not dopamine-ß-hydroxylase-, choline acetyltransferase- or serotonin-immunoreactive axons in the medial prefrontal cortices of adult male rats. Cereb Cortex. 2003;13:282–96.
141. Sanchez MG, Bourque M, Morissette M, et al. Steroids-dopamine interactions in the pathophysiology and treatment of CNS disorders. CNS Neurosci Ther. 2010;16:e43–71.
142. Maggi M, Ciana P, Belcredito S, et al. Estrogens in the nervous system: mechanisms and nonreproductive functions. Annu Rev Physiol. 2004;66:291–313.
143. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:22.
144. van der Staay FJ. Animal models of behavioral dysfunctions: basic concepts and classifications, and an evaluation strategy. Brain Res Rev. 2006;52:131–59.
145. Cryan JF, Mombereau C. In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. Mol Psychiatry. 2004;9:326–57.
146. Barr AM, Markou A, Phillips AG. A 'crash' course on psychostimulant withdrawal as a model of depression. Trends Pharmacol Sci. 2002;23:475–82.
147. Bevins RA, Besheer J. Novelty reward as a measure of anhedonia. Neurosci Biobehav Rev. 2005;29:707–14.
148. Von Frijtag JC, Reijmers LG, Van der Harst JE, et al. Defeat followed by individual housing results in long-term impaired reward- and cognition-related behaviours in rats. Behav Brain Res. 2000;117:137–46.
149. Miczek KA, Nikulina EM, Takahashi A, et al. Gene expression in aminergic and peptidergic cells during aggression and defeat: relevance to violence, depression and drug abuse. Behav Genet. 2011;41:787–802.
150. Razzoli M, Carboni L, Arban R. Alterations of behavioral and endocrinological reactivity induced by 3 brief social defeats in rats: relevance to human psychopathology. Psychoneuroendocrinology. 2009;34:1405–16.
151. Taylor GT, Smith SE, Kirchhoff BA. Differential effects of antipsychotics on lateral bias and social attention in rats. Psychopharmacology. 2013;225:453–60.
152. Hill MN, Hellemans KG, Verma P, et al. Neurobiology of chronic mild stress: parallels to major depression. Neurosci Biobehav Rev. 2012;36:2085–117.
153. Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology. 1997;134:319–29.

154. Bhutani MK, Bishnoi M, Kulkarni SK. Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes. Pharmacol Biochem Behav. 2009;92:39–43.
155. Dang H, Chen Y, Liu X, et al. Antidepressant effects of ginseng total saponins in the forced swimming test and chronic mild stress models of depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2009;33:1417–24.
156. Pan Y, Wang FM, Qiang LQ, et al. Icariin attenuates chronic mild stress-induced dysregulation of the LHPA stress circuit in rats. Psychoneuroendocrinology. 2010;35:272–83.
157. Grippo AJ, Francis J, Beltz TG, et al. Neuroendocrine and cytokine profile of chronic mild stress-induced anhedonia. Physiol Behav. 2005;84:697–706.
158. Grippo AJ, Sullivan NR, Damjanoska KJ, et al. Chronic mild stress induces behavioral and physiological changes, and may alter serotonin 1A receptor function, in male and cycling female rats. Psychopharmacology (Berl). 2005;179:769–80.
159. Buynitsky T, Mostofsky DI. Restraint stress in biobehavioral research: recent developments. Neurosci Biobehav Rev. 2009;33:1089–98.
160. Konkle ATM, Baker SL, Kentner AC, et al. Evaluation of the effects of chronic mild stressors on hedonic and physiological responses: sex and strain compared. Brain Res. 2003;992:227–38.
161. Dalla C, Antoniou K, Drossopoulou G, et al. Chronic mild stress impact: are females more vulnerable? Neuroscience. 2005;135:703–14.
162. Bachis A, Cruz MI, Nosheny RL, et al. Chronic unpredictable stress promotes neuronal apoptosis in the cerebral cortex. Neurosci Lett. 2008;442:104–8.
163. Garcia LS, Comim CM, Valvassori SS, et al. Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. Prog Neuro-Psychopharmacol Biol Psychiatry. 2009;33:450455.
164. Wiborg O. Chronic mild stress for modeling anhedonia. Cell Tissue Res. 2013;354(1):155–69. doi:10.1007/s00441-013-1664-0.
165. Elizalde N, Garcia-Garcia AL, Totterdell S, et al. Sustained stress-induced changes in mice as a model for chronic depression. Psychopharmacology. 2010;210:393–406.
166. Muscat R, Papp M, Willner P. Reversal of stress – induced anhedonia by the atypical antidepressants, fluoxetine and maprotiline. Psychopharmacology. 1993;109:433–8.
167. Grippo AJ, Beltz TG, Weiss RM, et al. The effects of chronic fluoxetine treatment on chronic mild stress-induced cardiovascular changes and anhedonia. Biol Psychiatry. 2006;59:309–16.
168. Bogdan R, Pizzagalli DA. Acute stress reduces reward responsiveness: implications for depression. Biol Psychiatry. 2006;60:1147–54.
169. Troisi A, Alcini S, Coviello M, et al. Adult attachment style and social anhedonia in healthy volunteers. Personal Individ Differ. 2010;48:640–3.
170. Bennett DS, Ambrosini PJ, Kudes D, et al. Gender differences in adolescent depression: do symptoms differ for boys and girls? J Affect Disord. 2005;89:35–44.
171. Bielajew C, Konkle AT, Kentner AC, et al. Strain and gender specific effects in the forced swim test: effects of previous stress exposure. Stress. 2003;6:269–80.
172. D'Aquila PS, Brain P, Willner P. Effects of chronic mild stress on performance in behavioural tests relevant to anxiety and depression. Physiol Behav. 1994;56:861–7.
173. Benelli A, Filaferro M, Bertolini A, et al. Influence of Sadenosyl-L-methionine on chronic mild stress-induced anhedonia in castrated rats. Br J Pharmacol. 1999;127:645–54.
174. Pitychoutis PM, Dalla C, Sideris AC, et al. 5-HT1A, 5-HT2A, and 5-HT2C receptor mRNA modulation by antidepressant treatment in the chronic mild stress model of depression: sex differences exposed. Neuroscience. 2012;210:152–67.
175. Kamper EF, Chatzigeorgiou A, Tsimpoukidi O, et al. Sex differences in oxidant/antioxidant balance under a chronic mild stress regime. Physiol Behav. 2009;98:215–22.
176. Gronli J, Murison R, Fiske E, et al. Effects of chronic mild stress on sexual behavior, locomotor activity and consumption of sucrose and saccharine solutions. Physiol Behav. 2005;84:571–7.
177. Herrera-Perez JJ, Martinez-Mota L, Chavira R, et al. Testosterone prevents but not reverses anhedonia in middle-aged males and lacks an effect on stress vulnerability in young adults. Horm Behav. 2012;61:623–30.

178. Carrier N, Kabbaj M. Extracellular signal-regulated kinase 2 signaling in the hippocampal dentate gyrus mediates the antidepressant effects of testosterone. Biol Psychiatry. 2012;71: 642–51.
179. Hellemans KG, Verma P, Yoon E, et al. Prenatal alcohol exposure increases vulnerability to stress and anxiety-like disorders in adulthood. Ann N Y Acad Sci. 2008;1144:154–75.
180. Bloch M, Schmidt PJ, Danaceau MA, et al. Dehydroepiandrosterone treatment of midlife dysthymia. Biol Psychiatry. 1999;45:1533–41.
181. Harden M, Smith SE, Niehoff JA, et al. Anti-depressive effects of the κ-opioid receptor agonist salvinorin A in a rat model of anhedonia. Behav Pharmacol. 2012;23:710–5.
182. Recamier-Carballo S, Estrada-Camarena E, Reyes R, et al. Synergistic effect of estradiol and fluoxetine in young adult and middle-aged female rats in two models of experimental depression. Behav Brain Res. 2012;233:351–8.
183. Taylor GT, Farr S, Klinga K, et al. Chronic fluoxetine suppresses circulating estrogen and the enhanced spatial learning of estrogen-restored ovariectomized female rats. Psychoneuroendocrinology. 2004;29:1241–9.
184. Romano-Torres M, Fernandez-Guasti A. Estradiol valerate elicits antidepressant-like effects in middle-aged female rats under chronic mild stress. Behav Pharmacol. 2010;21:104–11.
185. Schiller CE, O'Hara MW, Rubinow DR, et al. Estradiol modulates anhedonia and behavioral despair in rats and negative affect in a subgroup of women at high risk for postpartum depression. Physiol Behav. 2013;119:137–44.
186. Carroll ME, Anker JJ. Sex differences and ovarian hormones in animal models of drug dependence. Horm Behav. 2010;58:44–56.
187. Galankin T, Shekunova E, Zvartau E. Estradiol lowers intracranial self-stimulation thresholds and enhances cocaine facilitation of intracranial self-stimulation in rats. Horm Behav. 2010;58:827–34.
188. Quinones-Jenab V, Jenab S. Progesterone attenuates cocaine-induced responses. Horm Behav. 2010;58:22–32.
189. Auriacombe M, Reneric JP, LeMoal M. Animal models of anhedonia. Psychopharmacology. 1997;134:337–8.
190. Weiss JM, Kilts CD. Animal models of depression and schizophrenia. In: Schatzberg A, Nemeroff C, editors. Textbook of psychopharmacology. 2nd ed. Washington, DC: American Psychiatric Press; 1998. p. 89–131.
191. Morley JE, Kim MJ, Haren MT. Frailty and hormones. Rev Endocr Metab Disord. 2005;6:101–8.
192. Lam RW. Onset, time course and trajectories of improvement with antidepressants. Eur Neuropsychopharmacol. 2012;22 Suppl 3:S492–8.
193. Taylor GT, Weiss J, Rupich R. Male rat behavior, endocrinology and reproductive physiology in a mixed-sex, socially stressful colony. Physiol Behav. 1987;39:429–33.
194. Altemus M. Hormone-specific psychiatric disorders: do they exist? Arch Womens Ment Health. 2010;13:25–6.
195. Henry JF, Sherwin BB. Hormones and cognitive functioning during late pregnancy and postpartum: a longitudinal study. Behav Neurosci. 2012;126:73–85.

Chapter 11
Electrophysiological Signatures of Reward Processing in Anhedonia

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Abstract Anhedonia is characterized by a reduced capacity to experience pleasure in response to rewarding stimuli and has been considered a possible candidate endophenotype in depression and schizophrenia. In this chapter we will focus on recent studies in which new electrophysiological brain measures (event-related brain potentials and oscillatory activity) have been used to understand the deficits in reward processing in anhedonic subclinical and clinical samples. The advantage of these neuroimaging techniques is that they provide time-sensitive measures that could be especially relevant to disentangle the differences between anticipatory

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and/or consummatory experiences of pleasure in anhedonia. Furthermore, because of the close interrelationship between reward and learning processes, we will review evidence showing how learning and reinforcement styles could influence the capacity to accurately anticipate positive rewarding experiences in anhedonics as well as in depressive patients. At the motivational level, this cognitive bias could be translated not only into an increased susceptibility to avoid potential negative events but also into a reduced tendency to seek positive experiences or rewards. This interpretation is therefore in agreement with the idea that the effects observed in anhedonia with regard reward processing are more related to anticipatory rather than consummatory processes.

Keywords Anhedonia • Depression • Reward processing • Feedback processing • Learning • Feedback-related negativity • Medial-frontal theta oscillatory activity • Beta–gamma oscillatory • Motivation

Abbreviations

ACC	Anterior Cingulate Cortex
BOLD	Blood-Oxygenation-Level Dependent contrast
BRS	Brain Reward System
DBS	Deep Brain Stimulation
ERN	Error related negativity
ERPs	Event-related brain potentials
FCPS	Fawcett-Clarke Pleasure Scale
fMRI	Functional Magnetic Resonance Imaging
FRN	Feedback related negativity
MFN	Medial Frontal Negativity
MDD	Major Depressive Disorder
NAcc	Nucleus Accumbens
OFC	Orbitofrontal cortex
PAS	Chapman Physical Anhedonia Scale
SAS	Chapman Social Anhedonia Scale
SHAPS	Snaith–Hamilton Pleasure Scale
VMPFC	Ventro medial Prefrontal Cortex

11.1 Introduction

Anhedonia, described as the diminished motivation for and sensitivity to rewarding experiences, has long been considered a fundamental symptom of depression as well as a residual condition in schizophrenic patients. However many researchers and clinicians have observed its presence before the onset of the mentioned

disorders advocating for a possible implication of anhedonia in the development of both psychopathological conditions [1]. The current perspective on anhedonia and the latest advances in research are based on this view. From this perspective, anhedonia could be considered a vulnerability marker of depression and it is envisioned as a candidate psychopathological endophenotype that could help to understand the neurobiological and genetic bases of certain clinical phenotypes [2, 3].

Recent years have shown a renewed interest in the study of affective processes, particularly in the psychological and neural mechanisms that explain the interaction between goal-directed behavior, reward and motivation. One of the most important aspects that has been somehow neglected, and crucial to understanding motivated behavior, is individual differences in anhedonia. The concept of anhedonia refers to a reduction of the ability to experience pleasure [4, 5] as reflected in a diminished interest in rewarding stimuli and pleasurable events. Anhedonia has been described as a prominent symptom and potential trait marker of major depression [6] and is currently one of the two required symptoms for a diagnosis of major depressive disorder (MDD) [7, 8]. In addition, anhedonia is broadly studied in relation to schizophrenia and the negative symptoms spectrum [9, 10]. For example, in a recent report, nearly 37 % of patients with MDD experience clinically significant anhedonia [11].

In this chapter, by adopting a personality-trait approach of anhedonia, we first review neuroimaging, behavioral and psychometric data supporting that anhedonia is related to impairment in the anticipation component of reward, leaving intact the consummatory and pleasure experience *per se*. We also review different neuroscientific studies showing to which degree learning and reward processing are implicated in the appearance of anhedonia. In this sense we will focus on recent evidence using electrophysiological measures (event-related brain components) associated to reward processing of the possible association between anticipatory reward processes and anhedonia.

11.2 The Trait of Anhedonia as an Endophenotype

The limited success of gene studies regarding mental health disorders has led to a more focused approach based on the identification of intermediate endophenotypes associated both with the genetic variance and the phenomenology of a given disorder [12]. In this sense, because of its clinical importance and substantial heridability [13], anhedonia has been considered an important candidate and putative endophenotype both for schizophrenic-like conditions and depression. Endophenotypes represent subclinical traits associated with vulnerability to expressing a determined mental disorder. They are heritable and state-independent, and can manifest in individuals whether or not illness is active [2, 14]. According to this, anhedonia cannot be considered exclusively as a state triggered by the onset of the pathology, nor a residual symptom developed by a progressive functional deterioration, but an endurable trait present before the appearance of the disorder and manifested also in both healthy and subclinical individuals.

Adopting this perspective, anhedonia as a trait has been characterized in clinical, sub-clinical and non-clinical populations, showing stable individual differences across time [1, 10]. Epidemiological studies consider clinical individuals as those affected by a given disorder or illness; on the other hand sub-clinical individuals are those affected with a mild form of a disorder that stays below the surface of clinical detection; finally non-clinical individuals are those who are healthy regarding a particular disorder. Several studies have addressed the issue of the persistence of anhedonia across time. The majority of them have evaluated clinical samples and their evolution over a given period of time. For example, a recent study followed a cohort of 49 MDD patients for 20 years and clearly showed relative stability of physical anhedonia over time in the six evaluations carried out [1]. These authors also identified that the severity of physical anhedonia was related to an increase in depressive symptoms, interpreting that trait anhedonia could be a useful behavioral marker for identifying at-risk cases of MDD. These results are partially in agreement with previous studies showing stability of physical anhedonia over time [15] even when improvements of depressive or psychotic symptoms were identified [10, 16, 17]. For example, in a cohort of 127 schizophrenic patients that were followed for 10 years, physical anhedonia was found to show intra-individual stability supporting the trait-like perspective [17, 18]. However, it is worth noting that the authors of this study found little relationship between physical anhedonia and positive, negative or depressive symptoms, supporting the idea that the anhedonia trait appears to be an independent construct. In a similar way, Horan and co-workers [10] also proposed that physical anhedonia shows the characteristics of a stable vulnerability indicator in recent-onset psychotic patients, being relatively stable across time (3 evaluations in 15 months) and showing only slight increases over time. These authors reported also that changes in physical anhedonia did not covariate with clinical symptoms and remained persistently elevated even in a subsample of patients who achieved a fully remitted state (see for similar findings, [19, 20]).

To summarize, psychometric studies demonstrate a tendency to highlight the stability of the anhedonia trait and its presence before the onset of the depression or psychosis in a similar way as some neurocognitive or neurophysiological deficits that have been identified as candidate endophenotypes for vulnerability in schizophrenia [21]. Moreover its endurance over time has been related to a poorer functional status in schizophrenia pointing out its possible relation with those schizophrenic forms characterized by severity of negative symptoms and cognitive/behavioral disorganization (‘negative’ or ‘deficit’ syndromes; [11, 18]).

11.3 The Measurement of Hedonic Trait and State

Self-reported measures of trait anhedonia have been actively used in many research studies with the aim of underpinning “anhedonia” and “hedonic capacity” as a psychopathology vulnerability trait stable over time. Briefly, in 1976, Chapman and Chapman [22] published a pair of scales with the aim of measuring

anhedonia as a characteriological defect in the ability to experience pleasure as observed in the poor premorbid adjustment of some schizophrenic patients [22]. These authors distinguished between physical and social anhedonia, the former being associated with sensitive pleasures (e.g., eating, touching, sex, etc.…) (measured using the Physical Anhedonia Scale, PAS, 61 items, *yes-no* responses) and the later with interpersonal interactive situations (measured using the Social Anhedonia Scale, SAS, 45 items). These items were worded so that they cover long-standing characteristics of anhedonia throughout the lifetime (e.g. '*the taste of food has always been important to me*' for physical anhedonia, and '*Getting together with old friends has been one of my greatest pleasures*' for social anhedonia). The higher the score on both scales, PAS or SAS, means increased anhedonia in a particular subject. The reliable psychometric properties of both scales, especially the PAS, have been demonstrated in several studies, all of them reaching an internal consistency parameter over 0.80 [1, 10, 17]. Even though there is active and current usage in anhedonia studies of the PAS due to its trait-centered measurement and extensive content coverage, some limitations of the instrument are worth mentioning. The content of some items is outdated (e.g. "*I have always found organ music dull and unexciting*") and there is some content overlap between both instruments (e.g., *sex items are included in both instruments*). Furthermore, some items are worded negatively, so its rating can induce confusion. Finally the length of the administration (especially for the PAS) makes its usage not completely optimal in clinical settings. Interestingly, the anhedonia trait measured using the PAS in non-clinical populations offers a normal distribution, as has been reported in many studies.

Fawcett et al. [15] developed another self-reported psychometric instrument for the measurement of the *current hedonic state* known as the *Fawcett-Clark pleasure scale* (FCPS; 36 items, 5-point rating scale). In this case, the authors were interested in anhedonia as a temporary state conditioned by the severity of depression. This scale evaluates different situations like winning the lottery, sexual climax, a tender hug from spouse, etc. The higher the score on the test, the more vigorous was the hedonic capacity of the person.

Another well-known self-rated instrument is the Snaith-Hamilton Pleasure Scale (SHAPS, 14 items; 4-point agreement) originally developed to assess the hedonic tone or enjoyment in engaging certain common situations experienced during the last week (e.g. "*I would enjoy my favorite television or radio program*") in both clinical and non-clinical populations [23]. The instrument was designed to overcome some of the limitations of the PAS, for example its cultural bias and the length of its administration. The items selected cover four domains of hedonic experience: interests, social interaction, sensory experiences and food/drink pleasures. Higher scores indicate less hedonic tone, i.e. more anhedonic levels. A recent study demonstrated very good internal consistency of the SHAPS and the ability to discriminate between clinical and non-clinical individuals [24]. Albeit laudable, the author's effort to build a non-culturally biased instrument seems a difficult point to be attained given that pleasure, from its very experience to its continuous acquisition via learning, is always shaped by culture.

The self-reported instruments mentioned so far were designed to measure online hedonic capacity, i.e. the capacity to experience pleasure *per se* or what has been identified as *consummatory* pleasure. But the motivational aspects that guide goal-directed behavior and pleasure anticipation have been somewhat neglected at a psychometrical level. The Temporal Experience of Pleasure Scale (TEPS; 18-items, 6-point rating) represents an advance in this regard [25, 26]. These authors aimed to distinguish between the consummatory (e.g. "*I appreciate the beauty of a fresh snowfall*") and anticipatory components of pleasure (e.g. "*When ordering something off the menu, I imagine how good will it taste*") focusing exclusively on sensory and physical experiences. Higher scores on the both TEPS subscales indicate persons with high hedonic tone. The TEPS distinguishes individuals with a diminished ability to experience anticipatory pleasure from those with a consummatory pleasure deficit. There was only a 10 % of overlap in both subscales indicating the convenience of measuring distinctive aspects of the complex and multifaceted constructs of reward and hedonic capacity. Although its optimal length and advance in parsing reward phases, the final version of the TEPS seems to neglect some aspects central to pleasure and reward in humans (e.g. sex or eating your favorite meal are not included in the consummatory subscale). Furthermore it is unclear if the anticipatory factor of this scale is more centered in measuring the experience of pleasure when anticipating rewards than the construct of reward motivation, which is more related to its behavioral component (triggering reward-seeking behaviors).

Other anhedonia studies have used clinical depression scales to measure the construct of anhedonia. For example, some authors have used the Beck Depression Inventory, and more precisely the analysis of the four items related to pleasure experience and loss of interest [27, 28]. Other studies have used the item#17 of the Hamilton Depression Scale. Finally, another instrument used with similar aims is the Mood and Anxiety Symptom Questionnaire [29] that includes some items related to lowered positive affect and interest related to anhedonia aspects [30, 31]. The fact that these instruments were designed to measure depression severity in patients could clearly affect the measurement of this trait in healthy samples.

Finally an often cited confirmatory factor analysis conducted with some of the mentioned scales and some other symptom measures that aimed to measure hedonic capacity in depression, encountered three distinct latent variables; hedonic capacity, anxiety and depression [27]. These results demonstrated different loadings of the hedonic scales on the hedonic capacity factor, and for example, the SHAPS and the FCPS showed more communality with the factor of hedonic capacity than the PAS. One possible explanation provided by the authors relied on the fact that the PAS is a trait measure of enduring characteristics while the other scales are more centered in a short temporal domain (right now or in the last few days). Further research is clearly needed in this domain to improve the assessment of the complex concept of hedonic capacity.

11.4 Pleasure, Reward and Its Different Components: From Theoretical to Empirical Studies

Reward processing is not a unitary construct and can be divided into distinct psychological, neural, and neurochemical subcomponents to understand its functioning [32, 33]. At the psychological level, our desire to maximize rewards and to minimize negative possible outcomes is an important drive of human behavior and we are constantly trying to identify and seek possible cues in the environment which might predict the possible appearance of rewards or negative outcomes, as well as instrumental behaviors which could cause the appearance of these outcomes. The association of an event with a reward or a punishment therefore constitutes a powerful learning signal. In addition, we use information from the feedback signals elicited by our actions to influence our future decisions. However, in ambiguous situations in which different outcomes are probable or when feedback information is not available, humans might need to make decisions which can be considered risky, erratic or impulsive. Interestingly, the cognitive processes required for successful adaptation in these situations might require the elicitation of affective responses (emotional valuation), the ability to associate neutral events to the appearance of an emotionally-charged outcome (learning) and the ability to store this information in order to make predictions (memory). Importantly, this intersection between affective processes, learning and memory is a core aspect of reward processing, motivated behavior and decision making in humans [34].

At the neural level, the Brain Reward System (BRS) is an important extended neural network of cortical-subcortical structures and circuitries involved in the regulation of motivational states, anticipation and prediction of reward, the pleasure triggered by a sensory event and finally the modulation of this subjective experience via other complex cognitive processes [35]. Thus, an interaction from external and internal conditions is needed to fulfill what is currently known as reward processing. Some stimuli (i.e., primary reinforcers) have innate strong interactions with the BRS (e.g. food, liquids) while others (i.e., secondary reinforcers) are weakly related but have the potential to acquire their rewarding properties through a process of association and learning with a primary reinforcer (e.g. money, drugs) [34, 36]. The neural bases of the BRS have been well described by many studies during the last decade (see for review, [32, 34, 36–44]). The utilization of different neuroimaging techniques during reward processing have allowed the identification of increments of the hemodynamic signal in a common set of regions in the mesocorticolimbic circuits: The ventral striatum (including the nucleus accumbens, NAcc), the amygdala, prefrontal cortex (including the orbitofrontal cortex – OFC, ventromedial prefrontal cortex – VMPFC or the anterior cingulate cortex – ACC), as well as the hippocampal, hypothalamus and insular cortex [45, 46]. This network is not only implicated in reward consumption but in learning, memory and motivation processes (see Fig. 11.1 for a schematic differentiation between the reward-motivation circuit and the learning-memory subcomponents; from [48]).

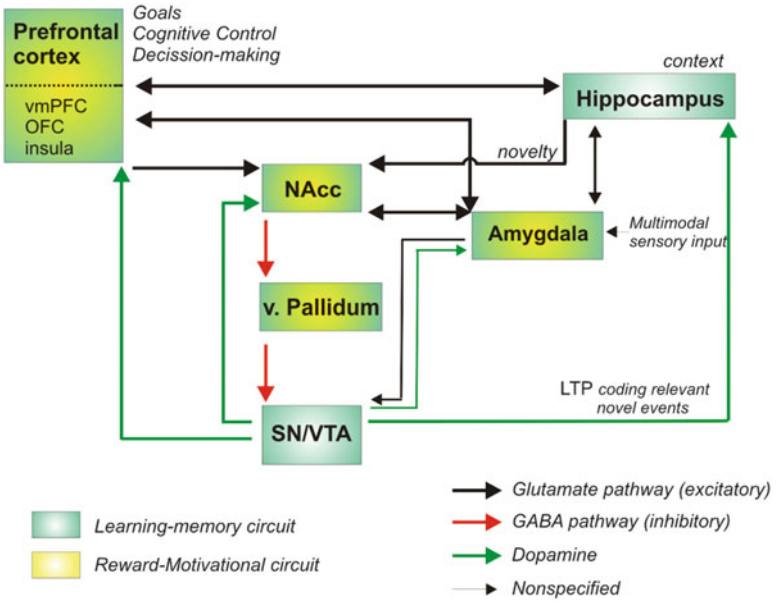

Fig. 11.1 Schematic representation of the principal structures involved in reward processing, their interconnectivity and principal neurotransmitter systems. The diagram shows the interaction between the reward processing networks with the regions involved both in learning and memory processes. *Green boxes* highlight the hippocampal-midbrain (VTA) learning-memory circuit described by Lisman and Grace [40]. The reward-motivational system has been adapted partially from Kelley [47] (*green-yellow boxes*) [Adapted from Ref. [34], *LTP* long-term potentiation, *v* ventral]

Figure 11.2 shows an illustration of the brain regions usually activated in monetary gambling tasks in which the outcome (monetary gains or losses) were unpredicted (see Fig. 11.2a). Notice that a broad network of brain regions are activated and that an extensive overlap is shown for the processing of both monetary gains and losses (Fig. 11.2b) (see [51] for a recent meta-analysis of the BRS). Advanced functional connectivity analyses in this study showed an extensive network of regions supporting similar responses to reward and punishment valuation including the insular cortex and OFC, the amygdala, the hippocampus and the SN/VTA midbrain regions. Besides, the crucial comparison between gains vs. losses showed the activation in one of the core regions of reward processing, the ventral striatum (including the NAcc; see also the reconstruction of the BOLD (Blood-Oxygenation-Level Dependent contrast) response for gains and losses in this region, Fig. 11.2c, d; [49]). The ventral striatum is an important center for the regulation of reward-appetitive and consummatory behaviors and its activity is modulated by (i) the presence of unpredicted positive and negative reward outcomes (e.g., monetary gains and losses) [48], (ii) when an expected reward is not received (decreasing its activation) and depending on the amount of the potential loss [52], (iii) anticipation of reward,

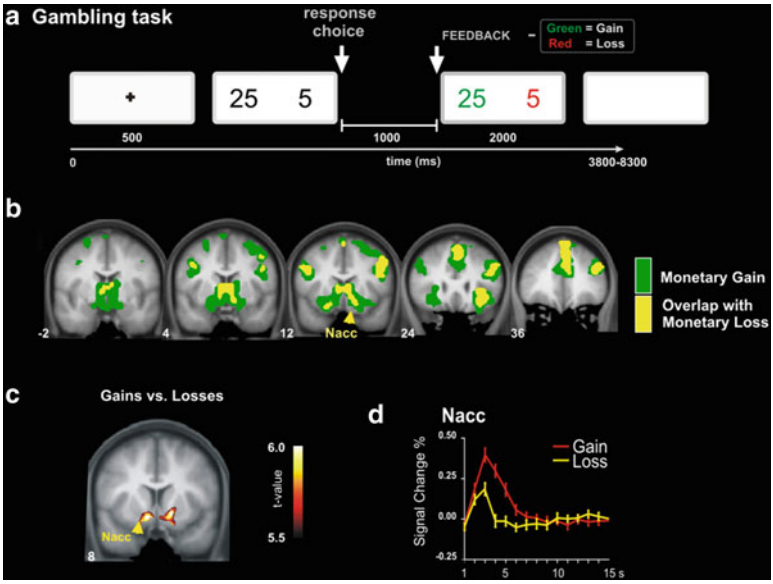

Fig. 11.2 (**a**) Sequence of stimulus and response events in the gambling task used in our laboratory for fMRI reward gambling studies [48–50]. After a warning signal, a pair or numbers ([5, 25] or [5, 25]) is presented and participants are forced to select one of the numbers by pressing the corresponding button with the left or right hand (response choice). One second after the choice, one of the numbers turn *red* and the other *green* (feedback) indicating, respectively, a loss (*red*) or gain (*green*) of the corresponding amount of money in Euro cents. (**b**) fMRI brain activations observed for monetary gains and monetary losses using the gambling paradigm (Adapted from Ref. [48]). Notice the large increase of activation observed in the ventral striatum (nucleus accumbens, NAcc), prefrontal cortex (including the orbitofrontal cortex – OFC, ventromedial prefrontal cortex – VMPFC or the anterior cingulate cortex – ACC) as well as insular cortex [48]. (**c**) Gain-versus-loss contrast superimposed on the group-averaged T1 MRI image in standard stereotactic space. On the right (**d**), representation of the BOLD time course reconstruction at the peak of the NAcc showing the differences in activation between gain and loss trials [49]

learning and motivation manipulations [34, 37, 43], and (iv) individual differences in the preferences of delayed versus immediate rewards [53]. The NAcc has also been implicated in addictive and impulsive decision making [54]. Notice, that the NAcc is a key integrative region weighting the different inputs coming from cortical areas (OFC, vmPFC – ACC, dorsolateral prefrontal cortex, insula), limbic regions (amygdala, hippocampus; [55]) and midbrain [substantia nigra (NS)/ventral tegmental area (VTA)] and therefore modulating the selection of appropriate responses and goal-directed behavior [39, 56, 57]. Moreover, the direct interactions of the medial prefrontal cortex (ACC) and the ventral striatum (both receiving dopamine input from the midbrain through the mesocortical and mesolimbic pathways, respectively) allow having interacting loops requested for the proper adjustment of behavioral patterns [58]. Indeed the VMPFC/ACC regions might have an important role integrating motivational and cognitive inputs into behavioral adjustments and decision making.

Currently one of the most influential approaches has been proposed by Berridge and collaborators [32, 35, 59]. These authors have introduced the distinction between "wanting" and "liking" components of reward based on a growing body of literature that shows different neural networks and neurotransmitters involved in consummatory and anticipatory phases of goal-directed motivation. The "liking" component is associated to the experience of pleasure, i.e. the hedonic impact of reward, while the "wanting" component is associated to the desire for pursue certain rewards and its anticipatory aspects (predictions about future rewards). For the "wanting" component, reward learning and reinforcement processes are crucial for remembering, updating and creating new associations and predictions (conscious goals) about future and potential rewards or desires based upon past experiences [32]. Dopamine has been proposed to be involved in both anticipatory and consummatory processes, although the current view favors the crucial role of this neurotransmitter in guiding reward prediction processes ("wanting" aspects) [59]. Indeed, recent research has shown that depletion of dopamine does not affect consummatory reactions, whereas the opioid and the gamma-aminobutyric acidergic systems in the ventral striatum are important in regulating the experiences of pleasure [60–63]. The "wanting" and "liking" components also belong to different temporal phases of motivated behavior [64]. The former is related with the appetitive, preparatory or anticipatory phases that are reflected in approach, instrumental or reward-seeking behaviors. In contrast, the "liking" component corresponds to a consummatory phase, that is, the actual interaction with the rewarding object (e.g., eating, drinking, etc.). Any impairment regarding any of the cited behaviors (e.g. a difficulty predicting the availability of an impending reward or an incapacity to integrate new sources of reward) could lead erroneously to the impression that a person is experiencing a simple loss of pleasure although the reward receipt/consumption could still be experienced as pleasurable [65].

Finally, it is important to mention that recent research has also highlighted the role of the amount of activation or invigoration of the organism in the anticipatory stages of motivated behavior in order to pursue particular desires or to engage in reward-seeking or goal-directed behaviors (see for a review, [43]). Indeed, this distinction between "activational" (vigor, persistence, maintancene of sustained activity) and "directional" (behaviors directed to a particular goal or stimulus) aspects of motivation is rather old in the field of psychology [66]. The activational aspects of motivated behavior are reflected in the amount of resources and substantial effort that can be invested in reward-seeking behaviors, especially considering that in some cases, there is a long temporal distance between the pursued goal and effort required to be sustained over long periods of time. Several studies have shown the importance of mesolimbic dopamine in the NAcc in the regulation of reward-related effort [43]. For example, it has been observed that in rats, dopamine depletion in the NAcc decreases the response for obtaining larger rewards that require more effort, but in contrast, it increased the amount of responses for smaller rewards that required less effort [67]. Similar results has been observed in humans, in which transient attenuation and potentiation of dopamine can decrease or increase the motivation to work for rewards [68, 69].

In summary, the most recent investigation of the behavioral and neural bases of reward-related behavior have provided a rich and multifaceted picture in which overlapped and distinct neural networks are involved in different subcomponents of reward processing as, for example, the hedonic impact of pleasurable experiences, affective valuation of rewards, reward anticipation, reward-seeking motivational aspects and the complex interaction between these processes in actual decision making.

11.5 Anhedonia in Brain Imaging Studies: Neural Substrates of Reward Parsing

Some studies have tried to link depression with a dysfunction relating the BRS, but only a few of them were focused exclusively on anhedonia. The majority of them present results obtained from depressed samples with high anhedonic symptoms. The tradition of studying anhedonia in the context of depressive disorders has been great in mental health and neuroscientific literature. In this section these studies will be briefly reviewed and presented chronologically (see Table 11.1 for a summary). In this manner, it is possible to show the evolution of the anhedonia-brain reward dysfunction hypothesis that runs from mere brain activation exploratory studies to new research oriented to connect specific brain regions and networks with more fine-grained subcomponents of reward (see previous section). It is worth mentioning that only three studies to our knowledge dealt with healthy populations in relation to the study of anhedonia and reward [30, 31, 72]. The existing literature of anhedonia in psychotic disorders and its relation to the BRS has increased significantly during recent years although the onset of this research approach has been slow compared to the study of MDD and reward (see [78–82]).

The first study to relate anhedonia with alterations in the BRS was conducted by Mitterschiffthaler and co-workers [70]. These authors wanted to explore whether anhedonia was related to a lack of activation in the brain regions related with pleasure or to abnormal overactivation in other regions. With this aim in mind, seven unipolar depressed female patients were compared to a control group while observing positive emotional stimuli inside the scanner. The results showed differential recruitment of frontal areas in the two groups when exposed to positive stimuli. Patients displayed significantly more activation in lateral OFC areas and the ACC than the control group. The authors argued that the frontal hyperactivation in high anhedonic patients might represent an attempt to experience positive emotions. Increased BOLD signal in the putamen was also encountered in the patient group, which was interpreted as a medication effect.

Two years later, Keedwell and cols. [71] explored anhedonia severity and its neural correlates in depressed individuals using an autobiographical memory task. Several structures related to reward processing were implicated in the processing of positive emotionally charged stimuli, as for example the VMPFC in higher anhedonic individuals. Those participants who felt happier as a reaction to positive

Table 11.1 Summary of the neuroimaging studies related to reward processing and anhedonia reviewed in the text

Study	Year	Sample	Technique	Anhedonia measure	Task	Activated regions in anhedonia
Mitterschiffthaler et al. [70]	2003	7 female depressed patients	fMRI	FCPS	IAPS Picture Attentive Observation	Increased activation in frontal lobes, thalamus, basal ganglia and insula
Keedwell et al. [71]	2005	12 MDD patients	fMRI	FCPS	Mood Provocation Paradigm (using autobiographical memories)	VMPFC and Anterior Caudate (in front of + stimuli)
Harvey et al. [72]	2007	29 non-clinical adults	fMRI/VBM	PAS	Emotional Memory Task as covert emotional processing using IAPS stimuli	VMPFC activation (for + stimuli) and volumetric reduction in the Anterior Caudate
Schlaepfer et al. [73]	2008	3 resistant MDD patients	PET	Subject Verbal Report	No task. Deep Brain Stimulation in NAcc (ventral striatum)	NAcc, Amygdala, DLPFC, DMPFC increased metabolism. Ventral and VLPFC decreased metabolism.
Heller et al. [74]	2009	27 MDD patients	fMRI	None	Emotion Regulation Paradigm by cognitive appraisal using IAPS stimuli	NAcc decreased activation across the task in front of positive stimuli. Reduced connectivity between NAcc and Left Middle Frontal Gyrus

Pizzagalli et al. [75]	2009	30 MDD patients	fMRI/VBM	BDI items referred to anhedonia	Monetary Incentive Delay Task	Left NAcc decreased activation when processing positive outcomes. Reduced Caudate volume bilaterally
Wacker et al. [31]	2009	33 non-clinical adults	Resting EEG/ fMRI/ Volumetry	MASQ-AD	Monetary Incentive Delay Task	NAcc decreased activation in front of + stimuli. NAcc volume reduction
Robinson et al. [76]	2012	13 MDD patients	fMRI	None	Reversal Learning Task	Right Putamen activation attenuated on unexpected rewards
Dowd et al. [77]	2012	29 patients with schizophrenia or schizoaffective disorders	fMRI	PAS and SAS	Pavlovian Reward Prediction Task	Decreased activation in the left ventral striatum and VMPFC during the anticipatory phase in patients who are higher in anhedonia. No differences between groups in the consummatory phase
Keller et al. [30]	2013	21 non-clinical adults	fMRI/Effective connectivity	PAS, SAS and MASQ-AD	Listening to familiar and unfamiliar musical pieces	Reduced reactivity and connectivity of the mesolimbic reward system. Decreased activation in NAcc, basal forebrain, hypothalamus, OFC and anterior insula

Notes: *FCPS* = Fawcett-Clarke Pleasure Scale, *BDI* = Beck Depression Inventory, *SAS* = Chapman Social Anhedonia Scale, *MASQ* = Mood and Anxiety Symptom Questionnaire, Anhedonia Depression Subscale

stimuli showed larger activation in the striatum (bilateral anterior caudate). The authors interpreted these findings considering that the frontal hyperactivity was due to an attempt to get into a happy mood particularly in the case of anhedonic participants [71]. According to more recent findings and the implication of the VMPFC in cognitive control and conflict monitoring [83, 84], we can also consider that this hyperactivation in highly anhedonic participants could be due to an increase in cognitive control due to the fact of viewing positive information; that is, the expected mood in front of the positive stimuli is not reached by the participant.

Harvey et al. [72] addressed the study of anhedonia as a trait in a non-clinical sample. Parallel to the previous study, participants underwent an emotional memory task [using the emotional pictures from the IAPS (International Affective Picture System)]. In agreement with previous studies, hyperactivation of the VMPFC in front of positive stimuli was found to be positively correlated with the anhedonia trait that was interpreted in the same vein as in the previous study. What's more, a volumetric reduction in the anterior caudate was also found, advocating for impairment in both motivational and hedonic systems [72]. The authors interpreted these results in relation to a possible dysfunction of the pleasure experience as well as a decreased willingness to engage in pleasurable activities. Thus, no differences between anticipation and consummation phases of reward processing were considered.

Schlaepfer et al. [73] reported that Deep Brain Stimulation into the reward circuitry ameliorated anhedonia symptoms in three patients affected with treatment resistant major depression. The patients received stimulation at increasing voltages for 7 days and were scanned 1 week before the stimulation and 1 week after it. The electrical stimulation was centered in the ventral striatum bilaterally. The results were obtained comparing the pre- and post-PET scans showing a significant increased metabolism in the NAcc, Amygdala, DLPFC, DMPFC and ACC. Additionally a decreased metabolism in each of the VLPFC, VMPFC, Dorsal Caudate and Thalamus was also observed. These results partially disagree with the hyperactivation pattern observed in prefrontal areas and hypoactivation of subcortical areas in depressed and highly anhedonic participants. Furthermore the authors of the study reported some immediate clinical effects of the stimulation in two of the participants of the study. These patients manifested 60 s after the stimulation their willingness to engage in exploratory pleasurable behaviors (e.g. visiting a monument and taking up bowling again) that contrasted with the severe lack of motivation during their depressive episodes. The authors highlighted the important role of the NAcc in reward seeking behaviors.

The described pattern of hyperactivation of prefrontal areas and hypoactivation of subcortical areas in relation to reward deficits has also been observed in a study comparing two different groups of healthy and anhedonic-depressed individuals during an emotion regulation paradigm in response to positive, neutral and negative images [74]. In this study, participants were told to use cognitive appraisal to enhance or suppress their emotional responses elicited by visual standardized stimuli. The authors hypothesized that this fronto-striatal network related to reward processing was also the area responsible for positive emotion regulation, and therefore anhedonia might reflect an inability to sustain positive affect over time. At the

neural level this impairment would be manifested in a difficulty to maintain the activation of the NAcc during the task, specifically in the condition of enhancing the emotional response in front of positive stimuli. The results confirmed the authors' predictions and anhedonic participants failed to sustain positive affect over time, reflecting a hypoactive fronto-striatal network that lead to abnormalities in reward processing and a general reduction in positive affect [74].

Interestingly, Pizzagalli and cols. [75] published for first time an fMRI study in which depressed-anhedonic individuals were presented with the Monetary Incentive Delay Task. This task is able to segregate the anticipatory and consummatory phases of reward processing, by first presenting a cue informing about the potential of receiving reward (monetary gain), punishment (monetary loss) or no-reward (no-incentive condition) and then later delivering the outcome (separated by a variable interval needed to allow for proper reconstruction of the BOLD response). The main results showed that depressed-anhedonic individuals displayed a decreased left NAcc activation when processing a positive outcome, during the consummation phase of reward processing. The authors claimed this finding could indicate a more primary deficit in hedonic coding. However no significant differences regarding reward anticipation were found in this study, with basal ganglia activations in this condition equal for both depressed and control participants. The authors also reported a bilateral reduction in the caudate nucleus for the depressed-anhedonic individuals that correlated with anhedonia severity scores. This result replicated a former study conducted with healthy high anhedonic participants previously mentioned [72].

Using the same Monetary Incentive task, the same research group conducted a follow-up study with healthy participants [31]. In this case different neuroimaging techniques were used (combining resting EEG frequency analysis, fMRI and volumetric techniques). Their results corroborated decreased NAcc responses to rewards and a reduction in NAcc volume was also found in accordance with the study of Harvey et al. [72]. This decrement during reward outcome processing lead the authors to interpret again that the differences in anhedonia were centered on the consummatory phase of reward processing, although findings in other studies using the same task defended the opposite hypothesis [85].

In a more recent study, Robinson and cols. [76] centered their aims on studying learning in depression. Although the focus of their research was depression and its cognitive and affective biases, these results are also relevant for a more thorough understanding of anhedonia symptomology and its relation with the BRS. Thirteen MDD patients and a control group were scanned while performing a reversal learning task. In each trial of the task, participants were presented with two squares, one of which was highlighted with a black border. One of the stimuli was associated with a reward and the other with a punishment. Participants were endeavored to predict whether the highlighted stimulus was related with a reward or a punishment. The trials were grouped in different mini-blocs (i.e. the rewarded stimuli was consecutively the same during some trials ranging from 4 to 6 correct responses in a row) including a variable number of reversal trials (changes in the rewarded stimuli). These reversal contingencies were marked with an unexpected reward or punishment

that was interspersed along the task. The analysis of the hemodynamic signal during these trials revealed no differences between groups during unexpected punishments. On the contrary, on unexpected rewards depressed individuals displayed diminished right putamen activation. The authors believed that this hypoactivation may be related to the impaired ability to derive pleasure from rewarding activities, i.e. the anhedodnic symptoms, and also a reduced dopaminergic release.

Recently also, Dowd and Barch [77] published a study conducted with schizophrenic patients. A Pavlovian Reward Prediction Paradigm was used where participants had to choose between two stimuli predicting if it was going to lead to a receipt of 75 cents or 0 cents. There was a cue-outcome association known by the participant, so one of the stimuli was rewarded 75 % of the time. This task permitted the dissociation between reward anticipation and consummation, i.e. the anticipatory and consummatory reward processing phases respectively. Interestingly, the results showed little activation differences between clinical and control groups during both experimental conditions. Those patients with higher anhedonia scores showed reduced left ventral striatal and VMPFC activations during the anticipatory phase. For the reward consummatory phase (outcome receipt), no differences were found between groups. Thus, these results point out an equal capacity to experience reward in the schizophrenic group (consummatory phase). However negative correlations between anhedonia and some brain activations were found to be significant, for example, higher physical anhedonia was associated with less ventral striatal and VMPFC activation during the anticipation of rewards.

A new study recently published [30] was conducted with healthy participants with no psychiatric history. In this case the authors examined brain responses and effective connectivity of the mesolimbic reward system in relation to the anhedonia trait. The authors used music pieces for the fMRI task, specifically 3 fragments of likely familiar music and 3 fragments of likely unfamiliar pieces that had been used in previous studies. The authors encountered that anhedonia had an impact in the reactivity and connectivity of the mesolimbic and paralimbic structures involved in reward processing. More precisely, the anhedonia trait was negatively correlated with activations of NAcc, basal forebrain and hypothalamus. Other areas related to the processing of salient emotional stimuli were also hypoactive in higher anhedonic individuals, as for example the OFC cortex and anterior insula.

In summary, the present review of neuroimaging studies points out a clear influence of anhedonia in the activation of several regions in the BRS network. Although the results might appear contradictory in some cases, it is clear that this research approach, studying the activation of this neural network involved in reward processing, can help to understand the specific impairments observed in anhedonia and in the different hedonic and motivational reward components. Further studies are needed with carefully selected and larger samples of clinical and sub-clinical populations and using more advanced and fine-grained behavioral tasks that permit a clear dissociation of the different reward components. One of the main problems of the previous studies is that different paradigms have been used, for example, autobiographical events, viewing pictures, receiving performance feedback, different rewards with time-pressure constraints, decision making, etc. An effort is needed

to use systematic well-validated experimental paradigms in order to firmly draw conclusions on the effects of depression and anhedonia on reward dysregulation.

11.6 Anhedonia Reward and Motivation

Interestingly to our aim, recent work in experimental economics [86] and decision making [87] suggests that there are large inter-individual differences with regard to the way we deal with rewards and punishments of different magnitudes in certain situations. Indeed, individual differences in the capacity to experience pleasure could be linked to a possible dysfunction in the reward and motivation systems as has been proposed for depression [71, 75, 88, 89]. However, unravelling which aspect of reward processing is altered in anhedonia is a current concern. The dissociation between consummatory and anticipatory processes suggests a specific deficit in keeping internal representations of possible rewarding experiences active, and therefore reducing the possibilities to correctly direct actions. Indeed, this notion is consistent with a recent neuroimaging study [74] showing that depression may not be solely due to a tonic reduction in the capacity to experience pleasure, but to the inability to sustain positive affect and reward responsiveness over time. Concurrent with this idea, in an excellent review, Treadway and Zald [89] have recently argued for the distinction between "consummatory anhedonia" (deficits in the hedonic responses) and "motivational anhedonia" (diminished motivation to pursue hedonic responses), which is based on the previous conceptualization of "liking" and "wanting" processes in reward processing.

This dissociation observed between reward consumption and the changes observed in motivational approach-behavior could help to understand the origin of the individual differences observed in anhedonia in sub-clinical populations. In this sense anhedonics usually show diminished motivation to engage in goal-directed behaviors and to use information about potentially rewarding events. This distinction is critical to better understand individual differences regarding hedonic experiences in clinical populations. Previous studies with schizophrenic patients suggested that while the experience to engaging in enjoyable activities seems to be more or less preserved [25, 90], these patients report less anticipatory pleasure in goal-directed activities that could potentially allow them to obtain desired rewarding experiences [91]. Moreover, two recent clinical studies of anhedonia and depression in a college student population primarily reflect low levels of anticipation of reward and a tendency to accurately estimate their enjoyment of future rewards [92, 93]. Moreover, several studies in depressed patients have shown relatively normal self-rated experience of encounters with pleasurable stimuli suggesting a preserved hedonic capacity to experience a primary reinforcer (see for a review, [89]). For example, across four studies on the "sweet taste test", which is one of the measures used for evaluating hedonic capacity, no differences were observed between depressed patients and matched control participants [94–97]. These findings give support to the idea that anhedonia in clinical settings might be a consequence of deficits in motivation and anticipatory but not consummatory pleasure.

Besides, reward and learning brain systems are inherently interconnected (see above, Fig. 11.1a), which could explain the differences in motivation approach-behavior patterns and decision making observed in anhedonics and the development of different learning patterns across life. Previous studies have shown that depressed patients tend to focus on negative rather than positive aspects of their lives [98, 99] and that they have experienced less positive reinforcements along their life [100]. These results suggest that anhedonics might show increased attention in risky situations (that could potentially result in a punishment) and less expectation of receiving positive feedback. In line with classic theories of depression [101], anhedonics might have a lower propensity to perceive reality in an optimistic fashion and consequently avoid occasions that could potentially be highly positive and pleasurable. Indeed a very prominent cognitive theory of depression emphasizes the role of dysfunctional negative schemas or attitudes in biasing the processing of feedback information [102].

In this concern and in agreement with the importance of anhedonia in taking risks or motivational-approach behaviors, a recent study demonstrated that schizophrenic patients with high levels of anhedonia are less prone to explore uncertain environments, probably due to their prior negative expectations and reduced sensitivity to assess opportunities that could be better than expected [103]. Moreover, in examining the effects of negative feedback on subsequent performance it has been shown that depressed and anhedonic participants show abnormal responses to negative feedback [104–107] and had attenuated trial-by-trial changes in reaction after reward and punishment trials [108]. These attenuated adjustments observed in patients or anhedonic participants might be associated either to inefficiency in using feedback knowledge to monitor their performance or alternatively to an inherent lack of motivation to obtain potential positive rewards with the consequence of not experimenting the same drive to improve their performance along the task.

Importantly, for the present review, while the studies presented before in which metabolic or hemodynamic brain techniques (PET or fMRI) have been used to unravel the emotional impact of reward in clinical and sub-clinical anhedonic populations, these studies are certainly blind to the temporal dynamics of anticipatory and consummatory brain activity. Other neuroimaging techniques as for example, Event-related brain potentials or Time-frequency analysis of electroencephalographic activity are more suited.

11.7 Electrophysiological Responses Associated to Reward Processing

In humans, electrophysiological (Event-Related Brain Potentials, ERPs) studies have identified several components that specifically indicate the processing of negative outcomes, such as negative feedback, monetary loss, or the detection of performance errors, as well as positive outcomes, such as monetary gains and positive feedback. With regard to negative outcomes, a negative deflection over frontocentral

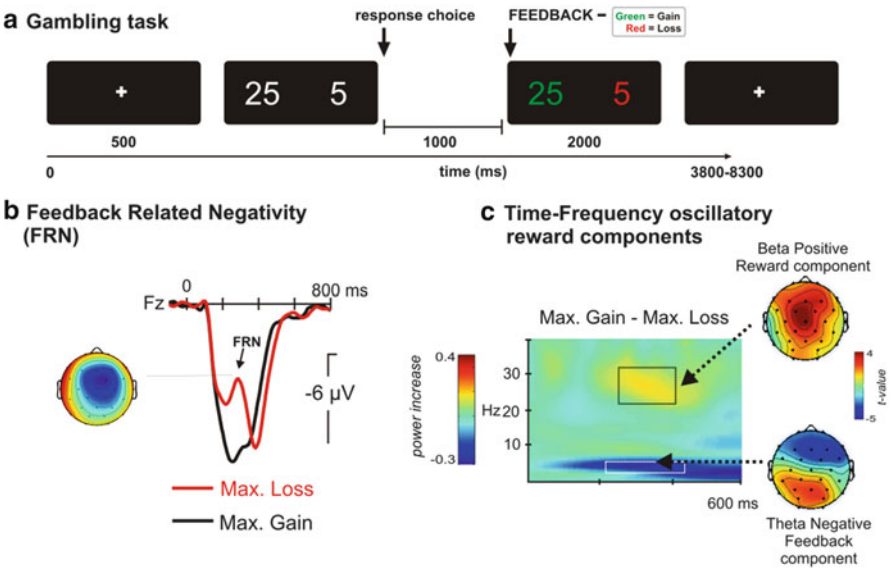

Fig. 11.3 (**a**) Illustration of the monetary gambling paradigm used to evaluate reward processing in several ERPs studies from our laboratory [109–111] (see previous figure for an explanation). (**b**) ERPs associated to monetary gains (*black line*) and monetary losses (*red line*) at a frontal-central electrode location (Fz). Notice the increase of the negativity in monetary loses compared to gains observed at about 250 ms, which is called *Feedback Related Negativity* (FRN) [58, 112, 113]. The topographical scalp distribution of the FRN (*blue* means increase of negative voltage in μV and *red* represents positive voltage values) is depicted, showing a clear fronto-central distribution of the FRN which is compatible with the location of the component near the VMPFC/ACC [114]. (**c**) Time-Frequency oscillatory analysis resulting from the contrast of monetary gains vs. monetary loses. Loses show a clear increase of power (*blue* color scale) between 4 and 6 Hz (*theta oscillatory band*), while gains presented an increase in oscillatory activity between 20 and 30 Hz (hot color scale, which is in the range of Beta-Gamma component [110, 115]). It is mentioned in the text that this Theta oscillatory increase as associated with the processing of monetary losses or negative feedbacks and that Beta-Gamma oscillatory increases are associated with monetary gains or the processing of positive feedback

scalp locations (see Fig. 11.3a), known as Feedback Related Negativity (FRN) [58] or Medial Frontal Negativity (MFN) [112], has been described peaking at 250–300 ms after the presentation of a negative feedback or monetary losses in a gambling task (see for a recent review, [116]). The neural sources of this component have been located in the anterior and the posterior cingulate cortex [114]. The dynamics of the FRN have been explained using the reinforcement learning theory (RL theory; [58, 117]), which proposes that when an action produces a worse than expected consequence (e.g. an error in a selection task or a loss in a gambling task) there is a decrease in the mesencephalic midbrain dopaminergic activity that is transmitted to the anterior cingulate cortex (ACC) through the mesocortical pathway (see for a recent review, [118]). Thus the FRN has been related to midbrain dopaminergic modulations of a reinforcement learning system that evaluates events to guide

reward-seeking behavior. This ERP component is thought to reflect the degree of negative prediction error, a signature of when events are worse than expected [58, 119]. Accordingly, these dopaminergic reinforcement learning signals in the ACC might help the organism to cope with potential cognitive conflicts arising from previous expectations and unexpected outcomes. Thus, ACC might enhance action monitoring and control processes that will help to improve task performance and to increase the adjustment of further decision making processes [58, 83, 84].

It is important to bear in mind that the FRN component has been consistently associated to medial frontal *theta* oscillatory activity (4–8 Hz) [109, 120–122]. It has been proposed that increases of medial-frontal theta component may represent a general top-down mechanism operating over expectation violation and behavioral adaption in order to improve performance and learning [120, 123–127]. Consistent with this idea many studies have shown the involvement of medial-frontal *theta* oscillations in error monitoring [115, 121, 128], processing of negative experiences [110, 129], rule/expectation violations [123, 125] and in the computation of prediction errors in service of behavioral adaption and learning [126, 127, 129].

Finally, recent studies from our laboratory and others have found a power enhancement of high frequency beta-gamma (27–32 Hz, 270–310 ms) oscillatory activity associated to the processing of positive feedback or outcomes [109, 121, 126, 129, 130] (see Fig. 11.3c), sensitive to the reward magnitude [121], and probability [129]. For example, in a recent study we showed that unexpected large monetary gains elicited a larger increase in the power of this beta-gamma oscillatory component [130]. In humans, consummatory behavior (drinking) was associated with an increase in cortical EEG beta power [131]. Animal studies have also observed an increase of beta activity in the striatum after reward delivery [132]. These studies together suggest that beta-gamma oscillatory activity might be a potential neural signature of consummatory reward processing. Due to the large network involved in the processing of reward and positive affect (see Fig. 11.2b), our group has proposed that beta activity orchestrates reward processing through such aforementioned fronto-striatal circuits [110, 130].

In summary, crucially for the evaluation of the neural dynamics of reward processing, two electrophysiological components have been well delineated during the last decade: (i) the *Feedback-related negativity* and its underlying *Theta-oscillatory activity* which has been related to the processing of negative outcomes (e.g., monetary losses) and unexpected negative consequences of our actions; and (ii) *Beta-Gamma oscillatory activity* related to the processing of positive feedback events related to our actions (e.g., monetary gains).

11.8 Electrophysiological Studies Associated to Reward Processing and Anhedonia

Recently in our lab we evaluated the neurophysiological dynamics of reward processing using EEG in a carefully selected group of highly anhedonic participants (using the PAS physical anhedonia scale) [111]. From a large group of university

participants, we selected two groups of extreme PAS scores: (i) the anhedonic group (PAS mean anhedonia score, 26.0 ± 3.2 (standard deviation)) and (ii) a non-anhedonic group (highly hedonic participants; PAS mean value of 3.4 ± 1.2). Notice that the anhedonic group show high values of the anhedonia trait considering that in major depression samples, normal values of the PAS scale are close to 37 (see for example, [133]). In our study, we applied the previous ERP methodology in a very simple gambling task (based on [48, 121]; see Fig. 11.3a for the design), in which participants were requested to choose the amount of money they wanted to gamble in each trial (either choosing a small amount, 5 euro cents or a large amount, 25 euro cents). Participants randomly received positive or negative feedback about their decisions, informing them if they had won or lost the amount of money they had gambled. The instructions of the task requested participants to make an effort to gain as much money as possible, however the monetary gains and losses were assigned randomly. Thus, no rule or pattern was able to be discovered in order to increase the amount of monetary gains; both groups received equal amount of monetary gains and losses and gained equal amount of money. Using this task, we were able to evaluate two important aspects using the previous electrophysiological signature detailed in the previous section: (i) if the emotional impact of monetary gains and losses was similar across groups (consummatory aspects), and (ii) to which degree, depending on the expectations generated by participants during the task, the ERP and Time-Frequency modulations observed could reflect different anticipatory or motivational-approach patterns to the current task.

One of the most important results of this study was the lack of electrophysiological differences observed in the consummatory responses in anhedonics in reward processing for monetary gains and losses. In Fig. 11.4a we can for example observe the ERP pattern for both groups and for the monetary gains and monetary losses (when the feedback they received informed them that they had lost or won 25 euro cents). Notice the large similarity in both cases, for the Feedback related component (FRN) as well as for the increased positive component (P300) associated to the processing of monetary gains. In a similar fashion, no differences were observed for the positive-feedback related oscillatory component, the beta-band, in both groups (see Fig. 11.4b, where we depicted the difference between gains and losses in both groups). These results suggest normal processing of positive and negative outcomes in a monetary gambling task for highly anhedonic participants and concur with previous findings of intact hedonic responses in anhedonic and depressive patients [95, 134, 135]. The lack of differences in the FRN in our study for anhedonic participants somehow contrast with previous studies using similar ERP components in depression. For example, an association was encountered between the amplitude of the FRN and depression and stress scores in a recent study using a large group of undergraduate students [136]. However, the opposite results have been observed in others studies [137, 138]. In the study by Foti and Hajcak [136] the authors used a gambling task and it was observed that the amplitude of a principal component associated to the FRN (using the difference of non-reward vs. reward trials) was inversely related to depression and stress scores (the correlation value was relatively small, $r = .23$). The authors suggested that the FRN reduction in response to monetary loses in individuals with increased levels of depression could be driven by

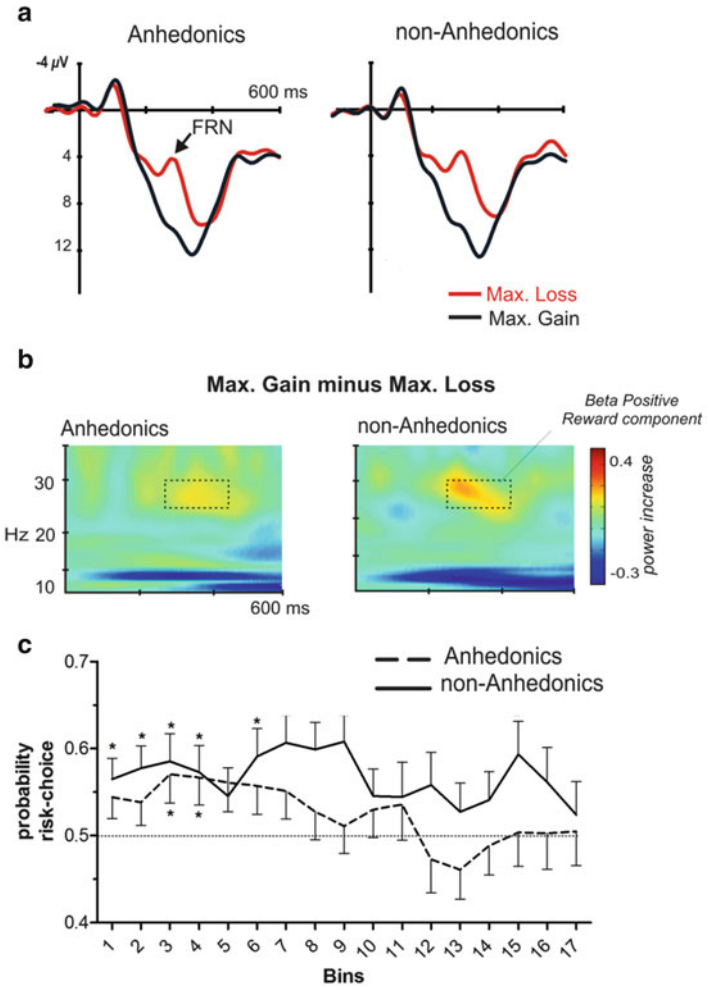

Fig. 11.4 (**a**) Grand average ERPs at frontal electrodes for Anhedonic and non-Anhedonic individuals regarding large monetary rewards and large monetary losses. Notice the similarity in both groups of the FRN component, indexing the evaluation of negative outcomes and the subsequent positive component (P300), associated to the processing of monetary gains (From Ref. [111]). (**b**) Time-frequency analysis showing the power change with respect to baseline between large monetary gain and large monetary loss at frontal electrodes. No differences between both groups were observed for the positive feedback-related oscillatory component in the beta-band (28–32 Hz, highlighted by the dotted square). (**c**) Evolution of the risky choices (choosing 25 euro cents instead of 5) across the whole task. Each bin is composed of 40 trials (mean proportion of choosing 25 in that particular bin). The *soft grey line* corresponds to the chance level ($p = 0.5$). The *asterisks* represent a serial one-sample t-test in which the 25/5 proportion was significantly above the chance level expected. Notice that a clear tendency exists in the non-Anhedonic group to show significant increases of risk along the task, when compared to the Anhedonic group

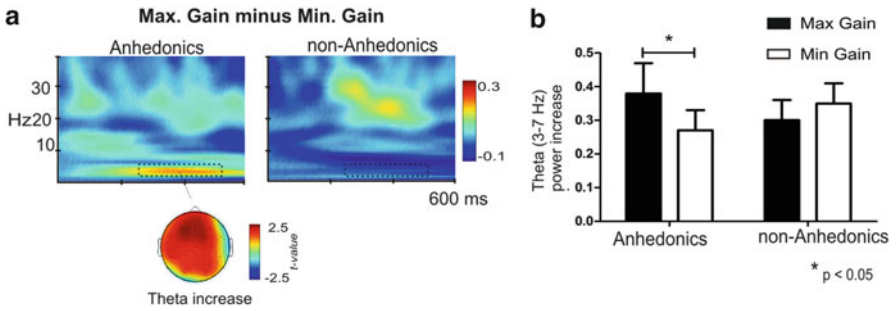

Fig. 11.5 (**a**) Medial-frontal theta oscillatory activity for the difference Maximum or large Gain minus Minimum or small Gains in Anhedonic and non-Anhedonic groups at frontal electrodes and the topographical distribution of the theta-related activity (3–7 Hz) [111]. Notice that a theta increase was observed for the Anhedonic group with a clear fronto-central scalp distribution. (**b**) Graphic representation (*t*-test comparison) of the difference between Maximum Gains and Minimum Gains in both groups. The figure highlights the increase of the theta band in the 250–450 ms time range for the Anhedonic group after receiving unexpected large monetary rewards (Max. Gain condition)

biased expectations for negative outcomes. In any case, although anhedonia is a core symptom of depression, it is difficult to compare our results with the ones obtained in clinical studies with depressive patients or in similar studies as the one from Foti and Hajcak, as other important factors affecting depression scores could be responsible for the differences observed in the FRN amplitude.

The most interesting aspect of this study is that we observed an unpredicted increase in theta-oscillatory activity after the processing of large gains only in the anhedonic group (see Fig. 11.5a, b). This is an interesting finding as the increase in theta-activity, as we explained above, has normally been reported exclusively for the processing of negative feedback, monetary losses, erroneous responses or the violation of current expectations (see [123]), but not for monetary gains. Thus considering that this medial-frontal theta component has been observed also in relation to an increase in cognitive control and conflict detection [84, 124] as well as the computation of expectancy deviation of the predicted outcome of the current action [120, 123, 125, 139, 140], we interpreted this finding as a violation of negative expectations in anhedonic participants created across the task. In this sense, when a large gain or positive outcome is received in these participants it might elicit an internal conflict between prior negative expectations and the unexpected positive outcome, increasing cognitive control and showing as a corresponding increase in theta activity. What's more, we found that this increase in the theta component was larger for monetary gains that were preceded by a prior large monetary gain. In this sense, receiving a large gain probably reduced the expectancy of sequentially receiving another large reward, and therefore increased the amount of conflict experienced (increase in theta) when receiving the large monetary gain in the subsequent trial. This interpretation is consistent with previous studies showing a tendency in depressive patients to create negative expectations about future events [98, 99].

In this sense anhedonia could be related to the difficulty of sustaining positive expectations over time about the outcomes of current actions [74, 89].

More evidence of this negative bias in the anhedonic group was shown when the behavioral risk pattern was analyzed in this group. As it is shown in Fig. 11.4c, the group of anhedonic participants showed a reduced tendency to make risky choices (gambling the largest amount instead for the smaller one) during the course of the task. This less risky pattern in anhedonics might restrict the possibility of obtaining larger monetary gains. Indeed this behavioral pattern concurs very well with the results obtained from the psychometric assessment of the susceptibility to avoid possible negative events (evaluated using the BIS/BAS scales [141] and the Sensitivity to Punishment and Reward questionnaire, SPSRQ [142]). Anhedonic participants characterized themselves as strongly willing to avoid possible punishment and therefore have a marked behavioral tendency to choose non-risky patterns. Overall these results are coherent with the negative bias hypothesis in anhedonics about future rewards and their impediment to sustain positive expectations about the results of their own actions. These results also agree with previous findings showing that anhedonia and depression are associated to certain incapacity to appropriately use feedback knowledge to monitor and improve their own performance [108]. Similarly, depressive individuals presume that negative outcomes are more likely for their actions in more uncertain situations [98, 99, 102] and might be less prone to perceive reality in an optimistic way and consequently avoid occasions that could potentially be highly positive and rewarding [101, 102]. In this regard and in agreement with the importance of anhedonia in risk-taking, a recent study demonstrated that schizophrenic patients with high levels of anhedonia are less prone to explore uncertain environments, probably due to their prior negative expectations and reduced sensitivity to assess opportunities that could be better than expected [103]. In the same vein it has been demonstrated that unmedicated depressed individuals display an impaired tendency to modulate behavior as a function of previous rewards indicating a lack of capacity to integrate a reinforcement history over time [143].

Interestingly, one of the first psychophysiological studies of the anhedonia trait [144] used slow-cortical related potentials and heart-rate responses to investigate the effects of anhedonia (measured using the PAS scale) during the anticipation of neutral (e.g., a folding chair) or emotionally interesting stimuli (e.g., a sexual-related slides). In this paradigm, an auditory warning stimuli (6 s duration) informed participants about the emotional category (neutral or high-interest) of the color slide that was about to appear. Normally, high interest events elicit a marked acceleration of heart rate and an increase in the amplitude of the Contingent Negative Variation (CNV), which is a slow frequency cortical ERP component. The CNV has been related to the amount of motivation, preparation or attentional anticipation to the appearance of the next informative stimuli (or emotional feedback). The most interesting finding was that anhedonic participants (with a mean PAS score of 27) showed diminished amplitude of the CNV in the high interest emotional condition when compared to the non-anhedonic or control participants (mean PAS score of 10). Indeed, no difference was observed

in the CNV amplitude between neutral and high-interest emotional anticipation in the anhedonic group while waiting for the presentation of the stimuli. Thus this study seems to be in agreement with the results presented above and point out the possibility that anhedonia reflects the inability or lack of desire to approach or anticipate pleasurable activities rather than consummatory pleasure (see [95, 134, 135, 145]). Overall these results suggest that once in a pleasurable situation, anhedonic individuals might experience as much pleasure from the situation as non-anhedonic individuals.

Finally, results from Padrao and co-workers [111] are also in concurrence with a recent study in which patients with MDD showed motivational and decision-making deficits evidenced using a new experimental task (Effort Expenditure for Rewards Task, EEfRT) that evaluated motivation and effort-based decision making [133]. MDD patients showed less willingness to expend effort with the aim of gaining larger amount of money when compared to healthy controls (see also [146], for similar results in healthy anhedonic participants). These results fit well with the risky avoidance pattern shown in Fig. 11.4c in our anhedonic participants and points to the crucial involvement of anticipatory and motivation reward-related processes in anhedonia and MDD. Similar results were presented by Sherdell and collaborators [93] and showed that MDD patients did not differ in their "liking" ratings of humorous and non-humorous cartoons but differed in the amount of effort invested in obtaining certain rewards and therefore on their anticipatory pleasure.

In relation to the hypothesis of effort and motivation deficits in anhedonics, early ERP studies were focused on the study of subtle cognitive and attentional deficits in highly anhedonic participants. For example, Miller et al. [147] used an auditory (tone) discrimination task and found that anhedonia was related to the difficulty in correctly using memory templates for correct discrimination. In this study, the authors observed enhanced amplitude of the N200 component in anhedonic participants suggesting a difficulty to habituate to previous presented auditory information (see for a replication, [148]). The authors argued that anhedonics processed each tone as novel events without showing repetition or familiarity effects. These results were somehow in agreement with existing interpretations at that moment regarding the cognitive deficits observed in schizophrenia, as for example, (i) perceptual gating problems, (ii) difficulty in forming sets of memory templates, (iii) difficulty in habituating to sensory stimuli and (iv) difficulty in the execution of automatic processes pertinent to sensory stimuli (see [148]).

Moreover, several ERP studies proposed that anhedonic participants show problems correctly allocating their attentional resources to simultaneous tasks (see [149]; see also [150–152]). In this sense, these studies concur with reductions of effortful cognitive processing in anhedonic participants [133, 146]. In agreement with this, a systematic trend has been observed in anhedonic participants that shows a reduction in the amplitude of the endogenous ERP component P300, which has been associated to effortful-attentional and decision-making processes [153] as well as contextual memory updating processes (see for example, [144, 147, 149, 150, 152, 154, 155]). However, this result is not completely consistent

in the literature and several studies have not encountered the reduction in the amplitude of P300 in anhedonic participants [111, 148, 156]. A possible explanation for the differences between these studies could be related to the different amount of effort and attentional control across the tasks, the effect being larger in those studies in which the task needed greater amounts of attentional resources due to complexity [147, 150, 157]. Further studies are needed to test the hypothesis of an overall deficit of attentional location in anhedonic participants, evaluating more systematically different levels of complexity and effort in different cognitive tasks as well as more specific evaluations of the different neural attention networks that have been recently proposed (see [158]). Finally, previous ERP studies [157, 159] have also shown evidence of intact early stimulus information processing (using stimulus-related exogenous ERP components, for example, the N1 and P2 components in auditory processing or the N2 in auditory oddball tasks) in anhedonic participants. These studies ruled out the possible influence of anhedonia in early information processing stages (but see for contradictory evidence in the auditory domain, [148, 154]).

Overall, the ERP studies reviewed above tend to suggest an important role of anhedonia in modulating reward anticipation and motivation. One interesting line of research, and following the early findings of Simons et al. [144] using slow ERP components (CNV), might be to investigate more carefully the temporal and time-frequency EEG dynamics of anticipatory periods during reward or learning tasks. In this regard, in two recent new studies of our group, we observed that a slow ERP component, the Stimulus Preceding Negativity (SPN; see for a review, [160]), could be used to track on-line the amount of anticipation built-up while waiting for a desired reward [161] as well as evaluating the temporal dynamics of the learning process in a trial-by-trial associative learning task [162]. In the study of Fuentemilla and co-workers [161], they showed a clear increase in the amplitude of this slow-ERP component, the SPN, in situations in which the appearance of a highly desired reward was very unlikely, compared to other outcomes that were more probable and equally desirable. Thus using this paradigm, we could evaluate to what extent, very unexpected but highly desired rewards, could show differences between anhedonics and non-anhedonics participants in anticipatory reward phases. In the second study, we investigated if this component, the SPN, could be used as a possible correlate of information expectation during associative learning. The results of this study showed that the SPN offers a reliable ERP component to measure on-line the cognitive processes that take place while waiting for forthcoming feedback, which might be crucial for successful learning. In both cases, the benefit of the ERPs in relation to its temporal sensitivity can clearly help to understand the amount of attention and emotional impact of anhedonic participants during anticipatory-reward phases. We believe that using this strategy, which is very well suited to ERPs, might help to understand better the impact of anhedonia in the temporal dynamics of the anticipatory phases of reward learning and reward processing.

11.9 Conclusions and Research Agenda

The studies reviewed here show clearly that a thorough understanding of anhedonia, traditionally seen as a unified concept, and its psychopathological implications require a distinction between consummatory and anticipatory reward components (see also [89]). From the electrophysiological data presented in relation to reward processing and previous behavioral studies reviewed, anhedonia seems to be characterized by a tendency to create negative expectations towards upcoming reward events, which might be reflected in an elevated avoidance of risky decisions, increased sensitivity to negative events and less capacity to appropriately integrate feedback knowledge and past learning experiences to increase the chances of obtaining positive outcomes [108, 146]. Importantly, no electrophysiological differences were observed due to anhedonia in reward processing of positive or negative outcomes which speaks in favor of preserved consummatory reward processing [111]. Therefore, anhedonic participants might have an intact hedonic capacity but an impairment in anticipating future positive outcome rewards that makes their engagement in pleasurable activities less likely. New research should be devoted to properly studying the implication of the multifaceted construct of anhedonia and its clinical symptoms in distinct reward-based subcomponents, for example the evaluation of the hedonic experience (pleasure effects), affective valuation of the possible rewards, anticipatory and motivational processes and finally the integration of these processes in actual decision-making. We believe that the incorporation of more fine-grained and sophisticated temporally sensitive techniques such as the ERPs will help in future to understand the neurobiological basis of reward-related dysfunctions and will allow the design of more effective treatments and preventive interventions.

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References

1. Shankman SA, Nelson BD, Harrow M, Faull R. Does physical anhedonia play a role in depression? A 20-year longitudinal study. J Affect Disord. 2010;120(1–3):170–6.
2. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology. 2004;29(10):1765–81.
3. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol Psychiatry. 2005;57(4):319–27.
4. Berrios GE, Olivares JM. The anhedonias: a conceptual history. Hist Psychiatry. 1995;6:453–70.
5. Meehl P. Hedonic capacity: some conjectures. Bull Menninger Clin. 1975;39:297–307.
6. Loas G. Vulnerability to depression: a model centered on anhedonia. J Affect Disord. 1996;41(1):39–53.

7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Revised 4th ed. Washington, DC: American Psychiatric Association; 2000.
8. World Health Organization. The ICD-10 classification of mental and behavioral diseases. Geneva: WHO; 1992.
9. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull. 2008;36(2):359–69.
10. Horan WP, Reise SP, Subotnik KL, Ventura J, Nuechterlein KH. The validity of psychosis proneness scales as vulnerability indicators in recent-onset schizophrenia patients. Schizophr Res. 2008;100(1–3):224–36.
11. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:22.
12. Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. Mol Psychiatry. 2011;16(6):604–19.
13. Bogdan R, Pizzagalli DA. The heritability of hedonic capacity and perceived stress: a twin study evaluation of candidate depressive phenotypes. Psychol Med. 2009;39(2):211–8.
14. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636–45.
15. Fawcett J, Clark DC, Scheftner WA, Gibbons RD. Assessing anhedonia in psychiatric patients. Arch Gen Psychiatry. 1983;40(1):79–84.
16. Clark DC, Fawcett J, Salazar-Grueso E, Fawcett E. Seven-month clinical outcome of anhedonic and normally hedonic depressed inpatients. Am J Psychiatry. 1984;141(10): 1216–20.
17. Herbener ES, Harrow M. The course of anhedonia during 10 years of schizophrenic illness. J Abnorm Psychol. 2002;111(2):237–48.
18. Herbener ES, Harrow M, Hill SK. Change in relationship between anhedonia and functional deficits over 20-year period in individuals with schizophrenia. Schizophr Res. 2005;75:97–105.
19. Blanchard JJ, Bellack AS, Mueser KT. Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. J Abnorm Psychol. 1994;103(4):719–28.
20. Katsanis J, Iacono WG, Beiser M, Lacey L. Clinical correlates of anhedonia and perceptual aberration in first-episode patients with schizophrenia and affective disorder. J Abnorm Psychol. 1992;101(1):184–91.
21. Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS. The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. Schizophr Bull. 2007;33(1):49–68.
22. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374–82.
23. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995;167(1):99–103.
24. Franken IH, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). J Affect Disord. 2007;99(1–3):83–9.
25. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93(1–3):253–60.
26. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers Study. 2006;40:1086–102.
27. Leventhal AM, Chasson GS, Tapia E, Miller EK, Pettit JW. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. J Clin Psychol. 2006;62(12):1545–58.
28. Pizzagalli D, Sherwood R, Henriques J, Davidson R. Frontal brain asymmetry and reward responsiveness: a source-localization study. Psychol Sci. 2005;16(10):805–13.
29. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol. 1995;104(1):3–14.

30. Keller J, Young CB, Kelley E, Prater K, Levitin DJ, Menon V. Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. J Psychiatr Res. 2013;47(10):1319–28.
31. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage. 2009;46(1):327–37.
32. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008;199(3):457–80.
33. Kringelbach ML, Berridge KC. The functional neuroanatomy of pleasure and happiness. Discov Med. 2010;9(49):579–87.
34. Camara E, Rodriguez-Fornells A, Ye Z, Munte TF. Reward networks in the brain as captured by connectivity measures. Front Neurosci. 2009;3(3):350–62.
35. Berridge KC, Kringelbach ML. Building a neuroscience of pleasure and well-being. Psychol Well Being Theory Res Pract. 2011;1:3.
36. Panksepp J. Affective neuroscience: the foundations of human and animal emotions. New York: Oxford University Press; 1998.
37. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35(1):4–26.
38. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci. 2002;22(9):3306–11.
39. Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiol Behav. 2005;86(5):773–95.
40. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron. 2005;46(5):703–13.
41. McClure SM, York MK, Montague PR. The neural substrates of reward processing in humans: the modern role of FMRI. Neuroscientist. 2004;10(3):260–8.
42. Robbins TW, Everitt BJ. A role for mesencephalic dopamine in activation: commentary on Berridge (2006). Psychopharmacology (Berl). 2007;191(3):433–7.
43. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron. 2012;76(3):470–85.
44. Wise RA. Brain reward circuitry: insights from unsensed incentives. Neuron. 2002;36(2): 229–40.
45. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci. 2001;21(16):RC159.
46. Yacubian J, Glascher J, Schroeder K, Sommer T, Braus DF, Buchel C. Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. J Neurosci. 2006;26:9530–7.
47. Kelley AE. Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron. 2004;44(1):161–79.
48. Camara E, Rodriguez-Fornells A, Munte TF. Functional connectivity of reward processing in the brain. Front Hum Neurosci. 2009;1(19):1–14.
49. Camara E, Rodriguez-Fornells A, Munte TF. Microstructural brain differences predict functional hemodynamic responses in a reward processing task. J Neurosci. 2010;30(34):11398–402.
50. Camara E, Kramer U, Cunillera T, Marco-Pallares J, Cucurell D, Nager W, Mestres-Missé A, Bauer P, Schule R, Schols L, Tempelmann C, Rodriguez-Fornells A, Munte T. The effects of COMT (Val108/158Met) and DRD4 (SNP-521) dopamine genotypes on brain activations related to valence and magnitude of rewards. Cereb Cortex. 2010;20(8):1985–96.
51. Sescousse G, Caldu X, Segura B, Dreher JC. Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. Neurosci Biobehav Rev. 2013;37(4):681–96.
52. Tom SM, Fox CR, Trepel C, Poldrack RA. The neural basis of loss aversion in decision-making under risk. Science. 2007;315(5811):515–8.
53. Hariri AR, Brown SM, Williamson DE, Flory JD, de Wit H, Manuck SB. Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. J Neurosci. 2006;26(51):13213–7.

54. Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci. 2005;8(2):147–8.
55. Groenewegen HJ, Wright CI, Beijer AV, Voorn P. Convergence and segregation of ventral striatal inputs and outputs. Ann N Y Acad Sci. 1999;877:49–63.
56. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward leaning, or incentive salience? Brain Res Rev. 1998;28:309–69.
57. Goto Y, Grace AA. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci. 2005;8(6):805–12.
58. Holroyd CB, Coles MG. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychol Rev. 2002;109(4):679–709.
59. Berridge KC. Motivation concepts in behavioral neuroscience. Physiol Behav. 2004;81(2): 179–209.
60. Barbano MF, Cador M. Opioids for hedonic experience and dopamine to get ready for it. Psychopharmacology (Berl). 2007;191(3):497–506.
61. Burgdorf J, Pankseep J. The neurobiology of positive emotions. Neurosci Biobehav Rev. 2006;30:173–87.
62. Richardson DK, Reynolds SM, Cooper SJ, Berridge KC. Endogenous opioids are necessary for benzodiazepine palatability enhancement: naltrexone blocks diazepam-induced increase of sucrose-'liking'. Pharmacol Biochem Behav. 2005;81:657–63.
63. Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci. 2007;27:1594–605.
64. Zald DH, Zatorre RJ. Music. In: Gottfried JA, editor. Neurobiology of Sensation and Reward. Boca Raton: CRC Press; 2011.
65. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35(1):68–77.
66. Toates FM. Motivational systems. Cambridge CB2 (UK): Cambridge University Press; 1986.
67. Salamone JD, Cousins MS, Bucher S. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. Behav Brain Res. 1994;65(2):221–9.
68. Venugopalan VV, Casey KF, O'Hara C, O'Loughlin J, Benkelfat C, Fellows LK, Leyton M. Acute phenylalanine/tyrosine depletion reduces motivation to smoke cigarettes across stages of addiction. Neuropsychopharmacology. 2011;36(12):2469–76.
69. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. J Neurosci. 2011;31(46):16597–602.
70. Mitterschiffthaler MT, Kumari V, Malhi GS, Brown RG, Giampietro VP, Brammer MJ, Suckling J, Poon L, Simmons A, Andrew C, Sharma T. Neural response to pleasant stimuli in anhedonia: an fMRI study. NeuroReport. 2003;14(2):177–82.
71. Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005;58(11):843–53.
72. Harvey PO, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry 2007;12(8):703, 767–03, 775.
73. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, Joe AY, Kreft M, Lenartz D, Sturm V. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology. 2008;33(2):368–77.
74. Heller AS, Johnstone T, Shankman AJ, Sharee NL, Peterson MJ, Kolden GG, Kalin NH, Davidson RJ. Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. Proc Natl Acad Sci U S A. 2009;106(52):22445–50.
75. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Losifescu DV, Rauch SL, Fava M. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166:702–10.
76. Robinson OJ, Cools R, Carlisi CO, Sahakian BJ, Drevets WC. Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. Am J Psychiatry. 2012;169(2):152–9.

77. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. PLoS One. 2012;7(5):e35622.
78. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry. 2010;67(10):902–11.
79. Morris RW, Vercammen A, Lenroot R, Moore L, Langton JM, Short B, Kulkarni J, Curtis J, O'Donnell M, Weickert CS, Weickert TW. Disambiguating ventral striatum fMRI-related BOLD signal during reward prediction in schizophrenia. Mol Psychiatry 2012;17(3):235, 280–35, 289.
80. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B. Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. Psychopharmacology (Berl). 2009;206(1):121–32.
81. Walter H, Heckers S, Kassubek J, Erk S, Frasch K, Abler B. Further evidence for aberrant prefrontal salience coding in schizophrenia. Front Behav Neurosci. 2010;3:62.
82. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, Rose EJ, Gold JM, Stein EA. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. Neuropsychopharmacology. 2010;35(12):2427–39.
83. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. Psychol Rev. 2001;108:624–52.
84. Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. Science. 2004;306(5695):443–7.
85. Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wustenberg T, Villringer A, Knutson B, Kienast T, Gallinat J, Wrase J, Heinz A. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology (Berl). 2006;187(2):222–8.
86. Glimcher PW. Indeterminacy in brain and behavior. Annu Rev Psychol. 2005;56:25–56.
87. Schall JD. Decision making. Curr Biol. 2005;15(1):R9–11.
88. Nestler EJ, Carlezon WA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006;59(12):381–91.
89. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35(3):537–55.
90. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. Schizophr Bull. 2008;34(5):819–34.
91. Barch DM, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr Bull. 2010;36(5):919–34.
92. Chentsova-Dutton Y, Hanley K. The effects of anhedonia and depression on hedonic responses. Psychiatry Res. 2010;179(2):176–80.
93. Sherdell L, Waugh CE, Gotlib IH. Anticipatory pleasure predicts motivation for reward in major depression. J Abnorm Psychol. 2011;2.
94. Amsterdam JD, Settle RG, Doty RL, Abelman E, Winokur A. Taste and smell perception in depression. Biol Psychiatry. 1987;22(12):1481–5.
95. Berlin I, Givry-Steiner L, Lecrubier Y, Puech AJ. Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. Eur Psychiatry. 1998;13:303–9.
96. Dichter GS, Smoski MJ, Kampov-Polevoy AB, Gallop R, Garbutt JC. Unipolar depression does not moderate responses to the Sweet Taste Test. Depress Anxiety. 2010;27(9):859–63.
97. Kazes M, Danion JM, Grange D, Pradignac A, Simon C, Burrus-Mehl F, Schlienger JL, Singer L. Eating behavior and depression before and after antidepressant treatment: a prospective, naturalistic study. J Affect Disord. 1994;30(3):193–207.
98. Lloyd GG, Lishman WA. Effect of depression on the speed of recall of pleasant and unpleasant experiences. Psychol Med. 1975;5:173–80.
99. Nelson RE, Craighead WE. Selective recall of positive and negative feedback, self-control behaviors, and depression. J Abnorm Psychol. 1977;86:379–88.
100. Lewinsohn PM, Youngren MA, Grosscup SJ. Reinforcement and depression. In: Depue A, editor. The psychobiology of depressive disorders: implications for the effects of stress. New York: Academic; 1979.

101. Alloy L, Abramsom L. Judgement of contingency in depressed and nondepressed students: sadder but wiser? J Exp Psychol Gen. 1979;108:441–85.
102. Beck A. Cognitive theory of depression. New York: Wiley; 1979.
103. Strauss GP, Frank MJ, Waltz JA, Kazanova Z, Herbener ES, Gold JM. Deficits in positive reinforcement learning and uncertainty-driven exploration are associated with distinct aspects of negative symptoms in schizophrenia. Biol Psychiatry. 2011;69(5):424–31.
104. Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. Psychol Med. 1996;26(3):591–603.
105. Elliott R, Sahakian BJ, Michael A, Paykel ES, Dolan RJ. Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression. Psychol Med. 1998;28:559–71.
106. Shah PJ, O'Carroll RE, Rogers A, Moffoot AP, Ebmeier KP. Abnormal response to negative feedback in depression. Psychol Med. 1999;29:63–72.
107. Steffens DC, Wagner HR, Levy RM, Horn KA, Krishnan KR. Performance feedback deficit in geriatric depression. Biol Psychiatry. 2001;50(5):358–63.
108. Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. Brain. 2007;130(Pt 9):2367–74.
109. Marco-Pallares J, Cucurell D, Cunillera T, Kramer UM, Camara E, Nager W, Bauer P, Schule R, Schols L, Munte TF, Rodriguez-Fornells A. Genetic variability in the dopamine system (dopamine receptor D4, catechol-O-methyltransferase) modulates neurophysiological responses to gains and losses. Biol Psychiatry. 2009;66(2):154–61.
110. Marco-Pallares J, Cucurell D, Cunillera T, Garcia R, Andres-Pueyo A, Munte TF, Rodriguez-Fornells A. Human oscillatory activity associated to reward processing in a gambling task. Neuropsychologia. 2008;46(1):241–8.
111. Padrao G, Mallorqui A, Cucurell D, Marco-Pallares J, Rodriguez-Fornells A. Neurophysiological differences in reward processing in anhedonics. Cogn Affect Behav Neurosci. 2013;13(1):102–15.
112. Gehring WJ, Willoughby AR. The medial frontal cortex and the rapid processing of monetary gains and losses. Science. 2002;295(5563):2279–82.
113. Miltner W, Braun C, Coles M. Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a generic neural system for error detection. J Cogn Neurosci. 1997;9:788–98.
114. Muller S, Moller J, Rodriguez-Fornells A, Munte T. Brain potentials related to self-generated and external information used for performance monitoring. Clin Neurophysiol. 2005; 116:63–74.
115. Cohen MX. Error-related medial frontal theta activity predicts cingulate-related structural connectivity. Neuroimage. 2011;55(3):1373–83.
116. Walsh MM, Anderson JR. Learning from experience: event-related potential correlates of reward processing, neural adaptation, and behavioral choice. Neurosci Biobehav Rev. 2012;36(8):1870–84.
117. Luque D, Lopez FJ, Marco-Pallares J, Camara E, Rodriguez-Fornells A. Feedback-related brain potential activity complies with basic assumptions of associative learning theory. J Cogn Neurosci. 2012;24(4):794–808.
118. Schultz W. Behavioral dopamine signals. Trends Neurosci. 2007;30(5):203–10.
119. Nieuwenhuis S, Yeung N, Holroyd C, Schurger A, Cohen J. Sensitivity of electrophysiological activity from medial frontal cortex to utilitarian and performance feedback. Cereb Cortex. 2004;14(7):741–7.
120. Cavanagh JF, Frank MJ, Klein TJ, Allen JJB. Frontal theta links prediction errors to behavioral adaption in reinforcement learning. Neuroimage. 2010;49:3198–209.
121. Marco-Pallares J, Camara E, Munte TF, Rodriguez-Fornells A. Neural mechanisms underlying adaptive actions after slips. J Cogn Neurosci. 2008;20(9):1595–610.
122. Trujillo LT, Allen JJ. Theta EEG dynamics of the error-related negativity. Clin Neurophysiol. 2007;118:645–68.
123. Cavanagh JF, Figueroa CM, Cohen MX, Frank MJ. Frontal theta reflects uncertainty and unexpectedness during exploration and exploitation. Cereb Cortex. 2012;22(11):2575–86.

124. Cunillera T, Fuentemilla L, Periañez J, Marco-Pallares J, Kramer UM, Camara E, Munte TF, Rodriguez-Fornells A. Brain oscillatory activity associated with task switching and feedback processing. Cogn Affect Behav Neurosci. 2012;12(1):16–33.
125. Tzur G, Berger A. Fast and slow brain rhythms in rule/expectation violation tasks: focusing on evaluation processes by excluding motor action. Behav Brain Res. 2009; 198(2):420–8.
126. van de Vijver I, Ridderinkhof KR, Cohen MX. Frontal oscillatory dynamics predict feedback learning and action adjustments. J Cogn Neurosci. 2011;23(12):4106–21.
127. Womelsdorf T, Johnston K, Vinck M, Everling S. Theta-activity in anterior cingulate cortex predicts task rules and their adjustments following errors. Proc Natl Acad Sci U S A. 2010;107(11):5248–53.
128. Luu P, Tucker DM, Makeig D. Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. Clin Neurophysiol. 2004;115(8): 1821–35.
129. Cohen MX, Elger CE, Ranganath C. Reward expectation modulates feedback-related negativity and EEG spectra. Neuroimage. 2007;35(2):968–78.
130. HajiHosseini A, Rodriguez-Fornells A, Marco-Pallares J. The role of beta-gamma oscillations on unexpected reward processing. Neuroimage. 2012;60:1678–85.
131. Hallschmid M, Molle M, Fisher S, Born J. EEG synchronization upon reward in man. Clin Neurophysiol. 2002;113(1059):1065.
132. Courtemanche R, Fuji N, Graybiel AM. Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. J Neurosci. 2003;23:11741–52.
133. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J Abnorm Psychol. 2012;121(3):553–8.
134. Berenbaum H, Snowhite R, Oltmanns TF. Anhedonia and emotional responses to affect evoking stimuli. Psychol Med. 1987;17(3):677–84.
135. Germans MK, Kring AM. Hedonic deficit in anhedonia: support for the role of approach motivation. Pers Individ Differ. 2000;28:659–72.
136. Foti D, Hajcak G. Depression and reduced sensitivity to non-rewards versus rewards: evidence from event-related potentials. Biol Psychol. 2009;81(1):1–8.
137. Santesso DL, Steele KT, Bogdan R, Holmes AJ, Deveney CM, Meites TM, Pizzagalli DA. Enhanced negative feedback responses in remitted depression. NeuroReport. 2008;19(10): 1045–8.
138. Tucker DM, Luu P, Frishkoff G, Quiring J, Poulsen C. Frontolimbic response to negative feedback in clinical depression. J Abnorm Psychol. 2003;112(4):667–78.
139. Matsumoto M, Matsumoto K, Abe H, Tanaka K. Medial prefrontal cell activity signaling prediction errors of action values. Nat Neurosci. 2007;10:647–56.
140. Oliveira FT, McDonald JJ, Goodman D. Performance monitoring in the anterior cingulate is not all error related: expectancy deviation and the representation of action-outcome associations. J Cogn Neurosci. 2007;19:1994–2004.
141. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol. 1994;67(2):319–33.
142. Torrubia R, Ávila C, Molto J, Caseras X. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers Individ Differ. 2001;31:837–62.
143. Pizzagalli DA, Losifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. J Psychiatr Res. 2008;43(1):76–87.
144. Simons RF, MacMillan III FW, Ireland FB. Anticipatory pleasure deficit in subjects reporting physical anhedonia: slow cortical evidence. Biol Psychol. 1982;14(3–4):298–310.
145. Klein D. Depression and anhedonia. In: Clark DC, Fawcett J, Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA; 1984. p. 1–14.

146. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. PLoS One. 2009;4(8):e6598.
147. Miller GA. Information processing deficits in anhedonia and perceptual aberration: a psychophysiological analysis. Biol Psychiatry. 1986;21(1):100–15.
148. Giese-Davis JE, Miller GA, Knight RA. Memory template comparison processes in anhedonia and dysthymia. Psychophysiology. 1993;30(6):646–56.
149. Yee CM, Miller GA. A dual-task analysis of resource allocation in dysthymia and anhedonia. J Abnorm Psychol. 1994;103(4):625–36.
150. Dubal S, Pierson A, Jouvent R. Focused attention in anhedonia: a P3 study. Psychophysiology. 2000;37(5):711–4.
151. Hazlett EA, Dawson ME, Filion DL, Schell AM, Nuechterlein KH. Autonomic orienting and the allocation of processing resources in schizophrenia patients and putatively at-risk individuals. J Abnorm Psychol. 1997;106(2):171–81.
152. Simons RF, Russo KR. Event-related potentials and continuous performance in subjects with physical anhedonia or perceptual aberrations. J Psychophysiol. 1987;2:27–37.
153. Strayer DL, Kramer AF. Attentional requirements of automatic and controlled processing. J Exp Psychol Learn Mem Cogn. 1990;16:67–82.
154. Franken IH, Van Strien JW, Nijs IM. Effect of hedonic tone on event-related potential measures of cognitive processing. Psychiatry Res. 2006;142(2–3):233–9.
155. Josiassen RC, Shagass C, Roemer RA, Straumanis JJ. Attention-related effects on somatosensory evoked potentials in college students at high risk for psychopathology. J Abnorm Psychol. 1985;94(4):507–18.
156. Ward PB, Catts SV, Armstrong MS, McConaghy N. P300 and psychiatric vulnerability in university students. Ann N Y Acad Sci. 1984;425:645–52.
157. Yee CM, Deldin PJ, Miller GA. Early stimulus processing in dysthymia and anhedonia. J Abnorm Psychol. 1992;101(2):230–3.
158. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 2002;3(3):201–15.
159. Bruder GE, Tenke CE, Towey JP, Leite P, Fong R, Stewart JE, McGrath PJ, Quitkin FM. Brain ERPs of depressed patients to complex tones in an oddball task: relation of reduced P3 asymmetry to physical anhedonia. Psychophysiology. 1998;35(1):54–63.
160. Brunia CH, Hackley SA, van Boxtel GJ, Kotani Y, Ohgami Y. Waiting to perceive: reward or punishment? Clin Neurophysiol. 2011;122(5):858–68.
161. Fuentemilla L, Cucurell D, Marco-Pallares J, Guitart-Masip M, Moris J, Rodriguez-Fornells A. Electrophysiological correlates of anticipating improbable but desired events. Neuroimage. 2013;78:135–44.
162. Moris J, Luque D, Rodriguez-Fornells A. Learning-induced modulations of the stimulus-preceding negativity. Psychophysiology. 2013;50(9):931–9.

Chapter 12
Anhedonia in Mouse Models of Methamphetamine-Induced Drug Seeking Behavior

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Abstract Mood enhancement induced by drugs of abuse, such as methamphetamine, is often followed by a period during which the mood state is depressed. This state is termed drug-induced withdrawal dysphoria. Desire to avoid this dysphoric state during withdrawal motivates drug seeking behavior to alleviate withdrawal symptoms, even in anticipation of those symptoms (e.g. negative reinforcement), and maintains drug seeking behavior in addicted individuals. The state associated with methamphetamine (METH) withdrawal has been characterized as a depressive-like syndrome characterized by dysphoria, anhedonia, anxiety, akinesia, self-injurious behavior, social inhibition and suicidal ideation. A core manifestation of the depressive symptoms of this state is anhedonia, defined as a diminished interest in or pleasure from rewarding stimuli. In human drug abusers it is difficult to dissociate pre-existing depressive symptoms from drug withdrawal-induced symptoms or exacerbation of existing symptoms. This may be particularly true for anhedonia, which may lead individuals to seek out stimuli that more strongly activate reward systems. Medication for the treatment of dysphoric and anhedonic states will be important for addiction treatment in METH abusers. There are currently no effective treatments for METH abuse, or for METH-induced withdrawal dysphoria or anhedonia. We have recently developed a mouse model of anhedonia in which social isolation reduces responses to a reinforcing stimulus (e.g. anhedonia), a state that is reversed by a type of environmental enrichment (i.e. a running wheel). These observations suggest that alleviation of METH-induced withdrawal dysphoria in mice may be effectively achieved by altering environmental conditions. This chapter considers this model and compares it to other models of anhedonia and considers the role that anhedonia may play in the maintenance of drug-seeking behavior.

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Abbreviations

ACTH	Adrenocorticotropic hormone
AMPH	Amphetamine
BDNF	Brain-derived neurotrophic factor
CB_1 receptor	Cannabinoid receptor 1
CCI	Chronic constriction injury
CMS	Chronic mild stress
DAT	Dopamine transporter
DISC1	Disrupted-in-Schizophrenia-1
EAAT2	Excitatory amino acid transporter 2
FH	Fawn-Hooded
FSL	Flinders sensitive line
GABA	γ-aminobutyric acid
GLT-1	Glial glutamate transporter 1
GluN1	Glutamate receptor, ionotropic, N-methyl-D-aspartate ζ1 subunit
Grin1	Same as GluN1
HPA	Hypothalamic-pituitary-adrenal
ICSS	Intracranial self-stimulation
LH	Learned helplessness
METH	Methamphetamine
NAc	Nucleus accumbens
NET	Norepinephrine transporter
NMDA	N-methyl-D-aspartate
NR1	Same as GluN1
SD	Sprague-Dawley
SERT	Serotonin transporter
VGLUT1	Vesicular glutamate transporter 1
WKY	Wistar-Kyoto

12.1 Introduction

Methamphetamine (METH) is a powerfully addictive psychomotor stimulant drug that is commonly abused by humans, and one of the more commonly abused amphetamine-(AMPH) related compounds. METH abuse is associated with substantial health and social problems resulting from both acute and chronic METH use [1–3]. The behavioral effects of METH include increased wakefulness, increased respiration, increased body movement, hyperthermia, euphoria, and decreased

appetite, and can also include psychotomimetic effects [4–7]. Many of these effects are often followed by a period in which the opposite effects are observed, including a period during which mood is depressed, termed drug-induced withdrawal dysphoria [8–10]. In some cases, avoidance of this dysphoric state during withdrawal motivates drug-seeking behavior to alleviate withdrawal symptoms, even in the anticipation of those symptoms [6, 8]. Indeed, the negative reinforcement associated with alleviation of this state may be more important for drug seeking behavior in later stages of addiction than positive reinforcement [11]. Despite this possibility, the negative reinforcing effects of drugs of abuse have been modeled in animals to only a limited extent. Drug withdrawal is also characterized by a more general malaise, generally reminiscent of depressive symptomatology, manifested by reduced activity, social interaction and anhedonia [8, 9, 12]. Anhedonia is a core manifestation of these depressive symptoms, defined as a diminished interest in, or derivation of pleasure from, rewarding stimuli [13–15]. METH abusers may commonly suffer from these severe symptoms during treatment for their addiction in part because they cease METH use as a part of treatment. Although it is common to treat some withdrawal symptoms in addicts undergoing treatment, the particular treatments often depending on the particular substance that is abused, effective treatments for dysphoria and anhedonia are lacking. Such symptoms may also be experienced periodically by METH users in between bouts of METH use, during the development of their addiction. This may indeed be an important part of the development of METH addiction, and a major factor driving continued METH use. Thus medication for the treatment of anhedonic and dysphoric states associated with METH withdrawal will be important for addiction treatment in METH abusers, as well as other negative consequences of their addiction and withdrawal [16]. To date there have been a few clinical trials that have attempted to alleviate these symptoms in AMPH users, albeit with very limited benefits, using the antidepressants mirtazapine, reboxetine, fluoxetine, and imipramine [17–19]. Thus, to date, there remain no effective pharmacotherapies for treating the full range of METH-induced withdrawal symptoms, including anhedonia [20, 21].

One complicating factor is that anhedonia is a core feature of schizophrenia and affective illnesses, as well as being experienced by drug addicts during drug withdrawal [22, 23]. When these symptoms present in METH users it is difficult to determine whether they result from comorbid and pre-existing psychiatric conditions or whether they result from drug withdrawal. This difficulty is overcome in animal models, although most models of anhedonia have focused on anhedonia associated with depression, not drug withdrawal. Dysphoria and anhedonia associated with METH withdrawal, despite their potential importance for treatment of METH abuse, have received relatively little attention compared to the psychotic symptoms associated with chronic METH use that include paranoia, hallucinations, delusions and bizarre behaviors [2]. Animals that exhibit behavioral features similar to affective illnesses like depression after pharmacological, environmental or genetic manipulations are used to study anhedonia and to identify anti-anhedonic drugs [24–28]. We have recently developed a mouse model of anhedonia in which social isolation reduces responses to reinforcing stimuli (e.g. anhedonia), a state

that is reversed by a type of environmental enrichment (i.e. a running wheel) [29]. These observations suggest that alleviation of METH-induced withdrawal dysphoria in mice may be produced by environmental manipulations. This chapter considers this model and compares it to other models of anhedonia and considers the role that anhedonia may play in drug-seeking behavior.

12.2 Animal Models of Anhedonia

This section aims to shed light on the validity and limitations of current animal models of anhedonia, or animal models in which anhedonic symptoms are observed. The observation of anhedonia is often part of a larger constellation of behaviors associated with depressive- and anxiety-like states, which include a variety of motivational, emotional and cognitive symptoms. Operationally these behaviors include, among others, decreases in preference/consumption of palatable solutions or foods, decreased sexual behavior, reduction of self-administration of drugs of abuse, increased immobility time in forced swim test, decreased general and/or rearing locomotion in open field test, decreased alternation behavior in T-maze test, and decreased total time spent in one quadrant where a platform has been set during training sessions in Morris water maze. There are many types of models that can induce anhedonic symptoms, of which those involving drug withdrawal are a subclass. Anhedonia has been characterized for a variety of different reinforcers, most commonly sucrose. Either consumption of a single concentration is measured, which does not allow an unequivocal assessment of anhedonia, or consumption at multiple concentration are measured, an anhedonic response being indicated by a rightward shift in the concentration-consumption relationship. In a few cases operant sucrose consumption has been measured using a progressive ratio schedule, which more unequivocally establishes the presence of anhedonia. Intracranial self-stimulation has also been used in this context, although, as discussed below, this has been used primarily to assess the effects of drug withdrawal induced anhedonia. The relationship between anhedonic-like phenotypes and abused-drug reward will be considered after a more general discussion of models of anhedonia. Table 12.1 summarizes findings from studies that have examined the animal models of anhedonia or that include anhedonic outcomes.

12.2.1 Stress-Induced Anhedonia

Chronic mild stress (CMS) is a procedure used widely in rats to induce depressive-like symptoms and to test for antidepressant efficacy. A number of CMS procedures have been validated by measuring depressive-like phenotypes, including a hedonic deficit most often characterized as a rightward shift in sucrose consumption curves, as well as deficits in cognitive behavior which resemble aspects of clinical

Table 12.1 Experimental results from animal models that produce depression- and anhedonic-like phenotypes

Experimental paradigm	Species	Phenotype, evaluation	References
Chronic mild stress	Rat	Anhedonia, Sucrose preference↓	[41]
	Rat	Anhedonia, ICSS thresholds↓	[43]
	Rat	Anhedonia, Sucrose preference↓	[42]
	Rat	Anhedonia, Sucrose preference↓	[37]
	Rat[a]	Anhedonia, Sucrose preference↓	[38]
	Rat[a]	Anxiety, # of center visits (OFT)↓	[38]
	Mouse	Anhedonia, Sucrose preference↓	[49]
	Rat	Anhedonia, Sucrose preference↓	[34]
	Rat	Anhedonia, Sucrose preference↓	[35]
	Rat	Anhedonia, Sucrose preference↓	[36]
	Rat	Depression, Immobility time (FST)↑	[36]
	Rat	Anhedonia, Sucrose preference↓	[46]
	Rat[b]	Anhedonia, Sucrose preference↓	[53]
	Rat[c]	Depression, Immobility time (FST)↑	[53]
	Mouse[d]	Anhedonia, Sucrose preference↓	[47]
	Rat	Anhedonia, Sucrose preference↓	[44]
	Rat	Cognitive dysfunction, # of SAB (Y-maze)↓	[44]
	Mouse	Anhedonia, Sucrose preference↓	[48]
	Mouse	Depression, Immobility time (FST)↑	[48]
	Mouse	Depression, Immobility time (TST)↑	[48]
	Mouse	Anxiety, NSF↓	[51]
	Rat	Anhedonia, Sucrose preference↓	[28]
	Rat	Anhedonia, Sucrose preference↓	[27]
	Rat	Anhedonia, Sweet food preference↓	[26]
	Mouse	Depression, Immobility time (TST)↑	[52]
Repeated social defeat	Mouse	Depression, Social contact↓	[56]
	Mouse	Depression, Social contact↓	[64]
	Rat[e]	Anhedonia, Sucrose preference↓	[63]
	Rat[e]	Anhedonia, Cocaine self-administration↓	[63]
	Rat[f]	Anhedonia, Sucrose preference↓	[62]
	Mouse	Anhedonia, Sucrose preference↓	[57]
	Mouse	Cognitive dysfunction, %SAB (T-maze)↓	[57]
	Rat	Anhedonia, Sucrose preference↓	[55]
	Rat	Anhedonia, Sexual pursuit↓	[55]
	Rat	Depression, Immobility time (FST)↑	[55]
	Mouse	Anhedonia, Sucrose preference↓	[60]
	Mouse	Anxiety, Immobility time (TST)↓	[60]

(continued)

Table 12.1 (continued)

Experimental paradigm	Species	Phenotype, evaluation	References
Prolonged social isolation	Rat	Depression, Immobility time (FST)↑	[75]
	Rat	Anxiety, %Open arm time (EPM)↓	[80]
	Rat	Anxiety, General locomotion (OFT)↑	[79]
	Rat	Anxiety, %Open arm time (EPM)↓	[90]
	Rat	Anhedonia, PPI↓	[96]
	Rat	Anxiety, %Open arm time (EPM)↓	[68]
	Mouse	Cognitive dysfunction, %Time in TQ (MWM)↓	[89]
	Rat	Depression, Immobility time (FST)↑	[78]
	Rat	Anhedonia, Sucrose preference↓	[73]
	Rat	Anhedonia, Ejaculation latency↓	[73]
	Rat	Depression, Immobility time (FST)↑	[77]
	Rat	Anhedonia, Sucrose preference↓	[77]
	Rat	Depression, Immobility time (FST)↑	[76]
	Rat	Depression, Immobility time (FST)↑	[74]
	Rat	Anxiety, NSF↓	[74]
	Rat	Depression, Immobility time (FST)↑	[72]
	Mouse	Anhedonia, METH reward (CPP)↓	[29]
Dihydrokainic acid, acute	Rat	Cognitive dysfunction, %Time in TQ (MWM)↓	[107]
Dexamethasone, acute	Rat	Anhedonia, Sucrose preference↓	[37]
Dexamethasone, chronic	Rat	Depression, Immobility time (FST)↑	[109]
Rimonabant, chronic	Rat	Anhedonia, Sucrose preference↓	[110]
	Rat	Depression, Immobility time (FST)↑	[110]
Sciatic nerve constriction injury	Rat	Anhedonia, Sucrose preference↓	[130]
	Mouse	Depression, Immobility time (FST)↑	[131]
Olfactory bulbectomy	Mouse	Anxiety, General locomotion (OFT)↑	[136]
	Rat	Anhedonia, Ejaculation latency↓	[137]
	Rat	Depression, Emotional responses↑	[144]
	Rat	Anxiety, General locomotion (OFT)↑	[145]
	Rat	Anxiety, General locomotion (OFT)↑	[146]
	Rat	Anxiety, General locomotion (OFT)↑	[147]
	Rat	Depression, Immobility time (FST)↑	[148]
	Rat	Anxiety, %Open arm time (EPM)↓	[138]
	Rat	Depression, Freezing time (FCT)↓	[138]
	Rat	Anhedonia, Sucrose preference↓	[134]
	Rat	Anxiety, General locomotion (OFT)↑	[134]
	Mouse$^{tac1+/+,\,g}$	Anhedonia, Saccharine preference↓	[135]
	Mouse	Anxiety, General locomotion (OFT)↑	[149]
	Mouse	Anxiety, Exploration time (NOR)↑	[149]

(continued)

Table 12.1 (continued)

Experimental paradigm	Species	Phenotype, evaluation	References
Genetically engineered	DN-DISC1 tg M[h]	Depression, Immobility time (FST)↑	[164]
	DN-DISC1 tg M[h]	Anxiety, General locomotion (OFT)↑	[164]
	Mouse$^{NR1-/-, i}$	Anxiety, Center distance (OFT)↓	[160]
	Mouse$^{VGLUT1+/-}$	Anhedonia, Sucrose preference↓	[162]
	Mouse$^{VGLUT1+/-}$	Depression, Immobility time (FST)↑	[162]
	Mouse$^{MOR-/-, j}$	Anhedonia, Social interest↓	[169]
AMPH/METH withdrawal	Rat	Depression, Spontaneous locomotion↓	[98]
	Rat	Depression, Spontaneous locomotion↓	[99]
	Rat	Depression, Spontaneous locomotion↓	[100]
	Rat	Depression, Spontaneous locomotion↓	[101]
	Rat	Anhedonia, Sucrose preference↓	[102]
	Rat	Anhedonia, Rearing↓	[103]
	Rat	Anxiety, Grooming↑	[103]
	Mouse	Depression, Immobility time (FST)↑	[105]
	Rat	Depression, Immobility time (FST)↑	[104]
	Mouse	Anxiety, Immobility time (TST)↓	[61]
	Rat	Anhedonia, PPI↓	[100]
Use of inbred animal model	WKY	Depression, General locomotion (OFT)↓	[179]
	WKY	Depression, Immobility time (FST)↑	[179]
	WKY	Depression, Immobility time (FST)↑	[180]
	WKY	Anhedonia, Saccharine preference↓	[181]
	WKY	Anhedonia, nicotine reward (CPP)↓	[54]
	FSL	Depression, Immobility time (FST)↑	[183]
	FSL	Anhedonia, Cocaine self-administration↓	[184]
	FH	Depression, Immobility time (FST)↑	[188]
	FH	Anxiety, %Open arm time (EPM)↓	[190]
	FH	Anxiety, Center distance (OFT)↓	[191]
	LH	Anhedonia, Sucrose preference↓	[177]
	LH	Anhedonia, Sucrose preference↓	[200]

Abbreviations: AMPH amphetamine, *CMS* condensed sweetened milk, *CPP* conditioned place preference, *EPM* elevated plus maze, *FCT* fear-conditioning test, *FH* Fawn-Hooded, *FSL* Flinders sensitive line, *FST* forced swim test, *ICSS* intracranial self-stimulation, *LH* learned helplessness, *METH* methamphetamine, *MOR* μ opioid receptor, *MWM* Morris water maze, *NOR* novel object recognition test, *NSF* novelty suppressed feeding test, *OFT* open field test, *PPI* pre-pulse inhibition, *SAB* spontaneous alteration behavior, *TQ* target quadrant, *TST* tail suspension test, *WKY* Wistar Kyoto

[a]This evaluation was performed using adult male rats (60 day-old) while negative results were obtained in young male rats (30 days-old)

[b]The CMS procedure significantly reduced sucrose consumption only in F344 rats (but not SD or LEW rats)

[c]The CMS procedure significantly increased total immobility time in F344 and LEW rats (but not SD rats)

[d]A decreased sucrose preference was observed in the majority but not all male C57BL/6 mice

[e]The "increased" cocaine self-administration was observed in mice under episodic social defeat stress. The mice after episodic social defeat stress do not seem to be anhedonic because their sucrose preference was the same as control mice

[f]Rats used for this table exhibited high locomotor activity and sustained exploration ("high responders")

[g]Wild-type mice. In contrast, Mice$^{tac1-/-}$ did not display a reduction in saccharine preference after bulbectomy compared to Mice$^{tac1-/-}$ after sham operation

[h]Dominant-negative DISC1 transgenic mouse

[i]Postnatal NMDA receptor NR1 subunit deletion in corticolimbic interneurons

[j]Social anhedonia was observed in juvenile mice

depression in humans [28, 30–33]. In the CMS procedure subjects experience a stress regimen over a period of several weeks (usually 4–8 weeks), consisting of daily "unpredictable" mild stressors. "Unpredictable" meaning that the order of the stressors is unpredictable and these occur at different, i.e. unpredictable, times of the day. The stressors used in these types of procedures include water and food deprivation, cage tilting (45°), paired housing (i.e. animals are paired with an unfamiliar animal of the same sex for a period of time), soiled bedding (i.e. wetted sawdust bedding), intermittent overnight illumination, reversal of lighting cycles, placement in a smaller cage, load noises, and forced swim stress [27, 28, 34–38]. Exposure to CMS reduces intake of palatable solutions [27, 28, 32, 34, 36–42] and sweet foods [26], reduces ICSS thresholds [43], reduces spontaneous alternation behavior in the Y-maze [44] and reduces the number of times that animals enter the center of the exploration box [38], while increasing the immobility time in the forced swim test [36]. These behavioral changes are reversed by chronic (but not acute; see [45]) treatment with a broad range of antidepressant and putative antidepressant drugs including imipramine, venlafaxine, escitalopram, fluoxetine and paroxetine [36, 37, 41, 42, 46], ketamine and memantine (N-methyl-D-aspartate (NMDA) receptor antagonists) [26, 34], and salvinorin A (a κ-opioid receptor agonist) [27]. The model has been proven to have considerable face and predictive validity for depression, and especially certain features such as anhedonia.

It has been suggested that the CMS procedure may not produce a consistent behavioral phenotype in mice based on the standard sucrose test (i.e. consumption of palatable sweet solution) [47], although other researchers have certainly found typical CMS-like effects in mice [48, 49]. One author suggested that more consistent CMS findings may be found in mice by just increasing a number of mice examined [50]. Indeed the CMS procedure in mice has been shown to reduce sucrose consumption [48, 49] and novelty suppressed feeding [51], to increase immobility in the forced swim test [48] and the tail suspension test [48, 52], and to increase anxiety-like behavior in the open field and light-dark tests [48]. The CMS procedure reduced hippocampal neurogenesis as well [49]. Importantly, some of these effects can be ameliorated by antidepressants [52].

Inconsistencies in CMS effects across studies in mice may happen for similar reasons to rats. In rats there are strain differences in response to CMS [53, 54], making it highly likely that there are strain differences in mice as well. Behavioral changes in response to the CMS procedure and the effect of chronic treatment with antidepressants also depend on age in rats [35, 38]. An age-dependent decrease in gonadal hormones affects the behavioral outcomes of CMS as well as the effect of antidepressants. Overall, although the CMS procedure is a common model of depression, the outcome depends on parameters of the CMS procedures as well as species, strain, and age, and studies in mice, particularly with the intention of leveraging the substantially greater potential to use genetic techniques in this species, will require understanding these variables to adapt the technique to mice, or the development of other techniques.

Of course a number of other animal models also exist, and many of these have been used more extensively in mice. The rodent resident-intruder/social defeat

paradigm can be considered to model depression because the paradigm induces several phenotypes indicative of anhedonia and other depressive-like symptoms, including diminished sexual behavior [55], social avoidance [56], and certain types of cognitive dysfunction that have been observed in other depression models [57]. Rodents that experience repeated social defeat become subordinate, with maladaptive psychological and deleterious physiological consequences, resulting in long-lasting stress-related behavioral effects [58, 59]. Social defeat-induced depressive-like phenotypes can be long-lasting, and associated with alterations in neurochemical parameters including changes in serotonin, adrenocorticotropic hormone (ACTH), orexin, dynorphin and brain derived neurotrophic factor (BDNF) [55, 56, 60]. Behavioral alterations (i.e. expression of depressive-like phenotypes) include increased immobility in the tail suspension test [60] (also see [61]), decreased consumption of sucrose solutions [55, 57, 60, 62, 63], decreased sexual pursuit [55, 63], increased immobility in forced swim test [55], social avoidance [56, 64] and a reduced rate of continuous alternation behavior in the T-maze test [57]. It must be noted that there are substantial differences in the severity of stress induced in many of these paradigms, with some models explicitly attempting to create severe and persistent psychological distress by repeated defeat and long exposures to aggressive mice [56]. In any case, based on the similarity of these behavioral changes to depressive-like symptoms, social defeat paradigms are likely to facilitate discovery of treatments for stress-related depressive disorders. Indeed, at least some of these effects can be reversed by antidepressant treatments [56, 64].

Social isolation is obviously an important aspect of many models of depression, and additionally is incorporated into many animal models where it is not explicitly a part of the model, including many social defeat and chronic mild stress paradigms. Long-lasting behavioral changes result from social isolation associated with deprivation of particular social interactions, such as play in adolescent rodents, as well as social deprivation in adult animals (for detailed review see [65, 66]). As we have summarized elsewhere, the consequences of social isolation are often assumed to be the result of isolation "stress", but this is not necessarily the case, particularly with models that involve isolation early in life [67], the most obvious reason being that different types of social isolation produce different consequences. Indeed, it has been argued that some effects of social isolation result from eliminating the repeated daily minor stressors that serve to desensitize stress systems (behaviorally at least) leading to increased anxiety [68]. On that basis it might be thought that some isolation paradigms work in a similar, although perhaps opposite, fashion to social defeat paradigms. However, many social defeat paradigms purposefully amplify the level of aggression, stress and subordination beyond "normal" levels with the intention of inducing psychosocial stress [56], which might not be seen in stable social circumstances.

Whether the isolation experience is stressful or not, which may depend on the particular conditions in which the isolation occurs, there are certainly adaptations in stress responsive systems that result from different types of social isolation. In animals isolated as adults this includes changes at a cellular level [69, 70], although under at least some conditions this seems to result in stress resistance [71], in

contrast to adaptations associated with other social isolation paradigms (e.g. maternal deprivation). An additional important consideration from these studies is that stress regulation, at the level of regulation of gene transcription, may work differently after a period of chronic social isolation in adult animals than it does in animals housed in social conditions.

In any case, procedures in which rodents are isolated at weaning and maintained in isolation into adulthood, or in which they are isolated as adults, have been shown to produce depressive-like symptoms. This occurs particularly when the isolation is prolonged, but some consequences can be noted after even a short period of isolation. The studies mentioned above most typically isolate animals for an extended period as adults, 2–8 weeks beginning at 8–12 weeks of age (sexually mature). This procedure is often termed "isolation-housing" to differentiate it from isolation of weanling animals, termed "isolation-rearing". Isolation-housing has been shown to produce a variety of behavioral and neurochemical effects (for full review see [65]), many of which could be characterized as depressive in nature. The majority of these studies have been conducted in rats, although many similar effects have been observed in mice. Depressive-like behaviors that have been observed include increased immobility time in the forced swim test [72], reduced sucrose consumption [73], and increased ejaculation latency, interpreted as reduced "sexual reward" [73]. The last two phenotypes would be specifically interpreted as anhedonic in nature. The effects of isolation-rearing have been studied more extensively, and this procedure also produces depressive-like and anxiety-like phenotypes, including increased latency to eat in the novelty suppressed feeding test [74] increased immobility in the forced swim test [74–78], reduced sucrose consumption [77], anxiety-like behavior in the open field test [79], reduced entry into open arms in the elevated plus maze test [76, 80] and reduced social interaction in the social interaction test [76].

Studies of depressive, anxious and anhedonic symptoms in isolated mice are more limited than in rats, but do contribute to this overall picture. A 24 h period of isolation around weaning increased immobility in the forced swim test in mice, but did not do so in mice just a week older [81]. A 24 h period of isolation in adulthood reduces sucrose preference [82], while even 12 h of social isolation produced depressive like-behavior in several behavioral tests [83]. Two weeks of isolation-housing increased immobility in the forced swim test, but the effects were dependent on both the strain tested and water temperature [84]. Antidepressant effects of desipramine were observed under some conditions however, and, importantly, corticosterone levels did not appear to be related to immobility. A longer period of isolation housing increased immobility in the forced swim test and the tail suspension test, as well as reducing transitions in the light-dark box [85]. That study specifically examined female mice, with the expectation that they might be more susceptible to the development of depressive symptomatology. The depressive phenotypes, but not the anxious phenotype, were reversed by chronic fluoxetine. Isolation-rearing has also been shown to produce both depressive and anxious phenotypes in mice [86], although other studies have found less consistent effects of isolation-rearing on similar measures [87, 88]. That study did find evidence for

substantial reductions in hippocampal neurogenesis, which was confirmed in another study, which also found reductions in spatial learning, both of which were reversed by chronic fluoxetine treatment [89].

Given the observation of similar depressive and anxious phenotypes resulting from isolation-housing and isolation-rearing, it would appear that the effects are more likely due to the current isolated state at the time of testing than any long-term or developmental consequences of the isolation. However, the basis of some of the effects resulting from isolation-housing and isolation-rearing, although similar on the surface, may have a different underlying basis. Thus, isolation-housing increases anxiety-like behavior in the elevated plus maze [73], but this is an effect that can be produced after only a short period of isolation, and can be reversed by later social housing [90]. This is not the case for animals isolated in adolescence, for which resocialization in adulthood does not reverse anxiety-like behavior in the elevated plus maze [80].

Importantly, many of the behavioral and biochemical changes described above, whether resulting from isolation in adolescence, in adulthood, or the result of current housing state, are reversed by chronic treatment with antidepressant, or putative antidepressant, drugs [72–76, 79, 91]. Isolation-housing and isolation-rearing have been shown to produce a number of long-term behavioral and neurochemical alterations that may be consistent with a depressive phenotype, including reductions in serotonin function [77, 92–94]. However, isolation-rearing, but not isolation-housing, has profound effects on dopaminergic systems and dopamine mediated behavior as well [95, 96] which resemble schizophrenia and many of which are reversed by antipsychotic drugs.

In any case social defeat and social isolation paradigms can produce some anhedonic-like behaviors. The conditions producing such effects in isolation models appear to involve current social state, although such effects get stronger with a longer duration of isolation. Indeed, although the effects of social defeat models tend to be associated with the "stress" of defeat, one of the consequences is certainly altered and reduced interaction with conspecifics.

Despite the importance of anhedonia in the symptomatology of depression, none of the studies in mice discussed above addressed anhedonia *per se*, although they have certainly shown that social isolation, even after a short time, can induce depressive-like symptoms in both rats and mice. There is no report of an anhedonic-like phenotype in mice after social isolation, whether it is prolonged isolation or not and using procedures very similar to those used in CMS, isolation-reared rats did not have shifts in sucrose consumption like those observed after CMS [97]. However, in a recent study [29], we housed mice under different conditions beginning just 1 day prior to a methamphetamine conditioning experiment. These mice were housed socially or in isolation. Additionally, half of the mice housed in isolation had a running wheel available, while half did not. We found that mice housed in isolation had reduced responses to the reinforcing effects of METH (e.g. anhedonia) compared to socially housed mice. Furthermore, we found that this state was reversed by a simple form of environmental enrichment (e.g. the availability of a running wheel).

12.2.2 Drug-Induced Anhedonia

Administration of a variety of addictive drugs has been shown to induce depressive-like symptoms, including anhedonia. These symptoms are generally the result of a chronic drug treatment regimen that leads to withdrawal-induced dysphoria, anhedonia and other depressive symptoms. Of greatest relevance to the current discussion, administration of psychostimulants, including cocaine, AMPH and METH have been shown to produce behavioral changes that include anhedonic-like phenotypes subsequent to chronic administration in rodents. Operationally these depressive and anhedonic-like phenotypes include decreased locomotion [98–101], decreased sucrose consumption [102], decreased rearing [103], increased grooming [103], increased immobility time in forced swim test [104, 105] and decreased immobility time in tail-suspension test [61] (for a review see [106]).

Other drugs that are not addictive have also been shown to induce depressive-like symptoms. These drug models of anhedonia have been investigated for a variety of reasons, but usually with either some idea of a potential mechanism underlying depressive symptomatology or the mechanisms underlying the development of depression. In many cases, although not all, these drugs do not have to be given in a chronic fashion to induce these symptoms. For instance administration of rats with acute dihydrokainic acid [107, 108] or dexamethasone [37], or chronic treatments with dexamethasone [109] or rimonabant [110] induce depressive-like phenotypes, including anhedonia.

Dihydrokainic acid blocks the glial glutamate transporter, GLT-1 (also called EAAT2), resulting in increased levels of glutamate in the synaptic cleft [111–113]. The basis of this approach is that recent studies have reported a causal relationship between increased excitatory glutamate neurotransmission in the central nervous system and expression of depressive-like phenotypes [114, 115]. Furthermore, blockade of glutamate receptor subtypes by ketamine (a non-competitive NMDA receptor antagonist) ameliorates depressive-like phenotypes in clinical and preclinical studies [34, 116, 117]. Dihydrokainic acid-treated animals also display impaired spatial memory as assessed in the Morris Water Maze but not dysphoria as determined by conditioned place aversion [107].

Dexamethasone is a synthetic glucocorticoid and induces a depressive-like phenotype in rats after both acute and chronic treatment [37, 109]. Acute administration of rats with dexamethasone reduces sucrose consumption, which is reversed by chronic paroxetine treatment [37]. Chronic dexamethasone treatment increases immobility time observed in the forced swim test [109]. The hypothalamic-pituitary-adrenal (HPA) axis controls the secretion of cortisol in humans (corticosterone in rodents) and hyperactivity of the HPA axis is considered to link at least in part to hypercortisolism, which is characteristic of at least some cases of depression. Indeed, stress, or increased sensitivity to stress, is considered to be a predisposing factor in some depressive disorders and a large part of the impetus for developing stress models of depression. Specifically, elevated blood levels of cortisol are considered to be causally associated with depression in some humans [118, 119].

Rimonabant (SR 141716A) is a cannabinoid receptor 1 (CB_1 receptor) inverse agonist and has adverse effects including nausea, emesis, anhedonia and other depression-related effects that limit its clinical use for the treatment of obesity and smoking cessation [120–125]. Indeed, part of the basis of withdrawal of the marketing authorization for rimonabant as a medicine used to treat obesity in the European Union was the observation of anhedonia in humans [125]. Rats treated with rimonabant once daily for 3 weeks display a depressive-like phenotype, including anhedonia, demonstrated by increased immobility time in the forced swim test and decreased sucrose consumption [110]. There is no report addressing whether or not rimonabant-induced anhedonia can be reversed by antidepressants.

12.2.3 Peripheral Neuropathy Model Induces Anhedonia

Neuropathic pain is highly comorbid with depression and anxiety in humans [126], and may share a number of common underlying mechanisms. For example norepinephrine transporter (NET) and serotonin transporter (SERT) knockout mice exhibit both differences in pain responses [127] and differences in animal models of depression, including anhedonia [128]. Investigations of the mechanisms underlying the development of neuropathic pain have utilized a number of models relevant to its diverse etiology. In one of the more commonly used models, the chronic constriction injury (CCI) model [129] a spinal nerve, such as the sciatic nerve, is exposed and a ligature is tied loosely around the nerve for a period of time (20 min typically). This procedure results in a chronic pain syndrome characterized by hyperalgesia and allodynia, but further observation using such models has also demonstrated depressive-like symptomatology. CCI produces depressive and anhedonic-like behavior as assessed by the forced swim test and sucrose consumption, although the mechanisms whereby anhedonia is induced in the model are unknown [130, 131]. However, this anhedonic state is reversed by treatment with amitriptyline but not by treatment with fluoxetine or buproprion [131], suggesting that the mechanism producing anhedonia in the CCI model may be different from CMS and social isolation models [42, 74] although certainly further work is necessary to confirm these observations.

12.2.4 Olfactory Bulbectomy

The olfactory system is a part of the limbic system which projects to the amygdala, olfactory tubercle and ventromedial temporal cortical areas, and thence to the hypothalamus and hippocampal formation thereby contributing to emotional and mnemonic aspects of behavior [132, 133]. Rats and mice display depressive-like symptoms after disruption of the limbic system produced by removal of the olfactory bulbs [134, 135]. However, unlike many other animal models of depression these

animals exhibit hyperactivity [134, 136] rather than hypoactivity, so olfactory bulbectomy has been described as a model of agitated depression [137] or depression with comorbid anxiety [138] in particular. An anhedonic-like phenotype is observed in terms of reduced sucrose intake [134] and sexual behavior [137] in olfactory bulbectomized rats (but see also [139], which reports negative results). The mechanisms underlying depressive symptoms produced by olfactory bulbectomy in rodents are not fully understood, but might result from stress or sensitization of stress systems [140], perhaps resulting from circadian disruptions of these systems [141]. There is a positive relationship between stress responsivity and substance P levels [142, 143], and Tac1 KO mice, which lack substance P, display no anhedonic phenotype after olfactory bulbectomy [135]. Olfactory bulbectomy has also been shown to reduce serotonin function [137].

The consequences of olfactory bulbectomy have been shown to be ameliorated by a variety of antidepressant and putative antidepressant drugs [136, 144–149]. The effects of olfactory bulbectomy include reduced hippocampal neurogenesis, which is also reversed by antidepressant treatments [150]. The studies mentioned above used both rats and mice, and unlike some other depression models, the effects of olfactory bulbectomy appear to be equally effective in both rats and mice. However, unlike some of the other models of depression discussed above olfactory bulbectomy produces hyperactivity, rather than hypoactivity.

12.2.5 Genetically Engineered Animal Models Expressing Anhedonia

Alterations in anhedonic phenotypes are observed in some genetically modified mouse models in which specific genes have been altered. In some cases, genetic modifications have been shown to alter sensitivity to some of the models discussed above. These mouse models directly implicate the involvement of specific genes in anhedonia and other aspects of depressive symptomatology.

Not surprisingly, gene knockout of any of the monoamine transporters, resulting in increased extracellular levels of the relevant monoamine [151], can produce antidepressant-like effects [128, 152–154], although these effects were not observed equally in all tests, nor for all three monoamine transporter knockouts. Surprisingly, dopamine transporter (DAT) knockout mice exhibit the most robust antidepressant-like phenotypes across multiple assessments of depressive symptomatology, including anhedonia as assessed by sucrose consumption [128]. Furthermore, SERT knockout mice showed the smallest and least consistent effects [128, 154] and indeed exhibited increased immobility in the forced swim test [154], although the result in that study may have been confounded by reduced muscle strength in SERT knockout mice. The lack of anhedonia prompted the suggestion that SERT knockout mice do not model depression [155]. This a little bit surprising given the wealth of involvement for both serotonin and SERT in depression, but may indicate that developmental compensations may occur in constitutive SERT knockout mice. Nonetheless,

there is other evidence from knockout mice that does support for a role of 5-HT in depression and anhedonia. Sucrose consumption is increased in mice with gene knockout of the serotonin 5-HT_{1A} or 5-HT_{1B} receptor subtypes [156].

A number of genetically modified mouse strains with modifications of genes affecting glutamatergic signal transduction appear to affect anhedonic or depressive phenotypes as well. These genes have recently become of interest in the study of depression as dysfunction of glutamate neurotransmission has been proposed to be an important factor determining the expression of mood disorders. Alterations in glutamate neurotransmission affect mood disorders in several ways dependent on the glutamate receptor subtypes affected and their localization on particular types of neurons [157–159]. A conditional knockout mouse strain has been produced that has early postnatal ablation of the glutamate receptor NMDA ζ1 subunit, GluN1 (also known as NR1 or Grin1; an essential component of all NMDA receptors), in cortical and hippocampal γ-aminobutyric acid-releasing (GABAergic) neurons [160]. These mice display anhedonia-like and anxiety-like behavioral alterations in terms of reduced saccharine preference, deficits in nesting/mating, and enhanced novelty-induced anxiety, as well as hyperlocomotion and cognitive dysfunction. A particular neuronal type (i.e. corticolimbic GABAergic neurons) and/or a particular critical period of the GluN1 ablation (i.e. postnatal day 7) may underlie induction of the anhedonic state because no anhedonic-like phenotype is reported in $Grin1^{D481N}$ mice, a genetically engineered mouse strain in which NMDA receptor glycine co-agonist site on GluN1 subunit is eliminated constitutively [161].

Mice heterozygous for the gene encoding the vesicular glutamate transporter 1 (VGLUT1) (homozygous VGLUT1 knockout is lethal within 2–3 weeks after birth) display depressive-like behavior including reduced sucrose consumption and increased immobility in the forced swim test [162]. More importantly, those authors demonstrated increased vulnerability to CMS, which augmented depressive-like phenotypes in $VGLUT1^{+/-}$ mice, and was reversed by chronic imipramine treatment. Mice lacking the Grik4 gene, which encodes the metabotropic kainate receptor subunit Gluk4, also exhibit anxiolytic and antidepressant-like behavior [24].

Polymorphisms in the disrupted-in-Schizophrenia-1 (DISC1) gene are a genetic risk factor across a spectrum of psychiatric disorders, including schizophrenia and depression [163]. Mice expressing a dominant-negative C-terminal truncated DISC1 display schizophrenia-like phenotypes including anhedonia and anxiety-like behaviors as assessed by increased immobility in the forced swim test and increased general and rearing locomotion in the open field test [164]. By contrast, another mouse model for schizophrenia, Csmd1 (CUB and Sushi multiple domains-1) knockout mice [165], do not display anhedonic-like phenotypes [166]. This gene has not been assessed for association with depression, but has been associated with methamphetamine dependence [167].

Gene knockout of the μ opioid receptor (MOR) reduces the reinforcing effects of a number of abused drugs including opiates, cocaine and ethanol (for review see [168]). On this basis, MOR knockout might also be thought to affect the hedonic impact of natural reinforcers. Indeed, social interest and the reinforcing value of social stimuli is reduced in juvenile MOR knockout mice, which was interpreted as

social anhedonia [169]. However, another study found that there were no differences in social approach in adult mice, and indeed the effects of defeat on social approach were eliminated in MOR knockout mice [170]. Thus, although it would appear that manipulations of MOR do indeed affect responses to drug and social reinforcers, the nature of these effects need further elucidation, as does whether or not these effects apply to other natural reinforcers that are commonly used to assess anhedonia.

Although genetic studies of anhedonia have not examined a large number of genes it is certainly clear that they provide evidence that manipulations of a number of genes thought to be involved in depression and schizophrenia produce depression-like or anhedonic phenotypes. Furthermore, it is clear that manipulations of some of those genes affect susceptibility to the effects of other models, such as CMS. Whether or not those genes, or others, contribute to susceptibility to drug-withdrawal induced anhedonia has yet to be determined.

12.2.6 Use of Inbred Animal Models for Clinical Depression

Prior to the availability of genetically modified mice, a number of inbred or selectively bred lines of rats and mice were evaluated or developed as models of depression, including the Wistar-Kyoto (WKY) rat, the Flinders sensitive rat line (FSL), the Fawn-Hooded (FH/Wjd) rat, and the congenital learned helplessness (cLH) rat [31, 171–177].

The WKY rat line was selectively bred from the Wistar strain in 1963 as the normotensive control strain for the spontaneously hypertensive rat [178]. The WKY rat is known for its stress-sensitive phenotype, which obviously relates to cardiovascular differences in this strain but also suggested a potential effect on depressive phenotypes. Indeed, the WKY rat displays hypoactivity in the open field test and increased immobility in the forced swim test, compared with control Wistar [179] or Sprague-Dawley (SD) [180] rats. The WKY rats also display a reduced conditioned place preference for nicotine, which might also be interpreted as an anhedonic-like phenotype compared with the control rat line [54]. More specifically addressing anhedonia prepubertal WKY rats show reduced saccharine preference [181].

The FSL rat line was derived by selective breeding from SD rats in 1979 [182]. The FSL rat was initially selected to be highly sensitive to diisopropyl fluorophosphate, an irreversible inhibitor of acetylcholinesterase, but the strain has subsequently been revealed to exhibit depressive traits [173, 176]. The FSL rat displays increased immobility in the forced swim test compared to SD rats, an effect that is reversed by desipramine [183]. The FSL rat also displays reduced cocaine-seeking behavior compared to the control SD rat line, an effect which is also normalized by chronic treatment with desipramine [184]. Prepubertal FSL rats did not exhibit anhedonia, in terms of reduced saccharine preferences, as did WKY rats, but this may reflect an age of onset difference between these strains [181].

There are two closely related substrains of FH rats, FH/Har and FH/Wjd (see [185] for an explanation of the origin of these strains), that exhibit an overlapping,

set of behavioral traits that include anxiety-like and depression-like phenotypes that appear to be related to differences in 5-HT function [186–188]. Initially it was unclear that there were differences between these two FH substrains, which both exhibit increased ethanol consumption [188, 189], albeit under somewhat different experimental conditions. The FH/Har substrain exhibits increased anxiety-like behavior and increased corticosterone release in response to a mild stressor [190–192]. Under some conditions the FH/Har substrain has high basal plasma corticosterone levels, which are normalized by chronic treatment with imipramine, clomipramine or clorgyline [193, 194]. However, FH/Har rats have reduced immobility in the forced swim test [192, 195, 196] and no evidence for anhedonia in terms of either sucrose or saccharine consumption [189]. Indeed, an anti-anhedonic effect was apparent for saccharine consumption in that study. By contrast, the FH/Wjd substrain does not exhibit an anxiety-like phenotype, but does exhibit reduced immobility in the forced swim test [187, 188]. In the studies mentioned above the usual control group for strain comparisons are Wistar rats. However, one study explicitly compared the two FH substrains [185], and found that FH/Wjd rats were more immobile in the forced swim test than FH/Har rats and consumed more ethanol and saccharin, while FH/Har rats were more anxious in the elevated plus maze. It is difficult to draw any conclusions about ethanol or saccharin consumption as only single concentrations were examined in that study, but obviously there are substantial differences between the two strains. The comparison between these two strains is especially interesting because they are closely related and share an overlapping set of behavioral traits. Both substrains exhibit behavioral differences from other strains that are relevant to depression, and perhaps anhedonia, but different behavioral features are shown in each substrain.

Different theories regarding the origins of depressive symptomatology have led to different approaches to modeling depression. The learned helplessness paradigm was developed based upon a certain conception that the primary changes in depressive symptomatology reflect differences in cognition, and that these may relate to experience with the degree of control over outcomes in response to stressful situations [197, 198]. This is not to say that there are not genetic contributions that predispose some individuals to be more likely to develop learned helplessness. Thus, the LH rat line was selectively bred from SD rats by selecting for greater helpless behavior after exposure to an uncontrollable and unpredictable stressor [199–201]. The LH rat displays a number of depressive features, including a low sucrose preference compared with the control rat line [200].

12.3 Comparison of METH-Induced Withdrawal Dysphoria to Other Models of Anhedonia

As described in the Introduction, METH-induced withdrawal dysphoria is a serious problem in METH abusers and effective treatments for METH dependence remain elusive [20, 21]. Animal models of anhedonia are essential for identifying

effective treatments for METH-induced withdrawal dysphoria. The most useful and widely accepted method for assessing anhedonia in most of the animal models discussed above is to measure a consumption/preference of a palatable solution or sweet food [28, 33] (also see Table 12.1). However, this type of behavioral measure has not been widely applied to animal models of anhedonia induced by AMPH or METH withdrawal [106]. However, there are two reports that rats withdrawn from intermittent AMPH have decreased sucrose consumption [102, 202]. Additionally, the Der-Avakian study (2020) demonstrated that there was a clear and persistent reduction in progressive ratio breakpoints for operant self-administration of sucrose. Furthermore, reduced dopamine release during anticipatory phases, but not during consummatory phases, of sucrose consumption testing is seen after AMPH withdrawal [203].

One potential problem with the use of sucrose consumption tests to assess drug withdrawal-induced anhedonia is that many psychostimulant drugs, especially AMPH-like compounds, are appetite suppressants. Thus the locomotor stimulant and appetite suppressant effects of these drugs could acutely affect sucrose consumption for reasons unrelated to reward function, and during withdrawal could produce the opposite actions. Perhaps for this reason the primary method used to assess anhedonia following drug withdrawal has been assessment of intracranial self-stimulation (ICSS) thresholds for rewarding brain stimulation. Indeed, withdrawal from a number of psychostimulant drugs including cocaine [204–206], AMPH [104, 207–210] and METH [211] have been shown to reduce ICSS thresholds. Withdrawal from AMPH or METH has also been shown to decrease locomotor behavior [212, 213], which might be associated with the malaise associated with drug withdrawal that is observed in humans. Like many of the other models discussed above, withdrawal from cocaine, AMPH or METH has also been shown to produce depression-like [104, 214] or anxiety-like [61, 214] behavior in a variety of standard animal models.

For the reasons stated above animal models other than AMPH/METH withdrawal should be chosen for the purpose of evaluating for the efficacy of treatments for anhedonia when assessing the consumption or preference for a palatable solution or sweet food. Stress-based paradigms including CMS, repeated social defeat and prolonged social isolation have been widely used for investigating anhedonia in the literature because measurement of consumption or preference for a palatable solution or sweet food produces consistent anhedonic symptoms in these models (Table 12.1). When assessing drug-withdrawal induced anhedonia, ICSS is obviously effective, but this has been used less widely in other models. Although obviously an effective way to examine hedonic sensitivity, ICSS differs from natural rewards in a variety of ways, including the dynamics of normal motivational states (there is no satiation associated with repeated self-administration of ICSS).

It would be highly desirable to be able to examine a natural reinforcer other than food in drug withdrawal-induced anhedonia models. Several types of reinforcers have been used, including novelty [215] and sexual motivation [216]. Indeed, comparison across several classes of reinforcers and circumstances would be highly desirable as it has not been revealed whether or not the anhedonic-like

phenotype observed during AMPH/METH withdrawal has the same features as the anhedonia observed in other animal models such as CMS, repeated social defeat and social isolation. Regarding this point, exposure to positive environmental conditions such as environmental enrichment can have therapeutic effects on cocaine and AMPH/METH craving [217–223]. Furthermore, exposure to environmental enrichment has been shown to attenuate cue-induced reinstatement of sucrose seeking (i.e. a natural reward) in rats [224]. Some effects of isolation-rearing can also be reversed by environmental enrichment [78, 225]. Thus it may be postulated that animal models of anhedonia displaying anhedonic-like symptoms which can be reversed by environmental enrichment will be useful for investigating anhedonic-like phenotypes observed during AMPH/METH withdrawal. Chauvet et al. reported that exposure of rats to environmental enrichment either in early or late phases of withdrawal reduces cocaine-seeking behavior and that this environmental enrichment needs to be provided continuously over long periods of withdrawal [226].

However, it has not been determined whether or not exposure to environmental enrichment can improve withdrawal dysphoria during the period of drug exposure. Using ICR mice we investigated the effects of isolation-housing and environmental enrichment on METH-induced CPP, and demonstrated that social isolation reduces responses to the reinforcing stimulus (anhedonia; a decrease in METH-induced CPP), a state that is reversed by environmental enrichment (aerobic exercise, i.e. a running wheel) [29]. These observations suggest that treatment for METH-induced withdrawal dysphoria (presuming that in the period following the CPP procedure the subjects experience some withdrawal) in mice may be effectively achieved by altering environmental conditions.

12.4 Role of Anhedonia in METH-Seeking Behavior

For METH abusers, expression of dysphoria and anhedonia during the drug withdrawal period may play a role in the maintenance of drug-seeking behavior because avoidance or attempts to ameliorate these states during drug withdrawal may motivate continued drug-seeking behavior [227]. Thus treatment of anhedonia is an important therapeutic goal for METH treatment. However, as mentioned in the introduction, when anhedonic-like symptoms present in METH abusers it is difficult to determine whether they result from comorbid and pre-existing, psychiatric conditions or whether they result from drug withdrawal. This difficulty using METH is overcome in animal models, although most models of anhedonia have focused on anhedonia associated with depression. We have developed a mouse model of anhedonia in which social isolation reduces responses to a reinforcing stimulus (e.g. anhedonia), a state that is reversed by a type of environmental enrichment (i.e. a running wheel). It will certainly be necessary to expand these observations to natural reinforcers as many of the models discussed above do show differences between responses to drug and natural reinforcers.

The reduction in METH-induced CPP in the model discussed above was reversed by alteration of housing conditions from individually housed to socially housed conditions. This reduction in responsiveness to METH occurred within a short period of time, but was reversed by a simple form of environmental enrichment, a running wheel [29]. These observations suggests that, consistent with some of the models discussed above, a short period of isolation produces changes in behavior that may reflect changes in hedonic states that may be effectively achieved by altering environmental conditions. In contrast to this observation desipramine in FSL rats increases cocaine-seeking behavior [184] in parallel with the observation of increases in dopamine release in the NAc. Thus, using isolation-based animal models for anhedonia we can investigate possible treatments for anhedonia-like phenotypes observed during METH withdrawal. These potential treatments will include alterations of environmental conditions, e.g. enrichment, as a candidate treatment for anhedonia, instead of pharmacotherapy, although it will certainly be necessary to translate enrichment in mice to an experience that is enriching in humans and produces similar effects.

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References

1. Murray JB. Psychophysiological aspects of amphetamine-methamphetamine abuse. J Psychol. 1998;132:227–37.
2. Panenka WJ, Procyshyn RM, Lecomte T, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend. 2012. doi:10.1016/j.drugalcdep.2012.11.016.
3. Barr AM, Panenka WJ, MacEwan GW, et al. The need for speed: an update on methamphetamine addiction. J Psychiatry Neurosci. 2006;31:301–13.
4. Randrup A, Munkvad I. Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacologia. 1967;11:300–10.
5. National Institute on Drug Abuse. NIDA InfoFacts: methamphetamine. 2004. http://www.drugabuse.gov/publications/drugfacts/methamphetamine
6. Kramer JC, Fischman VS, Littlefield DC. Amphetamine abuse. Pattern and effects of high doses taken intravenously. JAMA. 1967;201:305–9.
7. Ujike H, Sato M. Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis. Ann N Y Acad Sci. 2004;1025:279–87.
8. Lago JA, Kosten TR. Stimulant withdrawal. Addiction. 1994;89:1477–81.
9. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997;278:52–8.
10. Gawin FH, Ellinwood Jr EH. Cocaine and other stimulants. Actions, abuse, and treatment. N Engl J Med. 1988;318:1173–82.
11. Koob GF, Le Moal M. Neurobiological mechanisms for opponent motivational processes in addiction. Philos Trans R Soc B Biol Sci. 2008;363:3113–23.
12. Rothman RB, Partilla JS, Dersch CM, et al. Methamphetamine dependence: medication development efforts based on the dual deficit model of stimulant addiction. Ann N Y Acad Sci. 2000;914:71–81.

13. Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci. 2008;10:291–9.
14. Snaith P. Anhedonia: a neglected symptom of psychopathology. Psychol Med. 1993;23:957–66.
15. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278–96.
16. Kalechstein AD, Newton TF, Longshore D, et al. Psychiatric comorbidity of methamphetamine dependence in a forensic sample. J Neuropsychiatry Clin Neurosci. 2000;12:480–4.
17. Cox D, Bowers R, McBride A. Reboxetine may be helpful in the treatment of amphetamine withdrawal. Br J Clin Pharmacol. 2004;58:100–1.
18. Kongsakon R, Papadopoulos KI, Saguansiritham R. Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. Int Clin Psychopharmacol. 2005;20:253–6.
19. Srisurapanont M, Jarusuraisin N, Kittirattanapaiboon P. Treatment for amphetamine dependence and abuse. Cochrane Database Syst Rev, Wiley. 2001. doi:10.1002/14651858.CD003022.
20. Shoptaw Steven J, Kao U, Heinzerling K, et al. Treatment for amphetamine withdrawal. Cochrane Database Syst Rev, Wiley. 2009. doi:10.1002/14651858.CD003021.pub2.
21. Karila L, Weinstein A, Aubin HJ, et al. Pharmacological approaches to methamphetamine dependence: a focused review. Br J Clin Pharmacol. 2010;69:578–92.
22. D'Souza MS, Markou A. Neural substrates of psychostimulant withdrawal-induced anhedonia. Curr Top Behav Neurosci. 2010;3:119–78.
23. Hatzigiakoumis DS, Martinotti G, Giannantonio MD, et al. Anhedonia and substance dependence: clinical correlates and treatment options. Front Psychiatry. 2011;2:10.
24. Catches JS, Xu J, Contractor A. Genetic ablation of the GluK4 kainate receptor subunit causes anxiolytic and antidepressant-like behavior in mice. Behav Brain Res. 2012;228:406–14.
25. Warren BL, Iniguez SD, Alcantara LF, et al. Juvenile administration of concomitant methylphenidate and fluoxetine alters behavioral reactivity to reward- and mood-related stimuli and disrupts ventral tegmental area gene expression in adulthood. J Neurosci. 2011;31:10347–58.
26. Reus GZ, Abelaira HM, Stringari RB, et al. Memantine treatment reverses anhedonia, normalizes corticosterone levels and increases BDNF levels in the prefrontal cortex induced by chronic mild stress in rats. Metab Brain Dis. 2012;27:175–82.
27. Harden MT, Smith SE, Niehoff JA, et al. Antidepressive effects of the κ-opioid receptor agonist salvinorin A in a rat model of anhedonia. Behav Pharmacol. 2012;23:710–5.
28. Papp M. Models of affective illness: chronic mild stress in the rat. Curr Protoc Pharmacol. 2012; Chapter 5:Unit 5.9.
29. Kitanaka N, Kitanaka J, Hall FS, et al. Attenuation of methamphetamine-induced conditioned place preference in mice after a drug-free period and facilitation of this effect by exposure to a running wheel. J Exp Neurosci. 2012;6:11–9.
30. Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology (Berl). 1997;134:319–29.
31. Overstreet DH. Modeling depression in animal models. Methods Mol Biol. 2012;829:125–44.
32. Henningsen K, Andreasen JT, Bouzinova EV, et al. Cognitive deficits in the rat chronic mild stress model for depression: relation to anhedonic-like responses. Behav Brain Res. 2009;198:136–41.
33. Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci Biobehav Rev. 1992;16:525–34.
34. Garcia LS, Comim CM, Valvassori SS, et al. Ketamine treatment reverses behavioral and physiological alterations induced by chronic mild stress in rats. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:450–5.
35. Herrera-Perez JJ, Martinez-Mota L, Fernandez-Guasti A. Aging impairs the antidepressant-like response to citalopram in male rats. Eur J Pharmacol. 2010;633:39–43.
36. Larsen MH, Mikkelsen JD, Hay-Schmidt A, et al. Regulation of brain-derived neurotrophic factor (BDNF) in the chronic unpredictable stress rat model and the effects of chronic antidepressant treatment. J Psychiatr Res. 2010;44:808–16.

37. Casarotto PC, Andreatini R. Repeated paroxetine treatment reverses anhedonia induced in rats by chronic mild stress or dexamethasone. Eur Neuropsychopharmacol. 2007;17: 735–42.
38. Toth E, Gersner R, Wilf-Yarkoni A, et al. Age-dependent effects of chronic stress on brain plasticity and depressive behavior. J Neurochem. 2008;107:522–32.
39. Jayatissa MN, Henningsen K, West MJ, et al. Decreased cell proliferation in the dentate gyrus does not associate with development of anhedonic-like symptoms in rats. Brain Res. 2009;1290:133–41.
40. Orsetti M, Di Brisco F, Canonico PL, et al. Gene regulation in the frontal cortex of rats exposed to the chronic mild stress paradigm, an animal model of human depression. Eur J Neurosci. 2008;27:2156–64.
41. Papp M, Klimek V, Willner P. Effects of imipramine on serotonergic and beta-adrenergic receptor binding in a realistic animal model of depression. Psychopharmacology (Berl). 1994;114:309–14.
42. Grippo AJ, Beltz TG, Weiss RM, et al. The effects of chronic fluoxetine treatment on chronic mild stress-induced cardiovascular changes and anhedonia. Biol Psychiatry. 2006;59:309–16.
43. Lin D, Bruijnzeel AW, Schmidt P, et al. Exposure to chronic mild stress alters thresholds for lateral hypothalamic stimulation reward and subsequent responsiveness to amphetamine. Neuroscience. 2002;114:925–33.
44. Andreasen JT, Henningsen K, Bate S, et al. Nicotine reverses anhedonic-like response and cognitive impairment in the rat chronic mild stress model of depression: comparison with sertraline. J Psychopharmacol. 2011;25:1134–41.
45. Willner P. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. Neuropsychobiology. 2005;52:90–110.
46. Jayatissa MN, Bisgaard C, Tingstrom A, et al. Hippocampal cytogenesis correlates to escitalopram-mediated recovery in a chronic mild stress rat model of depression. Neuropsychopharmacology. 2006;31:2395–404.
47. Strekalova T, Steinbusch HW. Measuring behavior in mice with chronic stress depression paradigm. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:348–61.
48. Ma XC, Jiang D, Jiang WH, et al. Social isolation-induced aggression potentiates anxiety and depressive-like behavior in male mice subjected to unpredictable chronic mild stress. PLoS One. 2011;6:e20955.
49. Koo JW, Duman RS. IL-1 beta is an essential mediator of the antineurogenic and anhedonic effects of stress. Proc Natl Acad Sci U S A. 2008;105:751–6.
50. Schmidt HD, Duman RS. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacology. 2010;35:2378–91.
51. Harauma A, Moriguchi T. Dietary n-3 fatty acid deficiency in mice enhances anxiety induced by chronic mild stress. Lipids. 2011;46:409–16.
52. Mutlu O, Gumuslu E, Ulak G, et al. Effects of fluoxetine, tianeptine and olanzapine on unpredictable chronic mild stress-induced depression-like behavior in mice. Life Sci. 2012;91:1252–62.
53. Wu HH, Wang S. Strain differences in the chronic mild stress animal model of depression. Behav Brain Res. 2010;213:94–102.
54. Rauhut AS, Zentner IJ, Mardekian SK, et al. Wistar Kyoto and Wistar rats differ in the affective and locomotor effects of nicotine. Physiol Behav. 2008;93:177–88.
55. Nocjar C, Zhang J, Feng P, et al. The social defeat animal model of depression shows diminished levels of orexin in mesocortical regions of the dopamine system, and of dynorphin and orexin in the hypothalamus. Neuroscience. 2012;218:138–53.
56. Berton O, McClung CA, DiLeone RJ, et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science. 2006;311:864–8.
57. Yu T, Guo M, Garza J, et al. Cognitive and neural correlates of depression-like behaviour in socially defeated mice: an animal model of depression with cognitive dysfunction. Int J Neuropsychopharmacol. 2011;14:303–17.

58. Schloesser RJ, Lehmann M, Martinowich K, et al. Environmental enrichment requires adult neurogenesis to facilitate the recovery from psychosocial stress. Mol Psychiatry. 2010;15:1152–63.
59. Koolhaas JM, De Boer SF, De Rutter AJ, et al. Social stress in rats and mice. Acta Physiol Scand Suppl. 1997;640:69–72.
60. Bowens N, Heydendael W, Bhatnagar S, et al. Lack of elevations in glucocorticoids correlates with dysphoria-like behavior after repeated social defeat. Physiol Behav. 2012;105:958–65.
61. Kitanaka N, Kitanaka J, Tatsuta T, et al. Withdrawal from fixed-dose injection of methamphetamine decreases cerebral levels of 3-methoxy-4-hydroxyphenylglycol and induces the expression of anxiety-related behavior in mice. Neurochem Res. 2010;35:749–60.
62. Hollis F, Duclot F, Gunjan A, et al. Individual differences in the effect of social defeat on anhedonia and histone acetylation in the rat hippocampus. Horm Behav. 2011;59:331–7.
63. Miczek KA, Nikulina EM, Shimamoto A, et al. Escalated or suppressed cocaine reward, tegmental BDNF, and accumbal dopamine caused by episodic versus continuous social stress in rats. J Neurosci. 2011;31:9848–57.
64. Yan HC, Qu HD, Sun LR, et al. Fuzi polysaccharide-1 produces antidepressant-like effects in mice. Int J Neuropsychopharmacol. 2010;13:623–33.
65. Hall FS, Perona MTG. Have studies of the developmental regulation of behavioral phenotypes revealed the mechanisms of gene-environment interactions? Physiol Behav. 2012;107:623–40.
66. Hall FS. Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioral consequences. Crit Rev Neurobiol. 1998;12:129–62.
67. Hall FS, Perona MTG. The role of serotonin in the neurodevelopmental consequences of early social experience. In: Hall FS, editor. Serotonin: biosynthesis, regulation and health implications. New York: NOVA Science Publishers; 2013.
68. Haller J, Halasz J. Mild social stress abolishes the effects of isolation on anxiety and chlordiazepoxide reactivity. Psychopharmacology (Berl). 1999;144:311–5.
69. Adzic M, Djordjevic A, Demonacos C, et al. The role of phosphorylated glucocorticoid receptor in mitochondrial functions and apoptotic signalling in brain tissue of stressed Wistar rats. Int J Biochem Cell Biol. 2009;41:2181–8.
70. Adzic M, Djordievic J, Djordievic A, et al. Acute or chronic stress induce cell compartment-specific phosphorylation of glucocorticoid receptor and alter its transcriptional activity in Wistar rat brain. J Endocrinol. 2009;202:87–97.
71. Adzic M, Djordjevic A, Djordjevic J, et al. Effect of different types of stress on adrenal gland parameters and adrenal hormones in the blood serum of male Wistar rats. Arch Biol Sci. 2009;61:187–94.
72. Djordjevic A, Djordjevic J, Elakovic I, et al. Fluoxetine affects hippocampal plasticity, apoptosis and depressive-like behavior of chronically isolated rats. Prog Neuropsychopharmacol Biol Psychiatry. 2012;36:92–100.
73. Wallace DL, Han MH, Graham DL, et al. CREB regulation of nucleus accumbens excitability mediates social isolation-induced behavioral deficits. Nat Neurosci. 2009;12:200–9.
74. Evans J, Sun Y, McGregor A, et al. Allopregnanolone regulates neurogenesis and depressive/anxiety-like behaviour in a social isolation rodent model of chronic stress. Neuropharmacology. 2012;63:1315–26.
75. Heritch AJ, Henderson K, Westfall TC. Effects of social isolation on brain catecholamines and forced swimming in rats: prevention by antidepressant treatment. J Psychiatr Res. 1990;24:251–8.
76. Kokare DM, Dandekar MP, Singru PS, et al. Involvement of alpha-MSH in the social isolation induced anxiety- and depression-like behaviors in rat. Neuropharmacology. 2010;58:1009–18.
77. Brenes JC, Fornaguera J. The effect of chronic fluoxetine on social isolation-induced changes on sucrose consumption, immobility behavior, and on serotonin and dopamine function in hippocampus and ventral striatum. Behav Brain Res. 2009;198:199–205.
78. Brenes JC, Rodriguez O, Fornaguera J. Differential effect of environment enrichment and social isolation on depressive-like behavior, spontaneous activity and serotonin and

norepinephrine concentration in prefrontal cortex and ventral striatum. Pharmacol Biochem Behav. 2008;89:85–93.
79. Plaznik A, Palejko W, Stefanski R, et al. Open field behavior of rats reared in different social conditions: the effects of stress and imipramine. Pol J Pharmacol. 1993;45:243–52.
80. Wright IK, Upton N, Marsden CA. Resocialization of isolation-reared rats does not alter their anxiogenic profile on the elevated X-maze model of anxiety. Physiol Behav. 1991;50: 1129–32.
81. Yates G, Panksepp J, Ikemoto S, et al. Social-isolation effects on the behavioral despair forced swimming test – effect of age and duration of testing. Physiol Behav. 1991;49:347–53.
82. D'Andrea I, Gracci F, Alleva E, et al. Early social enrichment provided by communal nest increases resilience to depression-like behavior more in female than in male mice. Behav Brain Res. 2010;215:71–6.
83. Takatsu-Coleman AL, Patti CL, Zanin KA, et al. Short-term social isolation induces depressive-like behaviour and reinstates the retrieval of an aversive task: mood-congruent memory in male mice? J Psychiatry Neurosci. 2013;38:259–68.
84. Bachli H, Steiner MA, Habersetzer U, et al. Increased water temperature renders single-housed C57BL/6J mice susceptible to antidepressant treatment in the forced swim test. Behav Brain Res. 2008;187:67–71.
85. Martin AL, Brown RE. The lonely mouse: verification of a separation-induced model of depression in female mice. Behav Brain Res. 2010;207:196–207.
86. Koike H, Ibi D, Mizoguchi H, et al. Behavioral abnormality and pharmacologic response in social isolation-reared mice. Behav Brain Res. 2009;202:114–21.
87. Workman JL, Fonken LK, Gusfa J, et al. Post-weaning environmental enrichment alters affective responses and interacts with behavioral testing to alter nNOS immunoreactivity. Pharmacol Biochem Behav. 2011;100:25–32.
88. Silva CF, Duarte FS, De Lima TCM, et al. Effects of social isolation and enriched environment on behavior of adult Swiss mice do not require hippocampal neurogenesis. Behav Brain Res. 2011;225:85–90.
89. Ibi D, Takuma K, Koike H, et al. Social isolation rearing-induced impairment of the hippocampal neurogenesis is associated with deficits in spatial memory and emotion-related behaviors in juvenile mice. J Neurochem. 2008;105:921–32.
90. Maisonnette S, Morato S, Brandao ML. Role of resocialization and of 5-HT1A receptor activation on the anxiogenic effects induced by isolation in the elevated plus-maze test. Physiol Behav. 1993;54:753–8.
91. Mitic M, Simic I, Djordjevic J, et al. The antidepressant fluoxetine normalizes the nuclear glucocorticoid receptor evoked by psychosocial stress. Russ J Phys Chem A. 2011;85:2422–5.
92. Jaffe EH, Defrias V, Ibarra C. Changes in basal and stimulated release of endogenous serotonin from different nuclei of rats subjected to 2 models of depression. Neurosci Lett. 1993;162:157–60.
93. Bickerdike MJ, Wright IK, Marsden CA. Social-isolation attenuates rat forebrain 5-Ht release induced by Kcl stimulation and exposure to a novel environment. Behav Pharmacol. 1993;4:231–6.
94. Dalley JW, Theobald DE, Pereira EAC, et al. Specific abnormalities in serotonin release in the prefrontal cortex of isolation-reared rats measured during behavioural performance of a task assessing visuospatial attention and impulsivity. Psychopharmacology (Berl). 2002;164:329–40.
95. Hall FS, Wilkinson LS, Humby T, et al. Isolation rearing in rats: pre- and postsynaptic changes in striatal dopaminergic systems. Pharmacol Biochem Behav. 1998;59:859–72.
96. Wilkinson LS, Killcross SS, Humby T, et al. Social-isolation in the rat produces developmentally specific deficits in prepulse inhibition of the acoustic startle response without disrupting latent inhibition. Neuropsychopharmacology. 1994;10:61–72.
97. Hall FS, Humby T, Wilkinson LS, et al. The effects of isolation-rearing on sucrose consumption in rats. Physiol Behav. 1997;62:291–7.

98. Herman ZS, Trzeciak H, Chrusciel TL, et al. The influence of prolonged amphetamine treatment and amphetamine withdrawal on brain biogenic amine content and behaviour in the rat. Psychopharmacologia. 1971;21:74–81.
99. Robinson TE, Camp DM. Long-lasting effects of escalating doses of D-amphetamine on brain monoamines, amphetamine-induced stereotyped behavior and spontaneous nocturnal locomotion. Pharmacol Biochem Behav. 1987;26:821–7.
100. Russig H, Murphy CA, Feldon J. Behavioural consequences of withdrawal from three different administration schedules of amphetamine. Behav Brain Res. 2005;165:26–35.
101. White W, White IM. An activity indicator of acute withdrawal depends on amphetamine dose in rats. Physiol Behav. 2006;87:368–76.
102. Der-Avakian A, Markou A. Withdrawal from chronic exposure to amphetamine, but not nicotine, leads to an immediate and enduring deficit in motivated behavior without affecting social interaction in rats. Behav Pharmacol. 2010;21:359–68.
103. Lynch MA, Leonard BE. Effect of chronic amphetamine administration on the behaviour of rats in the open field apparatus: reversal of post-withdrawal depression by two antidepressants. J Pharm Pharmacol. 1978;30:798–9.
104. Cryan JF, Hoyer D, Markou A. Withdrawal from chronic amphetamine induces depressive-like behavioral effects in rodents. Biol Psychiatry. 2003;54:49–58.
105. Kokkinidis L, Zacharko RM, Anisman H. Amphetamine withdrawal: a behavioral evaluation. Life Sci. 1986;38:1617–23.
106. Kitanaka J, Kitanaka N, Takemura M. Sequential expression of impaired psychomotor and sensorimotor activities in rodents during amphetamine withdrawal. In: Davies RS, editor. Handbook of neuropsychiatry research. New York: Nova Science Publishers; 2010. p. 97–112.
107. Bechtholt-Gompf AJ, Walther HV, Adams MA, et al. Blockade of astrocytic glutamate uptake in rats induces signs of anhedonia and impaired spatial memory. Neuropsychopharmacology. 2010;35:2049–59.
108. John CS, Smith KL, Van't Veer A, et al. Blockade of astrocytic glutamate uptake in the prefrontal cortex induces anhedonia. Neuropsychopharmacology. 2012;37:2467–75.
109. Sigwalt AR, Budde H, Helmich I, et al. Molecular aspects involved in swimming exercise training reducing anhedonia in a rat model of depression. Neuroscience. 2011;192:661–74.
110. Beyer CE, Dwyer JM, Piesla MJ, et al. Depression-like phenotype following chronic CB_1 receptor antagonism. Neurobiol Dis. 2010;39:148–55.
111. Anderson CM, Swanson RA. Astrocyte glutamate transport: review of properties, regulation, and physiological functions. Glia. 2000;32:1–14.
112. Arriza JL, Fairman WA, Wadiche JI, et al. Functional comparisons of three glutamate transporter subtypes cloned from human motor cortex. J Neurosci. 1994;14:5559–69.
113. Fallgren AB, Paulsen RE. A microdialysis study in rat brain of dihydrokainate, a glutamate uptake inhibitor. Neurochem Res. 1996;21:19–25.
114. Palucha A, Pilc A. The involvement of glutamate in the pathophysiology of depression. Drug News Perspect. 2005;18:262–8.
115. Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. Ann N Y Acad Sci. 2003;1003:250–72.
116. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47:351–4.
117. Zarate Jr CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63:856–64.
118. Pariante CM. Risk factors for development of depression and psychosis. Glucocorticoid receptors and pituitary implications for treatment with antidepressant and glucocorticoids. Ann N Y Acad Sci. 2009;1179:144–52.
119. Sher L. Combined dexamethasone suppression-corticotropin-releasing hormone stimulation test in studies of depression, alcoholism, and suicidal behavior. ScientificWorldJournal. 2006;6:1398–404.
120. Burch J, McKenna C, Palmer S, et al. Rimonabant for the treatment of overweight and obese people. Health Technol Assess. 2009;13 Suppl 3:13–22.

121. Le Foll B, Forget B, Aubin HJ, et al. Blocking cannabinoid CB1 receptors for the treatment of nicotine dependence: insights from pre-clinical and clinical studies. Addict Biol. 2008;13:239–52.
122. Le Foll B, Gorelick DA, Goldberg SR. The future of endocannabinoid-oriented clinical research after CB1 antagonists. Psychopharmacology (Berl). 2009;205:171–4.
123. Leite CE, Mocelin CA, Petersen GO, et al. Rimonabant: an antagonist drug of the endocannabinoid system for the treatment of obesity. Pharmacol Rep. 2009;61:217–24.
124. Horder J, Harmer CJ, Cowen PJ, et al. Reduced neural response to reward following 7 days treatment with the cannabinoid CB1 antagonist rimonabant in healthy volunteers. Int J Neuropsychopharmacol. 2010;13:1103–13.
125. Johansson K, Neovius K, DeSantis SM, et al. Discontinuation due to adverse events in randomized trials of orlistat, sibutramine and rimonabant: a meta-analysis. Obes Rev. 2009;10:564–75.
126. Bras M, Dordevic V, Gregurek R, et al. Neurobiological and clinical relationship between psychiatric disorders and chronic pain. Psychiatr Danub. 2010;22:221–6.
127. Hall FS, Schwarzbaum JM, Perona MTG, et al. A greater role for the norepinephrine transporter than the serotonin transporter in murine nociception. Neuroscience. 2011;175:315–27.
128. Perona MTG, Waters S, Hall FS, et al. Animal models of depression in dopamine, serotonin, and norepinephrine transporter knockout mice: prominent effects of dopamine transporter deletions. Behav Pharmacol. 2008;19:566–74.
129. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain. 1988;33:87–107.
130. Andersen ML, Hoshino K, Tufik S. Increased susceptibility to development of anhedonia in rats with chronic peripheral nerve injury: involvement of sleep deprivation? Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:960–6.
131. Jesse CR, Wilhelm EA, Nogueira CW. Depression-like behavior and mechanical allodynia are reduced by bis selenide treatment in mice with chronic constriction injury: a comparison with fluoxetine, amitriptyline, and bupropion. Psychopharmacology (Berl). 2010;212:513–22.
132. Song C, Leonard BE. The olfactory bulbectomised rat as a model of depression. Neurosci Biobehav Rev. 2005;29:627–47.
133. Cryan JF, Mombereau C. In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. Mol Psychiatry. 2004;9:326–57.
134. Romeas T, Morissette MC, Mnie-Filali O, et al. Simultaneous anhedonia and exaggerated locomotor activation in an animal model of depression. Psychopharmacology (Berl). 2009;205:293–303.
135. Frisch P, Bilkei-Gorzo A, Racz I, et al. Modulation of the CRH system by substance P/NKA in an animal model of depression. Behav Brain Res. 2010;213:103–8.
136. Otmakhova NA, Gurevich EV, Katkov YA, et al. Dissociation of Multiple Behavioral-Effects between Olfactory Bulbectomized C57b1/6j and Dba/2j Mice. Physiol Behav. 1992;52:441–8.
137. Lumia AR, Teicher MH, Salchli F, et al. Olfactory bulbectomy as a model for agitated hyposerotonergic depression. Brain Res. 1992;587:181–5.
138. Wang DY, Noda Y, Tsunekawa H, et al. Behavioural and neurochemical features of olfactory bulbectomized rats resembling depression with comorbid anxiety. Behav Brain Res. 2007;178:262–73.
139. Slattery DA, Markou A, Cryan JF. Evaluation of reward processes in an animal model of depression. Psychopharmacology (Berl). 2007;190:555–68.
140. McNish KA, Davis M. Olfactory bulbectomy enhances sensitization of the acoustic startle reflex produced by acute or repeated stress. Behav Neurosci. 1997;111:80–91.
141. Marcilhac A, Maurel D, Anglade G, et al. Effects of bilateral olfactory bulbectomy on circadian rhythms of ACTH, corticosterone, motor activity and body temperature in male rats. Arch Physiol Biochem. 1997;105:552–9.
142. Commons KG. Neuronal pathways linking substance P to drug addiction and stress. Brain Res. 2010;1314:175–82.

143. Ebner K, Sartori SB, Singewald N. Tachykinin receptors as therapeutic targets in stress-related disorders. Curr Pharm Des. 2009;15:1647–74.
144. Chaki S, Nakazato A, Kennis L, et al. Anxiolytic- and antidepressant-like profile of a new CRF1 receptor antagonist, R278995/CRA0450. Eur J Pharmacol. 2004;485:145–58.
145. Chaki S, Oshida Y, Ogawa S, et al. MCL0042: a nonpeptidic MC4 receptor antagonist and serotonin reuptake inhibitor with anxiolytic- and antidepressant-like activity. Pharmacol Biochem Behav. 2005;82:621–6.
146. Xu Y, Ku BS, Yao HY, et al. Antidepressant effects of curcumin in the forced swim test and olfactory bulbectomy models of depression in rats. Pharmacol Biochem Behav. 2005;82:200–6.
147. Pistovcakova J, Dostalek M, Sulcova A, et al. Tiagabine treatment is associated with neurochemical, immune and behavioural alterations in the olfactory bulbectomized rat model of depression. Pharmacopsychiatry. 2008;41:54–9.
148. Vieyra-Reyes P, Mineur YS, Picciotto MR, et al. Antidepressant-like effects of nicotine and transcranial magnetic stimulation in the olfactory bulbectomy rat model of depression. Brain Res Bull. 2008;77:13–8.
149. Machado DG, Cunha MP, Neis VB, et al. Fluoxetine reverses depressive-like behaviors and increases hippocampal acetylcholinesterase activity induced by olfactory bulbectomy. Pharmacol Biochem Behav. 2012;103:220–9.
150. Jaako-Movits K, Zharkovsky T, Pedersen M, et al. Decreased hippocampal neurogenesis following olfactory bulbectomy is reversed by repeated citalopram administration. Cell Mol Neurobiol. 2006;26:1559–70.
151. Shen HW, Hagino Y, Kobayashi H, et al. Regional differences in extracellular dopamine and serotonin assessed by in vivo microdialysis in mice lacking dopamine and/or serotonin transporters. Neuropsychopharmacology. 2004;29:1790–9.
152. Xu F, Gainetdinov RR, Wetsel WC, et al. Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. Nat Neurosci. 2000;3:465–71.
153. Spielewoy C, Roubert C, Hamon M, et al. Behavioural disturbances associated with hyperdopaminergia in dopamine-transporter knockout mice. Behav Pharmacol. 2000;11:279–90.
154. Holmes A, Yang RJ, Murphy DL, et al. Evaluation of antidepressant-related behavioral responses in mice lacking the serotonin transporter. Neuropsychopharmacology. 2002;27:914–23.
155. Kalueff AV, Gallagher PS, Murphy DL. Are serotonin transporter knockout mice 'depressed'?: hypoactivity but no anhedonia. Neuroreport. 2006;17:1347–51.
156. Bechtholt AJ, Smith K, Gaughan S, et al. Sucrose intake and fasting glucose levels in 5-HT1A and 5-HT1B receptor mutant mice. Physiol Behav. 2008;93:659–65.
157. Javitt DC. Glutamate as a therapeutic target in psychiatric disorders. Mol Psychiatry. 2004;9:984–97, 979.
158. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology. 2012;62:63–77.
159. Tanaka K. Role of glutamate transporters in the pathophysiology of major mental illnesses. Nihon Shinkei Seishin Yakurigaku Zasshi. 2009;29:161–4 (in Japanese).
160. Belforte JE, Zsiros V, Sklar ER, et al. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nat Neurosci. 2010;13:76–83.
161. Labrie V, Lipina T, Roder JC. Mice with reduced NMDA receptor glycine affinity model some of the negative and cognitive symptoms of schizophrenia. Psychopharmacology (Berl). 2008;200:217–30.
162. Garcia-Garcia AL, Elizalde N, Matrov D, et al. Increased vulnerability to depressive-like behavior of mice with decreased expression of VGLUT1. Biol Psychiatry. 2009;66:275–82.
163. Ishizuka K, Paek M, Kamiya A, et al. A review of Disrupted-In-Schizophrenia-1 (DISC1): neurodevelopment, cognition, and mental conditions. Biol Psychiatry. 2006;59:1189–97.
164. Hikida T, Jaaro-Peled H, Seshadri S, et al. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc Natl Acad Sci U S A. 2007;104:14501–6.

165. Havik B, Le Hellard S, Rietschel M, et al. The complement control-related genes CSMD1 and CSMD2 associate to schizophrenia. Biol Psychiatry. 2011;70:35–42.
166. Distler MG, Opal MD, Dulawa SC, et al. Assessment of behaviors modeling aspects of schizophrenia in Csmd1 mutant mice. PLoS One. 2012;7:e51235.
167. Uhl GR, Drgon T, Liu QR, et al. Genome-wide association for methamphetamine dependence. Arch Gen Psychiatry. 2008;65:345–55.
168. Hall FS. Transgenic mouse studies reveal substantial roles for opioid receptors in the rewarding effects of several classes of addictive drugs. Curr Psychiatry Rev. 2006;2:27–37.
169. Cinque C, Pondiki S, Oddi D, et al. Modeling socially anhedonic syndromes: genetic and pharmacological manipulation of opioid neurotransmission in mice. Transl Psychiatry. 2012;2:e155.
170. Komatsu H, Ohara A, Sasaki K, et al. Decreased response to social defeat stress in mu-opioid-receptor knockout mice. Pharmacol Biochem Behav. 2011;99:676–82.
171. Lahmame A, del Arco C, Pazos A, et al. Are Wistar-Kyoto rats a genetic animal model of depression resistant to antidepressants? Eur J Pharmacol. 1997;337:115–23.
172. Will CC, Aird F, Redei EE. Selectively bred Wistar-Kyoto rats: an animal model of depression and hyper-responsiveness to antidepressants. Mol Psychiatry. 2003;8:925–32.
173. Overstreet DH, Friedman E, Mathe AA, et al. The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. Neurosci Biobehav Rev. 2005;29:739–59.
174. Zambello E, Jimenez-Vasquez PA, El Khoury A, et al. Acute stress differentially affects corticotropin-releasing hormone mRNA expression in the central amygdala of the "depressed" flinders sensitive line and the control flinders resistant line rats. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:651–61.
175. Rezvani AH, Parsian A, Overstreet DH. The Fawn-Hooded (FH/Wjd) rat: a genetic animal model of comorbid depression and alcoholism. Psychiatr Genet. 2002;12:1–16.
176. Overstreet DH, Wegener G. The flinders sensitive line rat model of depression–25 years and still producing. Pharmacol Rev. 2013;65:143–55.
177. Vollmayr B, Bachteler D, Vengeliene V, et al. Rats with congenital learned helplessness respond less to sucrose but show no deficits in activity or learning. Behav Brain Res. 2004;150:217–21.
178. Okamoto K, Aoki K. Development of a strain of spontaneously hypertensive rats. Jpn Circ J. 1963;27:282–93.
179. Pare WP. Open field, learned helplessness, conditioned defensive burying, and forced-swim tests in WKY rats. Physiol Behav. 1994;55:433–9.
180. Lopez-Rubalcava C, Lucki I. Strain differences in the behavioral effects of antidepressant drugs in the rat forced swimming test. Neuropsychopharmacology. 2000;22:191–9.
181. Malkesman O, Braw Y, Zagoory-Sharon O, et al. Reward and anxiety in genetic animal models of childhood depression. Behav Brain Res. 2005;164:1–10.
182. Overstreet DH, Russell RW, Helps SC, et al. Selective breeding for sensitivity to the anticholinesterase DFP. Psychopharmacology (Berl). 1979;65:15–20.
183. Overstreet DH, Griebel G. Antidepressant-like effects of the vasopressin V1b receptor antagonist SSR149415 in the Flinders Sensitive Line rat. Pharmacol Biochem Behav. 2005;82:223–7.
184. Roth-Deri I, Friedman A, Abraham L, et al. Antidepressant treatment facilitates dopamine release and drug seeking behavior in a genetic animal model of depression. Eur J Neurosci. 2009;30:485–92.
185. Overstreet DH, Rezvani AH. Behavioral differences between two inbred strains of Fawn-Hooded rat: a model of serotonin dysfunction. Psychopharmacology (Berl). 1996;128:328–30.
186. Aulakh CS, Tolliver T, Wozniak KM, et al. Functional and biochemical-evidence for altered serotonergic function in the Fawn-Hooded rat strain. Pharmacol Biochem Behav. 1994;49:615–20.
187. Overstreet DH, Rezvani AH, Janowsky DS. Genetic animal-models of depression and ethanol preference provide support for cholinergic and serotonergic involvement in depression and alcoholism. Biol Psychiatry. 1992;31:919–36.

188. Rezvani AH, Overstreet DH, Janowsky DS. Genetic serotonin deficiency and alcohol preference in the Fawn Hooded rats. Alcohol Alcohol. 1990;25:573–5.
189. Hall FS, Huang S, Fong GW, et al. Effects of isolation-rearing on voluntary consumption of ethanol, sucrose and saccharin solutions in Fawn Hooded and Wistar rats. Psychopharmacology (Berl). 1998;139:210–6.
190. Hall FS, Huang S, Fong GW, et al. Effects of isolation rearing on locomotion, anxiety and responses to ethanol in Fawn Hooded and Wistar rats. Psychopharmacology (Berl). 1998;139:203–9.
191. Hall FS, Huang S, Fong GW, et al. Differential basis of strain and rearing effects on open-field behavior in Fawn Hooded and Wistar rats. Physiol Behav. 2000;71:525–32.
192. Hall FS, Sundstrom JM, Lerner J, et al. Enhanced corticosterone release after a modified forced swim test in Fawn Hooded rats is independent of rearing experience. Pharmacol Biochem Behav. 2001;69:629–34.
193. Aulakh CS, Hill JL, Murphy DL. Attenuation of hypercortisolemia in Fawn-Hooded rats by antidepressant drugs. Eur J Pharmacol. 1993;240:85–8.
194. Aulakh CS, Wozniak KM, Hill JL, et al. Differential neuroendocrine responses to the 5-HT agonist m-chlorophenylpiperazine in Fawn-Hooded rats relative to Wistar and Sprague-Dawley rats. Neuroendocrinology. 1988;48:401–6.
195. Hall FS, Huang S, Fong GF, et al. The effects of social isolation on the forced swim test in Fawn Hooded and Wistar rats. J Neurosci Methods. 1998;79:47–51.
196. Lahmame A, Gomez F, Armario A. Fawn-Hooded rats show enhanced active behaviour in the forced swimming test, with no evidence for pituitary-adrenal axis hyperactivity. Psychopharmacology (Berl). 1996;125:74–8.
197. Seligman ME, Maier SF, Geer JH. Alleviation of learned helplessness in dog. J Abnorm Psychol. 1968;73:256–62.
198. Seligman MEP, Rosellini RA, Kozak MJ. Learned helplessness in rat – time course, immunization, and reversibility. J Comp Physiol Psychol. 1975;88:542–7.
199. Henn FA, Vollmayr B. Stress models of depression: forming genetically vulnerable strains. Neurosci Biobehav Rev. 2005;29:799–804.
200. Sanchis-Segura C, Spanagel R, Henn FA, et al. Reduced sensitivity to sucrose in rats bred for helplessness: a study using the matching law. Behav Pharmacol. 2005;16:267–70.
201. Vollmayr B, Henn FA. Learned helplessness in the rat: improvements in validity and reliability. Brain Res Brain Res Protoc. 2001;8:1–7.
202. Barr AM, Fiorino DF, Phillips AG. Effects of withdrawal from an escalating dose schedule of D-amphetamine on sexual behavior in the male rat. Pharmacol Biochem Behav. 1999;64:597–604.
203. Vacca G, Ahn S, Phillips AG. Effects of short-term abstinence from escalating doses of D-amphetamine on drug and sucrose-evoked dopamine efflux in the rat nucleus accumbens. Neuropsychopharmacology. 2007;32:932–9.
204. Markou A, Koob GF. Bromocriptine reverses the elevation in intracranial self-stimulation thresholds observed in a rat model of cocaine withdrawal. Neuropsychopharmacology. 1992;7:213–24.
205. Stoker AK, Markou A. Withdrawal from chronic cocaine administration induces deficits in brain reward function in C57BL/6J mice. Behav Brain Res. 2011;223:176–81.
206. Chartoff E, Sawyer A, Rachlin A, et al. Blockade of kappa opioid receptors attenuates the development of depressive-like behaviors induced by cocaine withdrawal in rats. Neuropharmacology. 2012;62:167–76.
207. Wise RA, Munn E. Withdrawal from chronic amphetamine elevates base-line intracranial self-stimulation thresholds. Psychopharmacology (Berl). 1995;117:130–6.
208. Barr AM, Phillips AG. Increased successive negative contrast in rats withdrawn from an escalating-dose schedule of D-amphetamine. Pharmacol Biochem Behav. 2002;71:293–9.
209. Semenova S, Markou A. The alpha 2 adrenergic receptor antagonist idazoxan, but not the serotonin-2A receptor antagonist M100907, partially attenuated reward deficits associated with nicotine, but not amphetamine, withdrawal in rats. Eur Neuropsychopharmacol. 2010;20:731–46.

210. Zhornitsky S, Potvin S, Stip E, et al. Acute quetiapine dose-dependently exacerbates anhedonia induced by withdrawal from escalating doses of D-amphetamine. Eur Neuropsychopharmacol. 2010;20:695–703.
211. Takigawa M, Maeda H, Ueyama K, et al. A dual approach to self-stimulation and locomotor trace affected by chronic methamphetamine treatment for an animal-model of schizophrenia. Can J Physiol Pharmacol. 1993;71:321–5.
212. Pulvirenti L, Koob GF. Lisuride reduces psychomotor retardation during withdrawal from chronic intravenous amphetamine self-administration in rats. Neuropsychopharmacology. 1993;8:213–8.
213. Kitanaka N, Kitanaka J, Hall FS, et al. A single administration of methamphetamine to mice early in the light period decreases running wheel activity observed during the dark period. Brain Res. 2012;1429:155–63.
214. Perrine SA, Sheikh IS, NwaneshiudU CA, et al. Withdrawal from chronic administration of cocaine decreases delta opioid receptor signaling and increases anxiety- and depression-like behaviors in the rat. Neuropharmacology. 2008;54:355–64.
215. Fukushiro DF, Mari-Kawamoto E, Aramini TCF, et al. Withdrawal from repeated treatment with amphetamine reduces novelty-seeking behavior and enhances environmental habituation in mice. Pharmacol Biochem Behav. 2011;100:180–4.
216. Barr AM, Phillips AG. Withdrawal following repeated exposure to D-amphetamine decreases responding for a sucrose solution as measured by a progressive ratio schedule of reinforcement. Psychopharmacology (Berl). 1999;141:99–106.
217. Solinas M, Thiriet N, Chauvet C, et al. Prevention and treatment of drug addiction by environmental enrichment. Prog Neurobiol. 2010;92:572–92.
218. Thiel KJ, Pentkowski NS, Peartree NA, et al. Environmental living conditions introduced during forced abstinence alter cocaine-seeking behavior and Fos protein expression. Neuroscience. 2010;171:1187–96.
219. Gipson CD, Beckmann JS, El-Maraghi S, et al. Effect of environmental enrichment on escalation of cocaine self-administration in rats. Psychopharmacology (Berl). 2011;214:557–66.
220. Fukushiro DF, Josino FS, Saito LP, et al. Differential effects of intermittent and continuous exposure to novel environmental stimuli on the development of amphetamine-induced behavioral sensitization in mice: implications for addiction. Drug Alcohol Depend. 2012;124:135–41.
221. Nader J, Chauvet C, Rawas RE, et al. Loss of environmental enrichment increases vulnerability to cocaine addiction. Neuropsychopharmacology. 2012;37:1579–87.
222. Puhl MD, Blum JS, Acosta-Torres S, et al. Environmental enrichment protects against the acquisition of cocaine self-administration in adult male rats, but does not eliminate avoidance of a drug-associated saccharin cue. Behav Pharmacol. 2012;23:43–53.
223. Thiel KJ, Sanabria F, Pentkowski NS, et al. Anti-craving effects of environmental enrichment. Int J Neuropsychopharmacol. 2009;12:1151–6.
224. Grimm JW, Osincup D, Wells B, et al. Environmental enrichment attenuates cue-induced reinstatement of sucrose seeking in rats. Behav Pharmacol. 2008;19:777–85.
225. Brenes JC, Padilla M, Fornaguera J. A detailed analysis of open-field habituation and behavioral and neurochemical antidepressant-like effects in postweaning enriched rats. Behav Brain Res. 2009;197:125–37.
226. Chauvet C, Goldberg SR, Jaber M, et al. Effects of environmental enrichment on the incubation of cocaine craving. Neuropharmacology. 2012;63:635–41.
227. Murphy A, Taylor E, Elliott R. The detrimental effects of emotional process dysregulation on decision-making in substance dependence. Front Integr Neurosci. 2012;6:101.

Chapter 13
Neural Basis of Anhedonia Associated with Stress-Induced Eating Disorders

Jeong Won Jahng

Abstract Prolonged or repeated exposure to stressful events has been associated with clinical depression in humans, and also produces depressive-like behaviors in rodent models. Depression has been proposed to be associated with reduced reward-motivated learning. Anhedonia is a main symptom of depression, and the concept of anhedonia refers to a reduction of the ability to experience pleasure, as reflected in a diminished interest in rewarding stimuli and pleasurable events. Many studies have suggested that anhedonia could influence life function and increase vulnerability to the development of psychic disease. A possible dysfunction in the reward and motivation systems has been lately proposed to explain the link between anhedonia and depression. It has been hypothesized that a dysregulated reward system may be associated with the development and maintenance of eating disorders. Indeed, anhedonia is considered as a feature of anorexia nervosa and the most commonly co-morbid disorder in patients with eating disorders. Dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis activity are most commonly found in patients with eating disorders. We have previously reported that rats with stress experiences in early life show depression-like behaviors including anhedonia, binge-like eating when challenged with metabolic or social stressors, and the HPA axis dysfunctions. In this chapter, neural basis of anhedonia associated with stress-induced disordered eating behaviors in animal models will be discussed.

Keywords Body weight • Dopamine • Eating disorders • Hypothalamic-pituitary-adrenal axis • Leptin • Nucleus accumbens • Stress

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Abbreviations

HPA	Hypothalamic-pituitary-adrenal axis
MS	Neonatal maternal separation
NH	Non-handled
NAc	Nucleus accumbens
PND	Postnatal day
pSTAT3	Phosphorylated signal transducer and activator of transcription 3
TH	Tyrosine hydroxylase
VTA	Ventral tegmental area

13.1 Stress-Induced Disordered Eating Behaviors

Experience of childhood abuse, a type of early life trauma, is prevalent among patients with eating disorders [1]. Many patients with eating disorders particularly those with bulimia nervosa have reported to be abused in childhood [2–5]. However, few studies have focused on the association of feeding behaviors in later life with stress in childhood [6–8]. Neonatal maternal separation (MS) in rodents is a well known animal model of stressful experiences in childhood. Iwasaki et al. [8], hired a protocol of daily 6-h MS during the first 3 weeks of birth using Wistar rats, reported that there was no significant difference in normal daily food consumption and weight gain, except a transient decrease in body weight shortly after the separation period, both in male and female offspring. However, rebound hyperphagia following a time-restricted scheduled feeding was significantly increased in 6- to 9-week-old female MS rats, but no difference observed in males [8]. McIntosh et al. [7], hired a protocol of daily 3-h MS during the first 3 weeks of birth using Sprague–Dawley rats, reported that palatable snack consumption was increased in MS females, but not in MS males. We have followed a protocol of daily 3-h MS during the first 2 weeks of birth using Sprague–Dawley rats, found that daily chow intake of MS males did not differ from non-handled (NH) control males [9], and a transient increase was observed in MS females on postnatal day (PND) 36 compared with NH females [10]. Interestingly, repeated fasting/refeeding challenges during adolescent period induced binge-like eating in MS males [11]. When the weanling male pups were singly housed, significant increases in body weight gain were detected in MS pups from PND 36, and the weight difference between single caged NH and MS persisted until sacrificed [9]. Increased chow intake in single caged MS males appeared to contribute to their increased weight gain. Contrarily, post-weaning isolation (isolation rearing) did not affect weight gain and food intake of MS females (unpublished our observation). Collectively, it is concluded that repeated experience of maternal separation during pre-weaning period in rats may not permanently affect food intake and body weight gain of the offspring. However, stressful challenges, such as time-restricted scheduled feeding [8], repeated fasting/refeeding

cycles [11] and isolation rearing [9], or an exposure to palatable food [7] may evoke disordered eating behaviors in MS offspring with gender differences.

A large body of literature suggests post-weaning isolation rearing of rodents is one procedure that models some of the behavioral consequences of adverse early-life experiences in humans. A large number of studies employed chronic (longer than 1 week) post-weaning social isolation, also termed isolation rearing, as a rodent model of adverse early-life experience or social deprivation [12–15]. Rearing rodents in persistent social isolation from weaning, to deprive them of social play, is a relevant paradigm for studying early life stress and produces a large array of consistent long-lasting neuroendocrinological and behavioral alterations compared with group housed controls [12, 15, 16]. The reported behavioral and neuroendocrinological effects of post-weaning isolation in rats, which mostly studied in males, have strongly suggested its tentative impact on feeding behaviors; however, isolation rearing in male rats did not cause consistent alteration in body weight and food intake from age-matched controls [9]. The effect of adolescent social isolation on body weight and food intake of female rats has rarely been reported. We have demonstrated that adolescence social isolation may induce binge-like eating and promote weight gain in female rats [17].

13.2 Disordered Eating Behaviors and Psycho-emotional Symptoms

Early life stress, such as that induced by maternal separation, child physical, sexual and emotional abuse and general neglect has been associated with serious psychiatric impairments in adulthood [18]. Specifically, early parental loss, a stressful life event, is related to unipolar and bipolar depression, as well as anxiety disorders, beyond familial or genetic factors [19–22], and many human studies have reported that syndromal major depression and anxiety disorders are frequent in adults with a history of child hood abuse [23–25]. Our MS animal model that showed dysfunctions in the HPA axis activity [11, 26] exhibited depression- and anxiety-like behaviors in young adulthood [9, 27], in accordance with reports by others following a similar separation paradigm [28–32]. That is, ambulation and rearings were decreased, immobility during forced swim test increased, and time spent in the closed arms of elevated plus maze increased in our MS rats compared to non-handled (NH) control rats.

The behavioral scores of our MS rats, such as ambulatory counts, rearings, defecation scores, immobility duration during the swim test, and the arm stays and entries of elevated plus maze test, did not seem to be further worsened by isolation rearing [9]. However, statistical analyses of the behavioral scores with 2-way ANOVA suggested an impact of post-weaning isolation on anxiety-like behaviors of MS pups. Thus, isolation-induced increases in food intake and weight gain observed in our MS males is likely to be related with its impact on the psycho-emotional behaviors representing anxiety.

MS rats that showed depression and anxiety-like behaviors [9, 27] have developed a binge-like eating when they were challenged with repeated fasting/refeeding cycles [11]. Altered emotional and mood states, including depression and anxiety, affect eating behavior and food choice. Depression and anxiety can be linked to compulsive behaviors such as drug taking and craving for palatable food which induces feeling of pleasure [33, 34]. Human studies showed that most subjects reported a preference for palatable food rich in fat and sugar during negative emotions [35]. Thus, it is likely that a binge-like eating observed in our MS rats during repeated fasting/refeeding cycles may be related with their psycho-emotional status. Indeed, repeated fasting/refeeding cycles, metabolic stress challenges, not only resulted in a binge-like eating behavior but also improved depression-like behaviors of our MS rats [36].

Among women with bulimia nervosa, higher levels of negative interactions and conflict have been observed [37]. Feelings of alienation from friends and peers have also been associated with other problems among both adolescents and adults including depression [38], drug use and suicide [39]. A strong association between psychosocial stressors in early life and increased risks for depression, anxiety and substance abuse in adulthood has been reported in women [40]. The reported behavioral effects of post-weaning isolation in rats include changes in learning and memory [41, 42], increased anxiety [9, 43–46] and aggressiveness [47], and enhanced cocaine self-administration behavior [48].

Association of binge-like eating disorders with symptoms of anxiety and depression has been reported [49, 50]. Adolescence social isolation induced a binge-like eating with increased palatable food intake in female rats [17]. Increased food intake, especially palatable food intake, in chronically stressed rats has been suggested to be correlated with anxiety-like behaviors [51]. Although the behavioral scores of isolated females during elevated plus maze test did not differ from group-caged ones, number of rearings, repetitive standing with two forepaws up, was increased in isolated females during the activity test [17]. Increased rearing activity in rats has been reported to reveal an anxiety-related behavior responding to stress, as a proactive emotional coping behavior [52, 53]. It has been suggested that increased food intake responding to stress is a stress coping behavior and consumption of palatable food dampens psychological and physiological responses to stress [54, 55]. The stress-induced elevation of plasma corticosterone was blunted in our isolated females that ate more food than group-caged ones. Therefore, increased consumption of food in isolated females may be a stress coping behavior, likely in relation with anxiety-related behaviors, dampening psychological and physiological responses to chronic social isolation stress. Isolated females showed depression-like behaviors with increased immobility duration in the Porsolt swim test, and their basal corticosterone levels were increased [17]. Previous studies have suggested that increased serum cortisol levels are implicated in depression [56] and binge eating disorders [57, 58]. Thus, it is concluded that adolescence social isolation increases food intake and depression-like behaviors in female rats and a tonic increase of the HPA axis activity responding to chronic isolation stress may play a role in its pathophysiology.

13.3 Stress, Weight Loss, Anhedonia

Work performed by Katz and colleagues [59] in the early 1980s demonstrated that exposure of rodents to severe stressors resulted in a reduction in locomotor activity and of their consumption of rewarding palatable substances; i.e. sucrose *per se*. Chronic mild stress is in fact a well known animal model of depression and the neurobiological changes observed following chronic mild stress are consistent with those observed in major depression [60]. It has been reported that consumption of sucrose solution or sweet food is progressively reduced in rats by chronic mild stress [59, 61–64]. This reduction in sweet consumption was believed to be akin to the impairments in reward processing, which are the foundation for anhedonia, a core symptom of major depression [65]. The validity of this model for producing a state of "anhedonia" was supported by additional research demonstrating that deficits were also seen in other measures of reward and hedonic impact such as conditioned place preference, brain stimulation reward and dopaminergic release in response to rewarding stimuli [66]. Anhedonia by chronic mild stress appears to be associated with reductions of food intake and body weight gain [62, 63].

Several human studies have demonstrated that acute stress increases not only the frequency and amount of food intake but also intake of highly palatable food [67, 68]. Whereas, some other studies have reported that stress may result in a decreased energy intake in human [69, 70]. Stress, in fact, can lead to both under- and over-eating, and little is known about what determines direction of eating [70]. In contrast to humans, rats and mice consistently lose weight in response to stress, and it has been suggested that decreased food intake and weight loss serve as the most reliable marker of stress severity [71]. In adult rats, repeated exposure to restraint or immobilization results in reduction of food intake and body weight gain [72, 73]. Adult rats exposed to restraint stress for 3 h daily for three consecutive days showed decreases in food intake and body weight on the days of stress [74, 75]. However, 1 h of restraint stress given every other day during adolescent period (PND 28–40) did not affect chow intake and weight gain; however, it suppressed cookie intake on the days of stress (Fig. 13.1), revealing a stress-induced anhedonia without weight loss. Chow intake during the preference test on cookie did not differ between the control and restraint groups [76]. It is plausible that the restraint dose used in this study may not be so severe to affect weight gain or daily food intake of adolescent rats that are in a great demand for growth; however, it may still be enough to affect the brain reward system, suppress pleasure seeking behavior, such as caving for palatable food. Also, this result suggests that the development of anhedonia may not be necessarily associated with weight loss and/or reduced normal food intake.

We have demonstrated that consumption of chocolate cookie, but not standard chow, is reduced in adolescent rats that experienced neonatal maternal separation [76]. The maternally-deprived rhesus monkey has also been proposed as an animal model of depression [77, 78]. Maternally-deprived monkeys had a diminished preference for sweetened water than did controls [79]. Studies have reported that maternally separated rats show a slight suppression in body weight gain shortly after the

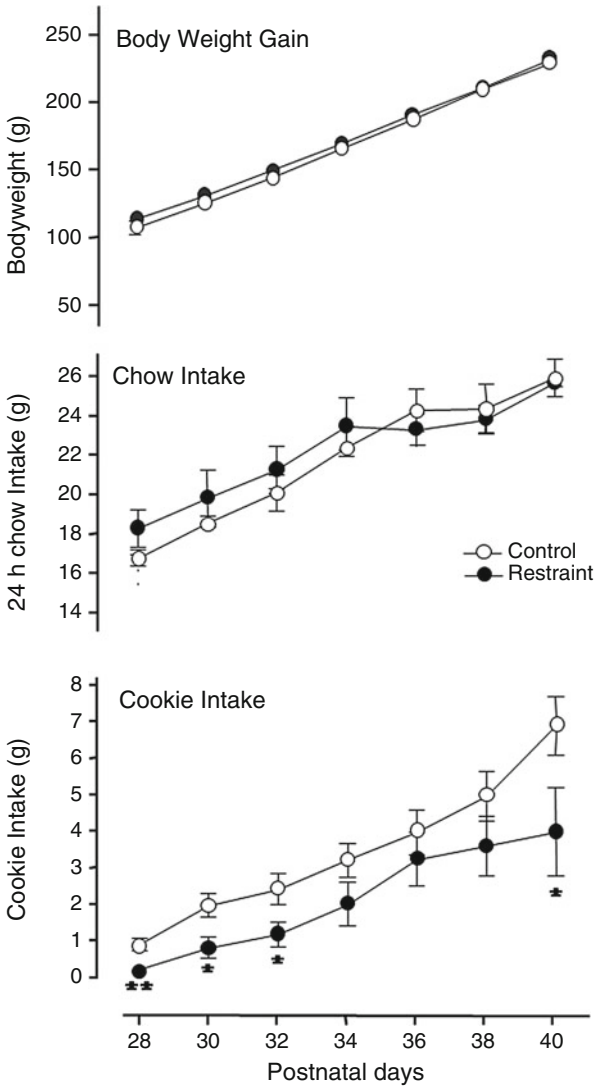

Fig. 13.1 Body weight gain, daily chow intake and 1 h cookie intake. Rats were placed in a restraint cage for 1 h at every even day during postnatal days 28–40, and had free choices of chow and chocolate cookie for 1 h immediately after each stress session. Control rats received free choices of chow and cookie in the same time schedule with the stress group, just omitting restraint stress. $^{*}P<0.05$, $^{**}P<0.01$ vs. controls on each day, Data are presented by means ± S.E.

separation period, but thereafter do not show significant differences in weight gain compared with age-matching non-handled controls [7, 8, 11, 26, 29]. Thus, it is concluded that the development of anhedonia by neonatal maternal separation is not associated with changes in weight gain.

Adolescence social isolation promoted food intake and weight gain in female rats and the isolated females showed increased immobility during forced swim test which reveals increased depression-like behavior [17]. Interestingly, cookie consumption was significantly increased in the isolated females compared with group-housed controls. These results suggest that depression-like behaviors with

hyperphagia and weight gain could be associated with craving for sweet food rather than anhedonia with decreased sweet intake. In another animal model, McIntosh et al. [7], hiring a protocol of daily 3-h maternal separation (MS) during the first 3 weeks of birth using Sprague–Dawley rats, reported that palatable snack consumption was increased in MS females, but not in MS males. We have reported that a protocol of daily 3-h MS during the first 2 weeks of birth using Sprague–Dawley rats significantly increases depression-like behaviors, i.e. increased immobility during forced swim test *per se*, not only in MS males but also in MS females [9, 27, 80]. As mentioned above, MS males that experienced daily 3-h MS during the first 2 weeks of birth showed anhedonia with decreased palatable snack consumption [76]. These results together suggest that symptoms of depression may not always comprise anhedonia or that sweet intake may not always reliable measurement for anhedonia symptom in rodents.

It was reported that depressed patients gave similar pleasantness ratings to water and lower sucrose solutions as did control group [81]. Surprisingly, in the same study, the depressed patients gave higher pleasantness ratings to more concentrated sucrose solutions. Steiner et al. [82] have reported that depressed and non-depressed subjects did not vary significantly in hedonic evaluation of food-related gustatory stimuli. The patients in both studies [81, 82] were hospitalized and treated with antidepressants and thus the results should be interpreted with caution though. However, studies have suggested that depressive mood may potentiate craving for sweets [83–85]. Also, sucrose and glucose detection thresholds did not vary by the severity of depression [86, 87].

13.4 Meso-limbic Dopamine Activity by Early Life Stress Experience

Development of anhedonia has been ascribed to dysfunction of the reward pathway, in which the nucleus accumbens (NAc) plays a pivotal role [88, 89]. Palatability and hedonic value of food play central roles in nutrient intake, and recent studies have demonstrated that the NAc is strongly implicated in the motivational mechanisms for feeding [90–92] and the hedonic property of palatable food ingestion [93–95]. It is well known that stress affects food intake, and chronic stress has been reported to induce dramatic neurochemical alterations in the NAc, leading to depressive phenotypes [88, 96]. The striatal dopaminergic activity was suggested to be associated with the severity of anhedonia in depressed patients [97], and it has been reported that acute and repeated immobilization stresses differentially affect dopaminergic activities in sub-regions of the striatum including NAc [98]. These reports together suggest that dopaminergic activity in the NAc may play a key role in the stress-induced disordered eating behavior associated with anhedonia symptom.

c-Fos expression, a conventional marker for neuronal activation, was increased in the NAc of maternally separated (MS) pups as compared with non-handled (NH) controls, and the increase was statistically significant in the NAc core [76]. Studies

have reported that the NAc core is required for normal preference for a large reward [99] and handles generic motivational value of food whereas the NAc shell integrates the motivational valence and novelty [90]. It has been suggested that increased Fos expression in the NAc may be related with decreased food intake [100] and aversive response to palatable food [101]. Thus, it is likely that increased neuronal activities in the NAc core of MS pups may be implicated in the decreased cookie intake; likely, suppressing motivational and/or reward values of palatable food. In other words, Fos-expressing neurons in the NAc of MS pups seem to play a role in anhedonia symptom by MS experience.

Repeated restraint stress suppressed cookie intake of NH pups, but it did not further suppress cookie intake of MS pups [76]. These results led us to assume that neuronal activation in the NAc of MS pups responding to restraint stress may differ from NH pups. Indeed, number of c-Fos expressing neurons was significantly increased in the NAc, both core and shell, of NH pups following repeated restraint; whereas, this increase was not observed in MS pups [76]. Therefore, it is concluded that c-Fos expression in the NAc neurons may play a role in the regulatory mechanism underlying restraint-induced anhedonia and reduce palatable food intake in non-handled control rats, and the experience of neonatal maternal separation blunts the activation of the NAc neurons responding to restraint stress later in life. Further studies are required to identify the neurons expressing c-Fos in the NAc by MS experience and ones by repeated restraint in control rats.

The dopaminergic system has been of particular interest, as dopamine in the NAc has been shown to be associated with motivation, reward, and hedonia [102]. Both the shell and core of NAc receive a dense afferent dopaminergic innervation from the ventral mesencephalon [103]. It has been reported that disruption of dopaminergic function within the NAc causes anhedonia in rodents [104] and that dopamine neurotransmission in the NAc responding to food is blunted by chronic mild stress, an animal model of depression [88], suggesting that reduced dopamine release in the NAc may cause anhedonia. We have demonstrated that the stress-induced dopamine increase is blunted not only in the midbrain dopaminergic neurons but also in the NAc of MS pups [105]. In the same study, stress-induced expression of tyrosine hydroxylase (TH), the rate limiting enzyme of dopamine biosynthesis, was blunted in MS pups both in the ventral tegmental area (VTA) and the substantia nigra. This result suggests that MS experience may blunt not only the meso-limbic but also the nigro-striatal dopaminergic activities responding to stressful stimuli later in life. Previous studies have reported that long-term exposure to various unavoidable stress factors may suppress the meso-limbic dopamine function [88, 106, 107]. However, the basal levels of dopamine contents in the midbrain and NAc and the VTA-TH expression did not differ between the pups that experienced maternal separation and the non-handled control pups [105]. That is, repeated exposure to maternal separation during neonatal period, a type of long-term exposure to unavoidable stress, does not appear to affect the basal activity of the meso-limbic dopamine system. Taken together, it is concluded that MS experience, although it may not affect the basal dopamine level, may result in a long-term suppression of dopaminergic function responding to stressful stimuli both in the

mesolimbic and the nigrostriatal dopamine pathways in the offspring later in life, which may be implicated in the symptom of anhedonia.

It has been shown that acute restraint stress induces c-Fos expression in the NAc core and shell [108]. Both the shell and core of NAc receive a dense afferent dopaminergic innervation from the ventral mesencephalon [103]. Studies have reported that acute exposure to different forms of stress activates the meso-limbic dopaminergic pathway, increases dopamine release in the NAc [51, 109, 110]. In our study, acute restraint increased not only dopamine contents in the NAc but also c-Fos expression in the NAc core and shell in non-handled (NH) controls [105]. Thus, it is likely that increased dopaminergic input in the NAc by acute restraint might have contributed, at least partly, to c-Fos expression in the NAc neurons of NH pups. Together with the result showing that 1 h of restraint stress suppressed cookie intake on the day of stress in NH pups [76], it is concluded that acute increase of dopaminergic input in the NAc, perhaps inducing c-Fos expression, may be implicated in the underlying mechanism of anhedonia symptom by acute stress.

13.5 Meso-limbic Dopamine Activity by Chronic Mild Stress

The majority of studies examining dopamine levels in the striatum, or more specifically in the nucleus accumbens (NAc), have demonstrated no effect of chronic mild stress on the basal dopamine transmission [88, 111–114]. In contrast a few studies have reported a reduction in striatal dopamine levels [115, 116]. Interestingly, previous exposure to chronic mild stress appears to potentiate stress-induced dopamine release in the NAc [88], while dopamine release responding to palatable food is reduced following chronic mild stress [88]. These data could indicate an enhancement of neurochemical responses to aversive stimuli and a blunting of responses to rewarding stimuli following chronic mild stress, which is conducive to the idea that processing of aversive and hedonic stimuli is disrupted in depression.

13.6 NAc Function and the HPA Axis Activity

Repeated exposure to restraint stress during adolescent period markedly increased the plasma corticosterone levels in rats (Fig. 13.2), concurring with other reports that repeated exposure to stressors induces a long-term increase of corticosterone levels [117, 118]. Interestingly, c-Fos expression was also increased in the NAc core and shell following repeated exposure to restraint stress (Fig. 13.2). Human studies have demonstrated that the secretion of dopamine over the NAc responding to stressors is proportional to cortisol responses [119, 120]. Thus, it is suggested that the increased c-Fos expression in the NAc responding to repeated restraints may be related with increased plasma corticosterone as a consequence of prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis. However, it is not likely that

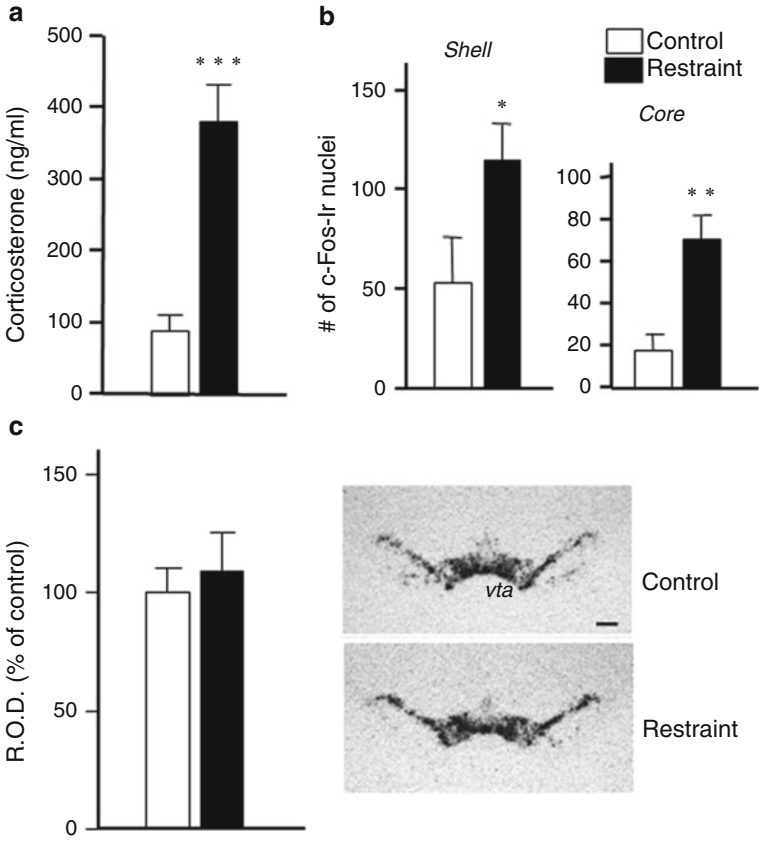

Fig. 13.2 Plasma corticosterone levels (**a**), number of c-Fos immuno-positive nuclei in the nucleus accumbens (**b**) and the quantitative analysis and representative photographs of tyrosine hydroxylase mRNA *in situ* hybridization in the ventral tegmental area (**c**). Rats were subjected to restraint stress for 1 h at every even day during postnatal days 28–40 and sacrificed immediately after the last stress session. Control rats left in home cages were sacrificed with the same time schedule. $*P<0.05$, $**P<0.01$, $***P<0.001$ vs. controls, *vta* ventral tegmental area, Scale bar; 500 um, Data are presented by means ± S.E.

the chronic increase of c-Fos expression in the NAc following repeated restraints may represent increased dopaminergic activity, because TH gene expression in the VTA was not changed after repeated restraints (Fig. 13.2).

Experience of neonatal maternal separation (MS) lead to a chronic increase of c-Fos expression in the NAc [76]. c-Fos, an immediate early gene, is expressed transiently following stressful stimuli. The increased c-Fos expression in the NAc of MS rats cannot be a direct consequence of MS stress, because MS stress was given during the first 2 weeks of birth and thereafter, the NAc c-Fos expression was examined at adolescence. Therefore, it is likely that MS pups might have become more sensitive and expressed c-Fos gene in the NAc neurons in response to mild stressors,

such as routine laboratory care. This idea is further supported by elevated basal levels of corticosterone in MS rats showing increased activities of the HPA axis [105], in accordance with other reports [11, 28, 121, 122]. Also, it is suggested that increased basal corticosterone levels may be implicated in the chronic increase of c-Fos expression in the NAc of MS rats.

The interaction between the responsivity of the HPA axis to stress and the development of anhedonia has been suggested to be mediated by dopamine neurotransmission in the reward pathway responding to stress. That is, dopamine neurotransmission in the NAc responding to food is blunted by chronic mild stress, showing anhedonia [88], and the striatal dopaminergic activity was associated with the severity of anhedonia in depressed patients [97]. Increases of the plasma corticosterone and the NAc c-Fos expression by repeated restraints were not observed in MS rats [76], and the stress-induced dopamine increase was blunted not only in the midbrain dopaminergic neurons but also in the NAc of MS rats [105]. Thus, it is concluded that MS experience may lead to the development of anhedonia in relation with a decreased responsivity of the HPA axis to stress, which is accompanied by a blunted dopaminergic activity in the brain reward system.

Acute stressors stimulate the secretion of dopamine over the NAc in proportion to cortisol responses [119, 120], and treatment with glucocorticoids increases mesolimbic dopamine levels [119]. Acute restraint increased the plasma corticosterone level not only in NH control rats but also in MS rats; however, dopamine contents and c-Fos expression in the NAc were increased only in NH, but not in MS rats [105]. This result suggests that a putative interaction between the HPA axis and the mesolimbic dopamine system responding to acute stress may be dis-regulated by MS experience. We have shown that the stress-responsive hypothalamic-NAc regulation may be a stressor specific event [123].

13.7 Anhedonia and the HPA Axis Function

Results from both clinical and preclinical studies suggest that long term dysfunction of the HPA axis due to early life stress may represent a key factor for the increased vulnerability to psychiatric diseases [30, 124]. Dysfunction of the HPA axis has been implicated in the pathogenesis of eating disorders [57, 58, 125]. Symptoms of anxiety and depression are associated with the pathophysiology of eating disorders [126], especially with binge-like eating disorders [49, 50]. A dis-regulation of the HPA axis activation is the most common and consistently reported symptom of depression [127], and increased serum cortisol levels are observed in anxiety [128], depression [56] and binge eating disorders [57, 58]. Neonatal maternal separation (MS) can permanently modify the characteristics of the HPA axis in the offspring [121, 122, 129–132]. As mentioned above, MS rats showed symptoms of depression including anhedonia, and disordered eating behaviors when they were challenged with stressors later in life. Together, it is suggested that the HPA axis dysfunction may play a role in the development of anhedonia associated with stress-induced eating disorders.

Stressful stimuli cause glucocorticoid release by the adrenal glands [133], and adrenal glucocorticoids have been implicated in the regulation of energy homeostasis [134]. In rodents, centrally administered glucocorticoids increase food intake and weight gain, but peripherally administered glucocorticoids suppress them [135]. It is suggested that adrenal glucocorticoids may mediate stress-induced anorexia; however, no clear link between increased plasma glucocorticoid concentration by stress and diminution in food intake and weight gain has been reported. We have demonstrated that repeated injections of dexamethasone (0.1 mg/kg or 1 mg/kg), synthetic glucocorticoid, suppress both food intake and body weight gain in a dose dependent manner [136]. Rats treated acutely with dexamethasone (5–10 mg/kg) showed anhedonia; i.e. a significant decrease in sucrose preference *per se* in comparison to vehicle treated rats, although 1 mg/kg dexamethasone did not acutely alter the sucrose preference [137]. However, rats treated daily with 1 mg/kg dexamethasone for 3 weeks showed not only anhedonia with decreased preference to sucrose but also depression-like behavior during forced swim test with increased immobility duration (unpublished our observation). These findings suggest that glucocorticoids may play a key role in the development of anhedonia related with stress-induced eating disorders.

13.8 Leptin in Stress-Induced Anhedonia

In the dexamethasone-induced anorexia described above [136], decreased energy intake did not appear to be a main cause for the decreased weight gain, because body weight gain of the rats that pair-fed with the high dose dexamethasone (1 mg/kg daily) group did not differ from the free fed control group. Leptin is an adipose-derived hormone that signals information on adiposity to the brain. Plasma leptin level is normally decreased with negative energy balance [26, 138] and it was decreased in the pair-fed group with reduced energy intake; however, daily dexamethasone at a dose of 1 mg/kg induced prolonged increase in the plasma leptin level despite of drastic decreases in food intake and weight gain [136]. Pro-longed hyperleptinemia by dexamethasone treatment was also reported by other researchers [139, 140]. In fact, leptin is considered as a stress-related hormone and its secretion is stimulated by stress [141–143], and synthetic glucocorticoid dexamethasone increases leptin synthesis and release in the adipose tissue [144]. It has been reported that leptin increases energy expenditure, and decreases food intake, resulting in a decrease in body mass [145–147]. Together, it is suggested that increased plasma leptin, possibly with glucocorticoid stimulation, may play a role in stress-induced anorexia.

Leptin receptors are expressed in the midbrain dopaminergic neurons, ventral tegmental area (VTA), where 75–90 % of the leptin receptor-positive neurons are dopaminergic [148–150]. Injection of leptin directly into the VTA increases phosphorylated signal transducer and activator of transcription 3 (pSTAT3) levels and activates Jak-2 signalling pathways [151, 152]. Leptin injections in the VTA

decrease concentrations of extracellular dopamine levels in the nucleus accumbens (NAc) [153], an effect that may be caused by a direct inhibitory effect of leptin on the VTA dopaminergic neurons [148]. Some of the leptin responsive dopaminergic neurons in the VTA project to the NAc [151]. Also, we have observed that systemic leptin increases pSTAT3 levels not only in the hypothalamic arcuate nucleus but also in the VTA of rats (unpublished our observation). Furthermore, intraventricular leptin decreased sucrose self-administration, i.e. performance on a progressive ratio task for a sucrose pellet, in rats [154]. Thus, it is hypothesized that leptin may play a role in stress-induced anhedonia accompanied with anorexia, possibly via reducing meso-limbic dopaminergic activity. However, studies indicate that dopamine signaling originating in the VTA is reduced in leptin-deficient animals [151, 155]. Mice that lack leptin (ob/ob mice) are obese, are hyperphagic and have decreased energy expenditure. They have reduced dopamine levels in the NAc and decreased tyrosine hydroxylase levels in the VTA [151], and showed depression-like behaviors [156]. Further studies are required to determine the role of leptin in the stress-induced anhedonia associated with eating disorders.

13.9 Conclusions and Future Direction

Repeated experience of maternal separation during pre-weaning period (MS) in rats may not permanently affect food intake and body weight gain of the offspring. However, stressful challenges, such as time-restricted scheduled feeding, repeated fasting/refeeding cycles and isolation rearing, or an exposure to palatable food may evoke disordered eating behaviors in MS offspring with gender differences. Disordered eating behaviors in MS rats appear to be related with their psycho-emotional status. Anhedonia by chronic mild stress appears to be associated with reductions of food intake and body weight gain; however, the development of anhedonia may not be necessarily associated with weight loss and/or reduced normal food intake, as revealed in anhedonia of adolescent rats following MS experience or restraint stress.

Dopaminergic activity in the NAc may play a key role in the stress-induced disordered eating behaviors associated with anhedonia symptom. MS experience, although it may not affect the basal dopamine level, may result in a long-term suppression of dopaminergic function in the mesolimbic dopamine pathways responding to stressful or reward stimuli, which may be implicated in the symptom of anhedonia. Acute increase of dopaminergic input in the NAc, perhaps inducing c-Fos expression, may be implicated in the underlying mechanism of anhedonia symptom by acute stress.

MS experience may lead to the development of anhedonia in relation with a decreased responsivity of the HPA axis to stress, which is accompanied by a blunted dopaminergic activity in the brain reward system. A putative interaction between the HPA axis and the mesolimbic dopamine system responding to acute stress may be dis-regulated by MS experience. Glucocorticoids appear to play a

key role in the development of anhedonia related with stress-induced eating disorders. It is hypothesized that increased plasma leptin, possibly with glucocorticoid stimulation, may play a role in stress-induced anhedonia accompanied with anorexia, possibly via reducing meso-limbic dopaminergic activity. Further studies are required to determine the role of leptin in the stress-induced anhedonia associated with eating disorders.

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References

1. Wonderlich SA, Brewerton TD, Jocic Z, et al. The relationship of childhood sexual abuse and eating disorders: a review. J Am Acad Child Adolesc Psychiatry. 1997;36:1107–15.
2. Fallon BA, Sadik C, Saoud JB, et al. Childhood abuse, family environment, and outcome in bulimia nervosa. J Clin Psychiatry. 1994;55:424–8.
3. McCarthy MK, Goff DC, Baer L, et al. Dissociation, childhood trauma, and the response to fluoxetine in bulimic patients. Int J Eat Disord. 1994;15:219–26.
4. Rorty M, Yager J, Rossotto E. Childhood sexual, physical, and psychological abuse and their relationship to comorbid psychopathology in bulimia nervosa. Int J Eat Disord. 1994;16:317–34.
5. Vize CM, Cooper PJ. Sexual abuse in patients with eating disorder, patients with depression, and normal controls. A comparative study. Br J Psychiatry. 1995;167:80–5.
6. Matthews K, Wilkinson LS, Robbins TW. Repeated maternal separation of preweanling rats attenuates behavioral responses to primary and conditioned incentives in adulthood. Physiol Behav. 1996;59:99–107.
7. McIntosh J, Animan H, Merali Z. Short- and long periods of neonatal maternal separation differentially affect anxiety and feeding in adult rats: gender-dependent effects. Brain Res Dev Brain Res. 1999;113:97–106.
8. Iwasaki S, Inoue K, Kriike N, et al. Effect of maternal separation on feeding behavior of rats in later life. Physiol Behav. 2000;70:551–6.
9. Ryu V, Yoo SB, Kang DW, et al. Post-weaning isolation promotes food intake and body weight gain in rats that experienced neonatal maternal separation. Brain Res. 2009;1295:127–34.
10. Yoo SB, Ryu V, Park EY, et al. The arcuate NPY, POMC, and CART expressions responding to food deprivation are exaggerated in young female rats that experienced neonatal maternal separation. Neuropeptides. 2011;45:343–9.
11. Ryu V, Lee JH, Yoo SB, et al. Sustained hyperphagia in adolescent rats that experienced neonatal maternal separation. Int J Obes. 2008;32:1355–62.
12. Hall FS. Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioral consequences. Crit Rev Neurobiol. 1998;12:129–62.
13. Gutman DA, Nemeroff CB. Persistent central nervous system effects of an adverse early environment: clinical and preclinical studies. Physiol Behav. 2003;79:471–8.
14. Lapiz MD, Fulford A, Muchimapura S, et al. Influence of postweaning social isolation in the rat on brain development, conditioned behavior, and neurotransmission. Neurosci Behav Phys. 2003;33:13–29.
15. Fone KCF, Porkess MV. Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders. Neurosci Biobehav Rev. 2008;32:1087–102.

16. Robbins TW, Jones GH, Wilkinson LS. Behavioural and neurochemical effects of early social deprivation in the rat. J Psychopharmacol. 1996;10:39–47.
17. Jahng JW, Yoo SB, Ryu V, et al. Hyperphagia and depression-like behavior by adolescence social isolation in female rats. Int J Develop Neurosci. 2012;30:47–53.
18. MacMillan HL, Fleming JE, Streiner DL, et al. Childhood abuse and lifetime psychopathology in a community sample. Am J Psychiatry. 2001;158:1878–83.
19. Kendler KS, Neale MC, Kessler RC, et al. Childhood parental loss and adult psychopathology in women. A twin study perspective. Arch Gen Psychiatry. 1992;49:109–16.
20. Furukawa TA, Ogura A, Hirai T, et al. Early parental separation experiences among patients with bipolar and major depression: a case–control study. J Affect Dis. 1999;52:85–91.
21. Agid O, Shapira B, Zislin J, et al. Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. Mol Psychiatry. 1999;4:163–72.
22. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001;49:1023–39.
23. Mullen PE, Martin JL, Anderson JC, et al. The long-term impact of the physical, emotional, and sexual abuse of children: a community study. Child Abuse Negl. 1996;20:7–12.
24. Stein MB, Walker JR, Anderson G, et al. Childhood physical and sexual abuse in patients with anxiety disorders in a community sample. Am J Psychiatry. 1996;153:275–7.
25. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14:245–58.
26. Kim HJ, Lee JH, Choi SH, et al. Fasting-induced increases of arcuate NPY mRNA and plasma corticosterone are blunted in the rat experienced neonatal maternal separation. Neuropeptides. 2005;39:587–94.
27. Lee JH, Kim HJ, Kim JG, et al. Depressive behaviors and decreased expression of serotonin reuptake transporter in rats that experienced neonatal maternal separation. Neurosci Res. 2007;58:32–9.
28. Ladd CO, Huot RL, Thrivikraman KV, et al. Long-term behavioral and neuroendocrine adaptations to adverse early experience. Prog Brain Res. 2000;122:81–103.
29. Kalinichev M, Easterling KW, Plotsky PM, et al. Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in long-Evans rats. Pharm Biochem Behav. 2002;73:131–40.
30. Newport JD, Stowe ZN, Nemeroff CB. Parental depression: animal models of an adverse life event. Am J Psychiatry. 2002;159:1265–83.
31. Daniels WM, Pietersen CY, Carstens ME, et al. Maternal separation in rats lead to anxiety-like behavior and a blunted ACTH response and altered neurotransmitter levels in response to a subsequent stressor. Metab Brain Dis. 2004;19:3–14.
32. Khoury AE, Gruber SHM, Mork A, et al. Adult life behavioral consequences of early maternal separation are alleviated by escitalopram treatment in a rat model of depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2006;30:535–40.
33. Kelley AE, Schiltz CA, Landry CF. Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. Physiol Behav. 2005;86:11–4.
34. Paterson NE, Markou A. Animal models and treatments for addiction and depression comorbidity. Neurotox Res. 2007;11:1–32.
35. Macht M. How emotions affect eating: a five-way model. Appetite. 2008;50:1–11.
36. Jahng JW, Yoo SB, Kim JY, et al. Increased mesohippocampal dopaminergic activity and improved depression-like behaviors in maternally separated rats following repeated fasting/refeeding cycles. J Obes. 2012; ID497101.
37. Grissett NI, Norvell NK. Perceived social support, social skills, and quality of relationships in bulimic women. J Consult Clin Psychol. 1992;2:293–9.
38. Bruce ML, Hoff RA. Social and physical health risk factors for first onset major depressive disorder in a community sample. Soc Psychiatry Psychiatr Epidemiol. 1994;29:165–71.

39. Darke S, Ross J. Suicide among heroin users: rates, risk factors and methods. Addiction. 2002;97:1383–94.
40. Kendler KS, Bulik CM, Silberg J, et al. Childhood sexual abuse and adult psychiatric and substance use disorders in women. Arch Gen Psychiatry. 2000;57:953–9.
41. Harmer CJ, Phillips GD. Isolation rearing enhances acquisition in a conditioned inhibition paradigm. Physiol Behav. 1998;65:525–33.
42. Wongwitdecha N, Marsden CA. Effects of social isolation rearing on learning in the Morris water maze. Brain Res. 1996;715:119–24.
43. Hall FS, Humby T, Wilkinson LS, et al. The effects of isolation-rearing on preference by rats for a novel environment. Physiol Behav. 1997;62:299–303.
44. Hellemans KG, Benge LC, Olmstead MC. Adolescent enrichment partially reverses the social isolation syndrome. Dev Brain Res. 2004;150:103–15.
45. Weiss IC, Pryce CR, Jongen-Relo AL, et al. Effect of social isolation on stress-induced behavioral and neuroendocrine state in the rat. Behav Brain Res. 2004;152:279–95.
46. Wright IK, Upton N, Marsden CA. Resocialisation of isolation-rared rats does not alter their anxiogenic profile on the elevated X-maze model of anxiety. Physiol Behav. 1991;50:1129–32.
47. Potegal M, Einon D. Aggressive behaviors in adult rats deprived of playfighting experience as juveniles. Dev Psychobiol. 1989;22:159–72.
48. Ding Y, Kang L, Li B, et al. Enhanced cocaine self-administration in adult rats with adolescent isolation experience. Pharmacol Biochem Behav. 2005;82:673–7.
49. Grilo CM, White MA, Masheb RM. DSM-IV psychiatric disorder comorbidity and its correlates in binge eating disorder. Int J Eat Disord. 2009;42:228–34.
50. Javaras KN, Pope HG, Lalonde JK, et al. Co-occurrence of binge eating disorder with psychiatric and mental disorders. J Clin Psychiatry. 2008;69:266–73.
51. Tidey JW, Miczek KA. Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. Brain Res. 1996;721:140–9.
52. Lowry CA, Hale MW, Plant A, et al. Fluoxetine inhibits corticotropin-releasing factor (CRF)-induced behavioural responses in rats. Stress. 2009;12:225–39.
53. Paul ED, Hale MW, Lukkes JL, et al. Repeated social defeat increases reactive emotional coping behavior and alters functional responses in serotonergic neurons in the rat dorsal raphe nucleus. Physiol Behav. 2011;104:272–82.
54. Dube L, LeBel JL, Lu J. Affect asymmetry and comfort food consumption. Physiol Behav. 2005;86:559–67.
55. Ulrich-Lai YM, Ostrander MM, Thomas IM, et al. Daily limited access to sweetened drink attenuates hypothalamic-pituitary-adrenocortical axis stress responses. Endocrinology. 2007;148:1823–34.
56. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000;284:593–7.
57. Koo-Loeb JH, Costello N, Light KC, et al. Women with eating disorder tendencies display altered cardiovascular, neuroendocrine, and physiological profiles. Psychosom Med. 2000;62:539–48.
58. Gluck ME, Geliebter A, Lorence M. Cortisol stress response is positively correlated with central obesity in obese women with binge eating disorder (BED) before and after cognitive-behavioral treatment. Ann N Y Acad Sci. 2004;1032:202–7.
59. Katz RJ. Animal model of depression: pharmacological sensitivity of a hedonic deficit. Pharmacol Biochem Behav. 1982;16:965–8.
60. Hill MN, Hellemans KGC, Verma P, et al. Neurobiology of chronic mild stress: parallels to major depression. Neurosci Biobehav Rev. 2012;36:2085–117.
61. Willner P, Moreau JL, Nielsen CK, et al. Decreased hedonic responsiveness following chronic mild stress is not secondary to loss of body weight. Physiol Behav. 1996;60:129–34.
62. Lin YH, Liu AH, Xu Y, et al. Effect of chronic unpredictable mild stress on brain-pancreas relative protein in rat brain and pancreas. Behav Brain Res. 2005;165:63–71.

63. Lucca G, Comim CM, Valvassori SS, et al. Chronic mild stress paradigm reduces sweet food intake in rats without affecting brain derived neurotrophic factor protein levels. Curr Neurovasc Res. 2008;5:207–13.
64. Tacchi R, Ferrari A, Loche A, et al. Sucrose intake: increase in non-stressed rats and reduction in chronically stressed rats are both prevented by the gamma-hydroxybutyrate (GHB) analogue, GET7. Pharmacol Res. 2008;57:464–8.
65. American Psychiatric Association and American Psychiatric Association Task Force on DSM-IV; 2000.
66. Willner P. Chronic mild stress (CMS) revisited: consistency and behavioural neurobiological concordance in the effects of CMS. Neuropsychobiology. 2005;52:90–110.
67. Oliver G, Wardle J, Gibson EL. Stress and food choice: a laboratory study. Psychosom Med. 2000;62:853–65.
68. Zellner DA, Loaiza S, Gonzalez Z, et al. Food selection changes under stress. Physiol Behav. 2006;87:789–93.
69. Pollard TM, Steptoe A, Canaan L, et al. Effects of academic examination stress on eating behavior and blood lipid levels. Int J Behav Med. 1995;2:299–320.
70. Adam TC, Epel ES. Stress, eating and the reward system. Physiol Behav. 2007;91:449–58.
71. Armario A. The hypothalamic-pituitary-adrenal axis: what can it tell us about stressors? CNS Neurol Disord Drug Targets. 2006;5:485–501.
72. Harris RB, Palmondon J, Leshin S, et al. Chronic disruption of body weight but not of stress peptides or receptors in rats exposed to repeated restraint stress. Horm Behav. 2006;49:615–25.
73. Makino S, Asaba K, Nishiyama M, et al. Decreased type 2 corticotropin-releasing hormone receptor mRNA expression in ventromedial hypothalamus during repeated immobilization stress. Neuroendocrinology. 1999;70:160–7.
74. Harris RB, Zhou J, Youngblood BD, et al. Effect of repeated stress on body weight and body composition of rats fed low- and high-fat diets. Am J Physiol Regul Integr Comp Physiol. 1998;275:R1928–38.
75. Miragaya JR, Harris RB. Antagonism of corticotrophin-releasing factor receptors in the fourth ventricle modifies responses to mild but not restraint stress. Am J Physiol Regul Integr Comp Physiol. 2008;295:R404–16.
76. Ryu V, Yoo SB, Kim BT, et al. Experience of neonatal maternal separation may lead to a long-term modulation in the neuronal activity of nucleus accumbens in the offspring. Exp Neurobiol. 2009;18:88–96.
77. Harlow HF, Suomi SJ. Production of depressive behaviors in young monkeys. J Autism Childh Schizophr. 1971;1:246–55.
78. Harlow HF, Suomi SJ. Induced depression in monkeys. Behav Biol. 1974;12:273–96.
79. Paul IA, English JA, Halaris A. Sucrose and quinine intake by maternally-deprived and control rhesus monkeys. Behav Brain Res. 2000;112:127–34.
80. Yoo SB, Kim BT, Kim JY, et al. Adolescence fluoxetine increases serotonergic activity in the raphe-hippocampus axis and improves depression-like behaviors in female rats that experienced neonatal maternal separation. Psychoneuroendocrinology. 2013;38:777–88.
81. Amsterdam JD, Settle RG, Doty RL, et al. Taste and smell perception in depression. Biol Psychiatry. 1987;22:1481–5.
82. Steiner JE, Lidar-Lifschitz D, Perl E. Taste and odor: reactivity in depressive disorders, a multidisciplinary approach. Percept Mot Skills. 1993;77:1331–46.
83. Arbisi PA, Levine AS, Nerenberg J, et al. Seasonal alteration in taste detection and recognition threshold in seasonal affective disorder: the proximate source of carbohydrate craving. Psychiatry Res. 1996;59:171–82.
84. Christensen L. The effect of carbohydrates on affect. Nutrition. 1997;13:503–14.
85. Willner P, Benton D, Brown E, et al. “Depression” increases “craving” for sweet rewards in animal and human models of depression and craving. Psychopharmacology (Berl). 1998;136:272–83.

86. Bruera E, Carraro S, Roca E, et al. Association between malnutrition and caloric intake, emesis, psychological depression, glucose taste, and tumor mass. Cancer Treat Rep. 1984;68:873–6.
87. Potts AJ, Bennett PJ, Kennedy SH, et al. Depressive symptoms and alterations in sucrose taste perception: cognitive bias or a true change in sensitivity? Can J Exp Psychol. 1997;51:57–60.
88. Di Chiara G, Loddo P, Tanda G. Reciprocal changes in prefrontal and limbic dopamine responsiveness to aversive and rewarding stimuli after chronic mild stress: implications for the psychobiology of depression. Biol Psychiatry. 1999;46:1624–33.
89. Yadid G, Overstreet DH, Zangen A. Limbic dopaminergic adaptation to a stressful stimulus in a rat model of depression. Brain Res. 2001;896:43–7.
90. Bassareo V, De Luca MA, Di Chiara G. Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. JNeurosci. 2002;22:4709–19.
91. Kirkham TC, Williams CM, Fezza F, et al. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. Br J Pharmacol. 2002;136:550–7.
92. Kelley AE, Baldo BA, Pratt WE, et al. Corticostriatal hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiol Behav. 2005;86:773–95.
93. Di Chiara G, Bassare V. Reward system and addiction: what dopamine does and doesn't do. Curr Opin Pharmacol. 2007;7:69–76.
94. Sahr AE, Sindelar DK, Alexander-Chacko JT, et al. Activation of mesolibic dopamine neurons during novel and daily limited access to palatable food is blocked by the opioid antagonist LY255582. Am J Physiol Regul Integr Comp Physiol. 2008;295:R463–71.
95. Yamamoto T. Central mechanisms of roles of taste in reward and eating. Act Physiol Hung. 2008;95:165–86.
96. Moreau JL, Scherschlicht R, Jenck F, et al. Chronic mild stress-induced anhedonia model of depression; sleep abnormalities and curative effects of electroshock treatment. Behav Pharmacol. 1995;6:682–7.
97. Gorwood P. Neurobiological mechanisms of anhedonia. Dial Clin Neurosci. 2008;10:291–9.
98. Lucasa LR, Wang CJ, McCall TJ, et al. Effects of immobilization stress on neurochemical markers in the motivational system of the male rat. Brain Res. 2007;1155:108–15.
99. Cardinal RN, Cheung THC. Nucleus accumbens core lesions retard instrumental learning and performance with delayed reinforcement in the rat. BMC Neurosci. 2005;6:9.
100. Konsman JP, Blomqvist A. Forebrain patterns of c-Fos and FosB induction during cancer-associated anorexia-cachexia in rat. Eur J Neurosci. 2005;21:2752–66.
101. Yamamoto T. Brain regions responsible for the expression of conditioned taste aversion in rats. Chem Sens. 2007;32:105–9.
102. Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. Science. 1988;242:715–23.
103. Meredith GE, Pennartz CM, Groenewegen HJ. The cellular framework for chemical signalling in the nucleus accumbens. Prog Brain Res. 1993;99:3–24.
104. Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci Biobehav Rev. 1992;16:525–34.
105. Jahng JW, Ryu V, Yoo SB, et al. Mesolimbic dopaminergic activity responding to acute stress is blunted in adolescent rats that experienced neonatal maternal separation. Neuroscience. 2010;171:144–52.
106. Di Chiara G, Tanda G. Blunting of reactivity of dopamine transmission to palatable food: a biochemical marker of anhedonia in the CMS model? Psychopharmacology (Berl). 1997;134:351–3.
107. Scheggi S, Leggio B, Masi F, et al. Selective modifications in the nucleus accumbens of dopamine synaptic transmission in rats exposed to chronic stress. J Neurochem. 2002;83:895–903.

108. Perrotti LI, Hadeishi Y, Ulery PG, et al. Induction of delta FosB in reward-related brain structures after chronic stress. J Neurosci. 2004;24:10594–602.
109. Kalivas PW, Duffy P. Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. Brain Res. 1995;675:325–8.
110. Saal D, Dong Y, Bonci A, et al. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron. 2003;37:577–82.
111. Dalla C, Antoniou K, Drossopoulou G, et al. Chronic mild stress impact: are females more vulnerable? Neuroscience. 2005;135:703–14.
112. Dalla C, Antoniou K, Kokras N, et al. Sex differences in the effects of two stress paradigms on dopaminergic neurotransmission. Physiol Behav. 2008;93:595–605.
113. Tannenbaum B, Anisman H. Impact of chronic intermittent challenges in stressor-susceptible and resilient strains of mice. Biol Psychiatry. 2003;53:292–303.
114. Johnson BN, Yamamoto BK. Chronic unpredictable stress augments +3,4-methylene dioxymethamphetamine-induced monoamine depletions: the role of corticosterone. Neuroscience. 2009;159:1233–43.
115. Rasheed N, Tyagi E, Ahmad A, et al. Involvement of monoamines and proinflammatory cytokines in mediating the anti-stress effects of Panax quinquefolium. J Ethnopharmacol. 2008;117:257–62.
116. Ahmad A, Rasheed N, Banu N, et al. Alterations in monoamine levels and oxidative systems in frontal cortex, striatum, and hippocampus of the rat brain during chronic unpredictable stress. Stress. 2010;13:355–64.
117. Marti O, Gavalda A, Jolin T, et al. Effect of regularity of exposure to chronic immobilization stress on the circadian pattern of pituitary adrenal hormones, growth hormone, and thyroid stimulating hormone in the adult male rat. Psychoneuroendocrinology. 1993;18:67–77.
118. Ottenweller JE, Servatius RJ, Natelson BH. Repeated stress persistently elevates morning, but not evening, plasma corticosterone levels in male rats. Physiol Behav. 1994;55:337–40.
119. Oswald LM, Wong DF, McCaul M, et al. Relationships among ventral striatal dopamine release, cortisol secretion, and subjective responses to amphetamine. Neuropsychopharmacology. 2005;30:821–32.
120. Wand GS, Oswald LM, McCaul ME, et al. Association of amphetamine-induced striatal dopamine release and cortisol responses to psychological stress. Neuropsychopharmacology. 2007;32:2310–20.
121. Ladd CO, Owens MJ, Nemeroff CB. Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. Endocrinology. 1996;137:1212–18.
122. Vazquez DM, Lopez JF, Van Hoers H, et al. Maternal deprivation regulates serotonin 1A and 2A receptors in the infant rat. Brain Res. 2000;855:76–82.
123. Noh SJ, Kang DW, Yoo SB, et al. Stress-responsive hypothalamic-nucleus accumbens regulation may vary depending on stressors. Ind J Exp Biol. 2012;50:447–54.
124. Arborelius L, Owens MJ, Plotsky PM, et al. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol. 1999;160:1–12.
125. Putignano P, Dubini A, Toja P, et al. Salivary cortisol measurement in normal-weight, obese and anorexic women: comparison with plasma cortisol. Eur J Endocrinol. 2001;145:165–71.
126. Goossens L, Braet C, Van Vlierberghe L, et al. Loss of control over eating in overweight youngsters: the role of anxiety, depression and emotional eating. Eur Eat Disord Rev. 2009;17:68–78.
127. Tichomirowa MA, Keck ME, Schneider HJ, et al. Endocrine disturbances in depression. J Endocrinol Invest. 2005;28:89–99.
128. Albenidou-Farmaki E, Poulopoulos AK, Epivatianos A, et al. Increased anxiety level and high salivary and serum cortisol concentrations in patients with recurrent aphthous stomatitis. Tohoku J Exp Med. 2008;214:291–6.
129. Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotrophin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Mol Brain Res. 1993;18:195–200.

130. Suchecki D, Tufik S. Long-term effects of maternal deprivation on the corticosterone response to stress in rats. Am J Physiol. 1997;273:R1332–8.
131. Van Oers HJ, de Kloet ER, Levins S. Early vs. late maternal deprivation differentially alters the endocrine and hypothalamic responses to stress. Brain Res Dev Brain Res. 1998;111:245–52.
132. Liu D, Caldji C, Sharma S, et al. Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinepherine release in the hypothalamic paraventricular nucleus. J Neuroendocrinol. 2000;12:5–12.
133. Axelrod J, Reisine TD. Stress hormones: their interaction and regulation. Science. 1984;224:452–9.
134. Cavagnini F, Croci M, Putignano P, et al. Glucocorticoids and neuroendocrine function. Int J Obes. 2000;24:S77–9.
135. Zakrzewska KE, Cusin I, Stricker-Krongrad A, et al. Induction of obesity and hyperleptinemia by central glucocorticoid infusion in the rat. Diabetes. 1999;48:365–70.
136. Jahng JW, Kim NY, Yoo SB, et al. Dexamethasone reduces food intake, weight gain and the hypothalamic 5-HT concentration and increases plasma leptin in rats. Eur J Pharmacol. 2008;581:64–70.
137. Casarotto PC, Andreatini R. Repeated paroxetine treatment reverses anhedonia induced in rats by chronic mild stress or dexamethasone. Eur Neuropsychopharmacol. 2007;17:735–42.
138. Velkoska E, Morris MJ, Burns P, et al. Leptin reduces food intake but does not alter weight regain following food deprivation in the rat. Int J Obes Relat Metab Disord. 2003;27:48–54.
139. Caldefie-Chezet F, Moinard C, Minet-Quinard R, et al. Dexamethasone treatment induces long-lasting hyperleptinemia and anorexia in old rats. Metabolism. 2001;50:1054–8.
140. Caldefie-Chezet F, Poulin A, Enreille-Leger A, et al. Troglitazone reduces leptinemia during experimental dexamethasone-induced stress. Horm Metab Res. 2005;37:164–71.
141. Hernandez C, Simo R, Chacon P, et al. Influence of surgical stress and parental nutrition on serum leptin concentration. Clin Nutr. 2000;19:61–4.
142. Konishi N, Otaka M, Odashima M, et al. Systemic stress increases serum leptin level. J Gastroenterol Hepatol. 2006;21:1099–102.
143. Wallace AM, Sattar N, Mcmillan DC. The co-ordinated cytokine/hormone response to acute injury incorporates leptin. Cytokine. 2000;12:1042–5.
144. Lee MJ, Wang Y, Ricci MR, et al. Acute and chronic regulation of leptin synthesis, storage and secretion by insulin and dexamethasone in human adipose tissue. Am J Physiol Endocrinol Metab. 2007;292:E858–64.
145. Campfield LA, Smith FJ, Guisez Y, et al. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. Science. 1995;269:546–9.
146. Grill HJ, Schwartz MW, Kaplan JM, et al. Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. Endocrinology. 2002;143:239–46.
147. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science. 1995;269:540–3.
148. Hommel JD, Trinko R, Sears RM, et al. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. Neuron. 2006;51:801–10.
149. Figlewicz DP, Evans SB, Murphy J, et al. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. Brain Res. 2003;964:107–15.
150. Leshan RL, Opland DM, Louis GW, et al. Ventral tegmental area leptin receptor neurons specifically project to and regulate cocaine- and amphetamine-regulated transcript neurons of the extended central amygdala. J Neurosci. 2010;30:5713–23.
151. Fulton S, Pissios P, Manchon RP, et al. Leptin regulation of the mesoaccumbens dopamine pathway. Neuron. 2006;51:811–22.
152. Morton GJ, Blevins JE, Kim F, et al. The action of leptin in the ventral tegmental area to decrease food intake is dependent on Jak-2 signaling. Am J Physiol Endocrinol Metab. 2009;297:E202–10.
153. Krugel U, Schraft T, Kittner H, et al. Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. Eur J Pharmacol. 2003;482:185–7.

154. Figlewicz DP, Bennett JL, Naleid AM, et al. Intraventricular insulin and leptin decrease sucrose self-administration in rats. Physiol Behav. 2006;89:611–16.
155. Thanos PK, Michaelides M, Piyis YK, et al. Food restriction markedly increases dopamine D2 receptor (D2R) in a rat model of obesity as assessed with in-vivo muPET imaging ([11C] raclopride) and in-vitro ([3H] spiperone) autoradiography. Synapse. 2008;62:50–61.
156. Collin M, Hakansson-Ovesjo M-L, Misane I, et al. Decreased 5-HT transporter mRNA in neurons of the dorsal raphe nucleus and behavioral depression in the obese leptin-deficient ob/ob mouse. Mol Brain Res. 2000;81:51–61.

Chapter 14
Brain Imaging Correlates of Anhedonia

Adrian Preda

Abstract In this chapter we will review the structural and functional neuroimaging correlates of anhedonia.

Regions associated with anhedonia range from the reward processing circuits of the medial orbitofrontal cortex in healthy subjects to the fear processing neurocircuitry of amygdala in patients with schizophrenia. The emerging picture of the hedonic brain imaging literature is one of a hedonic continuum, with a remarkable continuity between healthy and across affected individuals, suggesting that anhedonia might be a useful endophenotype or potential trait marker related to vulnerability to major psychiatric disorders such as depression and schizophrenia. However, the relatively small number of brain imaging studies to date, lack of precision in the definition of anhedonia, diagnostic heterogeneity of the study populations and heterogeneity of study methods indicate that this remains an incipient field of research. We conclude that the evidence to date about the brain correlates of anhedonia is preliminary and further research is indicated.

Keywords Accumbens • Amygdala • Anhedonia • Anterior cingulate cortex • Depression • fMRI • Insula • Mesolimbic reward system • MRS • Orbitofrontal cortex • PET • [ventromedial/dorsolateral] Prefrontal cortex • Raphe Nuclei • Reward • Schizophrenia • Striatum • Substantia Nigra • Ventral striatum • Ventral tegmental area

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Abbreviations

ACC	Anterior Cingulate Cortex
fMRI	functional MRI
MRS	Magnetic Resonance Spectroscopy
OFC	Orbitofrontal cortex
NAc	Nucleus Accumbens
[vm/dl]PFC	[ventromedial/dorsolateral] Prefrontal cortex
PET	Positron Emission Tomography
SN	Substantia Nigra
VS	Ventral striatum

"For it is then that we have need of pleasure, when we feel pain owing to the absence of pleasure." *Epicurus (341–270 B.C.)*

14.1 Introduction

Anhedonia is a key symptom of depression and schizophrenia as well as a well described and commonly reported symptom in a variety of neuropsychiatric disorders including Parkinson's disease, Alzheimer's dementia, and substance use disorders [1, 2].

14.2 The Neuroimaging of Anhedonia: Challenges and Opportunities

When compared to clinical syndromes such as depression and schizophrenia anhedonia would arguably make for a better neuroimaging target: anhedonia presents more homogeneity than clinical syndromes such as depression or schizophrenia; in addition, one can argue that measurements of anhedonia are less confounded than measurements of psychiatric clinical syndromes. Further, anhedonia has been conceptualized as a neurobiological endophenotype possibly mediating the occurrence of major neuropsychiatric disorders such as schizophrenia and depression [3, 4]. Accordingly, understanding the neural correlates of anhedonia can illuminate the neuropathological correlates of major psychiatric and neurological disorders as well as help identify individuals at risk.

At the same time, the ability to perceive pleasure is the result of a complex set of processes involving processing of sensorial stimuli, mitigated by higher cognitive inputs associated with perceived costs and rewards, including effort, resolving cognitive dissonance, and decision making. As each of these processes has a putative different neurocircuitry basis, separating the neural foundation of anhedonia is not a straightforward proposal.

Further, while the neural correlates of pleasure and reward are fairly well studied [5] the number of studies directly correlating brain structure and function with anhedonia severity is surprisingly low. A brief review of the specific challenges that any neuroimaging study of anhedonia faces will help understand this rather paradoxical and disconcerting state of affairs.

14.2.1 Anhedonia Lacks Diagnostic Specificity

Most clinical brain imaging studies compare affected subjects with a control group. As anhedonia is not a disorder *per se* data from brain imaging studies are limited to comparisons between patients diagnosed with a disorder where anhedonia is one of the many manifesting symptoms [6, 7]. An immediate limitation of any topographical location of anhedonia defined this way is that associated symptoms will be unaccounted for variables that could greatly affect the accuracy of the mapping. For example, the associated symptoms of anhedonia differ in patients with depression:schizophrenia which may affect the brain signature of anhedonia in these different patient groups [7].

14.2.2 Anhedonia Is a Poorly Defined Neuroimaging Target

Ideal functional neuroimaging targets are clearly and objectively defined states. That is not the case with anhedonia, an essentially subjective state which interpretation is to a good extent subject-dependent [8]. Is the intense negative emotion experienced by the depressed patient who is no longer able to enjoy anything [9] the same with the lack of emotion experienced by the patient with schizophrenia who finds himself indifferent to almost everything [10]? Both patients will likely score high on any given anhedonia scale but it is debatable if the same concept is measured all along.

In fact, several types of anhedonia have been described, including sensorial or physical anhedonia as distinct from interpersonal or social anhedonia [11], as well as anticipatory anhedonia as distinct from consummatory anhedonia [12]. Further, it is not clear if patients reporting anhedonia experience a deficit in their ability to experience pleasure [a predominantly emotional deficit] or rather an undervaluation of reward stimuli (a predominantly cognitive deficit) [13].

Secondly, ideal functional imaging targets are circumscribed states that can be easily, reliably and rapidly turned on and off. This unfortunately is not the case with anhedonia, a rather persistent and lingering state : trait, without clear modifying factors [7, 14].

Lastly, both the intensity and quality of any hedonic occurrence are essentially subjective experiences; as such, difficult targets for any scientific, i.e. objective data-driven, investigation.

A way of overcoming the stated challenges is to investigate the hedonic:anhedonic spectrum in non-clinical populations. As mentioned, the very nature of anhedonia allows its conceptualization not only as a state (associated with other clinical symptoms) but also as a trait; as such, present to some extent in all people. However, with the exception of resting state studies, neuroimaging trait studies are limited by the fact that trait severity neural correlates cannot be directly assessed. The alternative is to estimate trait severity correlates via surrogate state-dependent measures, with the added inherent limitation of any indirect measurement.

Considering these important limitations we decided to review the brain imaging correlates of anhedonia within the boundaries of predefined functional neural correlates of reward-hedonic capacity processing, specifically:

1. Hedonic Appraisal: Orbitofrontal Cortex (OFC) and Ventral Striatum (VS)
2. Reward Appraisal and Executive-Decision Making: the Prefrontal Cortex (PFC) and the Anterior Cingulate Cortex (ACC)
3. (The Mesolimbic) Reward Detection System: Nucleus Accumbens (NAc) and the Ventral Tegmental Area/Substantia Nigra (VTA/SN)
4. Emotional Context: the Insula Cortex and Amygdala
5. Other Regions of Interest: Cerebellum, Raphe Nuclei

Of note, as a number of brain regions belong to more than one reward/hedonic neurocircuits, we will attempt to sketch a functionally driven (as opposed to a structurally driven) map of the territory.

Thus our brain mapping review will follow a cross-diagnostic function-based neuroimaging strategy [15]. For each specific region of interest we will discuss findings from a variety of neuroimaging studies, including studies of anhedonia:hedonic capacity in clinical:non-clinical populations.

Last but not least, as a way of overcoming some of the mentioned difficulties, we will also review reward/pleasure based neuroimaging data under the assumption that the neural substrates of anhedonia and reward/pleasure overlap to a good extent [15].

14.3 Hedonic Appraisal: Orbitofrontal Cortex (OFC)

The OFC is a major information integration hub providing support for a variety of cognitive processes from decision making to sensory, reward and hedonic processing [16]. From a neural connectivity perspective, the OFC is an important center for integrating sensory-autonomic input with visceral-motor systems output [16]; as such an important hedonic focal point.

From the perspective of neuroimaging studies the OFC however is not the easiest target to investigate. Due to its proximity to the air-filled sinuses the quality of OFC MRI findings can be diminished by signal dropout, geometric distortion or susceptibility artifacts [17, 18]. Hence negative findings of fMRI OFC studies need to be considered with caution [16].

Limitations considered, the medial OFC activation has been consistently correlated with reinforcers pleasantness for a variety of gustative and olfactory stimuli (for review see Ref. [16]).

Quite a few studies focused on finding the hedonia "spot" in the OFC; however, very few studies approached the subject of anhedonia relationship to OFC.

In their comprehensive meta-analysis of neuroimaging and neuropsychological studies focused on the OFC Kringelbach and Rolls found that the OFC specializes in different types of hedonic processing along its medial-lateral and antero-posterior axes [19]. Specifically, reward-based processing correlates with activity in the medial while punishment processing correlates mostly with activity in the lateral OFC. Also, abstract/complex reinforcers associations (e.g. financial incentives) appear to be based in the anterior OFC, while more concrete/simple reinforcers associations are mostly based in the posterior OFC.

In a PET study using musical dissonance as an anhedonic-equivalent, OFC activity was correlated with the level of consonance/hedonic experience [20]. A more recent fMRI study, using an anhedonic stimulus in the form of a reinforcer devaluation paradigm found that the mid-anterior OFC and amygdala activity decreased in parallel with the reinforcer perceived hedonic value [21].

Trait-anhedonia negatively correlated with OFC activity in healthy subjects [22].

Consistent with the OFC and ventral striatum (VS) role in hedonic experiences, anhedonic patients with major depressive disorder (MDD) [23, 24] and schizophrenia [25, 26] usually present with lower than expected activity in both the OFC and. Of note, task-dependent increased or decreased OFC activation correlated with anhedonia severity in depressed patients [24].

14.4 Reward Appraisal and Executive-Decision Making: The Prefrontal Cortex (PFC) and the Anterior Cingulate Cortex (ACC)

The prefrontal cortex has long been known for its executive role including decision making, reward appraisal, and cost-benefit analysis as distinct functions contributing to normal cognitive processes such as learning and motivation, or pathological dysfunction such as addiction [27], negative symptoms in schizophrenia [28], or impaired decision making in depression [29].

Based on different connectivity patterns, the PFC is usually divided in two regions: the ventromedial PFC (vmPFC) and dorsolateral PFC (dlPFC), with the vmPFC traditionally seen as underlying emotional/affective processing ("what" function), while the dlPFC providing support for cognitive/executive processing ("how" function) [30].

In non-clinical subjects physical anhedonia inversely correlated with vmPFC and ACC activity [25, 31], anterior PFC activity [31], as well as with ACC and dlPFC resting state activity [32]. High levels of social anhedonia inversely correlated with

medial PFC activity during emotional discrimination tasks [33]. However, vmPFC activity has also been reported to positively correlate with the level of anhedonia-trait severity in both healthy individuals [34] and depressed patients [24].

In patients addicted to opioids anhedonia severity negatively correlated with activity in PFC and ACC [31].

In MDD patients anhedonia severity correlated with ventrolateral PFC and dorsal cingulate gyrus responses to sad stimuli but inversely correlated with ventral ACC activation to happy stimuli [24].

Anterior cingulate cortex GABA levels, as measured by proton magnetic resonance spectroscopy, negatively correlated with the severity of anhedonia in adolescents with MDD [35]. Emotional intensity ratings, an anhedonia surrogate, correlated with glutamate and N-acetylaspartate concentrations and inversely correlated with glutamine concentration and pregenual anterior cingulate activation in highly anhedonic depressed patients [36].

In patients with schizophrenia, in addition to an inverse correlation with activity in the OFC and VS [25] physical anhedonia has also been correlated with decreased activity in the vmPFC [25]. Structural and functional MRI as well as PET studies also suggest that in patients with schizophrenia physical anhedonia might be associated with volume deficits and hypo-activity in the default-mode neurocircuitry including the ventromedial prefrontal cortex [37].

In conclusion, decreased activity in the both the vmPFC and dlPFC as well as the ACC appear to contribute to anhedonia in affected and healthy individuals. This importance of this circuit in the genesis of anhedonia is emphasized by the fact that clinical findings have been consistent in both adolescent and adult samples.

14.5 (The Mesolimbic) Reward Detection System (MRDS): Nucleus Accumbens (NAc) and the Ventral Tegmental Area/Substantia Nigra (VTA/SN)

The ventral striatum (VS), and especially nucleus accumbens, with its strong OFC input, has been long associated with the pathology of addiction and reward [38].

More specifically, nucleus accumbens is an important reward-contingent as well as reward-independent pleasure processing center. NAc forms a functional unit with the VTA/SN via the medial forebrain bundle connection [39]. The NAc-VTA circuit is essential in detecting rewards and thus modulating responses to natural rewards such as food, sexual, and social intercourse. The activation of this circuit results increases the likelihood that a certain activity [labeled as pleasurable] will be repeated in the future. As such the MRDS plays in important role in the control of hedonic experiences and putatively MRDS dysfunctions may result in anhedonia.

Consistent with this understanding of the MRDS role, Wacker et al. [32] found that in a non-clinical sample anhedonia was inversely correlated with both NAcc volume and NAcc responses to reward feedback. In contrast to an initial finding of

a lack of correlation between anhedonia-trait and NAc activity [34] in a recent fMRI study healthy subjects activation in response to a musical stimulus in the right NAc, basal forebrain and bilateral hypothalamus was negatively correlated with trait anhedonia [22].

In depressed patients anhedonia severity did not correlate with NAc volume [40]. Blood et al. [41]. found that MDD patients have microstructural VTA abnormalities compared to health subjects; however, they also reported that in their sample anhedonia did not correlate with the severity of VTA abnormalities.

Lee et al. reported a significant percent signal change in NAc and hippocampus activity correlated with physical anhedonia severity in patients with schizophrenia compared to healthy controls, indicating that specific parts of the limbic and reward circuitry may be associated with physical anhedonia in schizophrenia [42].

Patients with schizophrenia differ from healthy individuals in that their anhedonia level inversely correlated with VS response to positive stimuli compared to negative and neutral stimuli [43].

In summary, decreased volume and activity in the (MRDS) appears to contribute to anhedonia in healthy and affected individuals. However, the relationship between the MDRS and anhedonia in clinical populations is less clear than in healthy individuals; this lack of clarity may be in part due the difficulties in higher level of confounding as well as more difficulties in reliably measuring primary:secondary anhedonia in clinical samples.

14.6 Emotional Context: The Insula Cortex and Amygdala

Alongside with the orbitofrontal, cingulate, and medial prefrontal the insular cortices complete the who's who list of hedonic hotspots [44].

In an fMRI study of healthy subjects Keller et al. [22] found that trait-anhedonia negatively correlated with activity in the anterior insula.

In a study of healthy individuals with high:low social anhedonia Germine et al. [33] reported that social anhedonia severity did not correlate with amygdala activity; however the study findings might be limited by amygdala's rapid habituation in the context of the study's rapid block-design, continuous presentation of faces, and emotion labeling demands, that might have resulted in a low signal:noise ratio.

In an early PET schizophrenia study Crespo-Facorro et al. [45] found that patients with schizophrenia had decreased activity in the insular cortex in response to unpleasant odors only. Of note, the patients showed impairment in the experience of pleasant odors when compared to healthy controls – consistent with an anhedonic presentation – but this experiential difference did not result in PET activity differences; on the contrary, it was their response to the unpleasant odors, which was experientially similar to healthy volunteers, that resulted in PET differences. It appears that the insular cortex functional abnormalities may contribute to anhedonia in schizophrenia; however further studies are recommended to clarify the directionality of this relationship.

In a recent PET resting-state paradigm study Park et al. [37] reported that in patients with schizophrenia physical anhedonia correlated with hypo-activity in the default-mode neurocircuitry including the insular cortex.

Dowd et al. [43] reported that physical anhedonia correlated with decreased bilateral amygdala activation to positive versus negative stimuli in patients with schizophrenia.

14.7 Other Regions of Interest: Cerebellum, Raphe Nuclei (RN)

In a recently published meta-analysis Kuhn et al. [46] found both positive and negative correlates of subjective pleasantness in the right cerebellum.

Using PET Park et al. [37] reported that cerebellum activity did not correlate with trait physical anhedonia severity in patients with schizophrenia.

In summary, the evidence to date does not support the hypothesis that cerebellum plays a significant role in the pathology of anhedonia.

Reward/castigatory stimuli correlated with neural activation within the dorsal RN indicative of a change in serotonergic transmission elicited by hedonic processing [47].

14.8 Conclusions and Future Directions

In summary, anhedonia is associated with decreased reactivity and connectivity in the neural substrates underlying sensing and appraisal of pleasant stimuli and rewards (OFC and VS/NAc), cost/benefit analysis and decision making (ACC, vmPFC and dlPFC), reward processing and consolidation (the mesolimbic system: VS/NAc, VTA/SN, and hippocampus connections), salience labeling (amygdala), as well as related limbic and paralimbic regions (Table 14.1).

A clear interpretation of the literature is limited by a lack of coherence in approaching the topic of anhedonia. Despite a wealth of studies on the neural substrates of reward and hedonia, there are relatively few studies addressing the subject of anhedonia *per se*. Moreover, the relationships between state:trait anhedonia or the different specific types of anhedonia (e.g. physical:social, anticipatory:consumatory) is yet to be explored in a well-articulated manner.

Despite the evidence to date shortcomings, the emerging picture of the hedonic brain imaging literature is one of a hedonic continuum, with a remarkable continuity between healthy and affected individuals.

This emerging theme of a linked set of neural hedonic circuits supports the view that anhedonia might be a useful endophenotype or potential trait marker related to vulnerability to major psychiatric disorders such as depression and schizophrenia.

Table 14.1 The neural substrates of anhedonia

Brain area	Role (in hedonic circuits)	Relevant efferents
Hedonic appraisal		
Orbitofrontal cortex [2, 16, 19, 21, 25, 27]	Sensory integration Reward/punishment appraisal	NAc, ACC
Ventral striatum [15, 23, 25–27, 43, 46]	Reward appraisal	
Reward appraisal and executive-decision making		
PFC [2, 15, 24–26, 31, 33, 34, 37, 48]	Reward value, effort and reinforcement cost/benefit appraisal	NAc
Anterior cingulate cortex [32]	Effort appraisal Decision making	vmPFC, dlPFC
The Mesolimbic Reward Detection System (MRDS)		
N Accumbens [2, 22, 23, 32, 40]	motivation Goal directed activity	VTA, vmPFC
Ventral Tegmental Area [22, 31, 41]	Reward	*Mesocortical*
Substantia Nigra [41]	Motivation Orgasm	PFC, insula *Mesolimbic* Limbic, NAc, amygdala, hippocampus,
Emotional context		
Insular cortex [22, 26]	Sensory-emotional integration	Amygdala
Amygdala [21, 24, 43]	Salience Emotional valence	VS
Other regions of interest		
Raphe nuclei [47]	Reward processing	VTA

In light of the relatively small number of brain imaging studies of anhedonia to date, lack of precision in the definition of anhedonia, diagnostic heterogeneity of the study populations and heterogeneity of study methods, the brain imaging of anhedonia remains an incipient field of research at this time.

The evidence to date about the brain correlates of anhedonia while promising, remains preliminary. Further research is indicated.

References

1. Loas G, Pierson A. Anhedonia in psychiatry: a review. Ann Medicopsychol. 1989;147:705–17.
2. Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci. 2008;10(3):291–9.
3. Meehl PE. Hedonic capacity: some conjectures. Bull Menninger Clin. 1975;39(4):295–307.
4. Bogdan R, Pizzagalli DA. The heritability of hedonic capacity and perceived stress: a twin study evaluation of candidate depressive phenotypes. Psychol Med. 2009;39(2):211–18.

5. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35:4–26.
6. Kaji Y, Hirata K. Apathy and anhedonia in Parkinson's disease. ISRN Neurol. 2011;2011:219427.
7. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:22.
8. Loas G, Perot JM, Boyer P, Gayant C, Fremaux D. Evaluation of the subjective component of emotions in normal subjects: relation between anhedonia and the capacity to perceive unpleasant feelings in a population of 221 normal subjects. Ann Medicopsychol. 1995;153:143–5.
9. Snaith P. Anhedonia: a neglected symptom of psychopathology. Psychol Med. 1993;23:957–66.
10. Kirkpatrick B, Buchanan RW. Anhedonia and the deficit syndrome of schizophrenia. Psychiatry Res. 1990;31:25–30.
11. Kerns JG, Docherty AR, Martin EA. Social and physical anhedonia and valence and arousal aspects of emotional experience. J Abnorm Psychol. 2008;117:735–46.
12. Gard D, Gard M, Kring A, John O. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.
13. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008;199(3):457–80.
14. Loas G, Monestes JL, Ingelaere A, Noisette C, Herbener ES. Stability and relationships between trait or state anhedonia and schizophrenic symptoms in schizophrenia: a 13-year follow-up study. Psychiatry Res. 2009;166:132–40.
15. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35(1):68–77.
16. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci. 2005;6(9):691–702.
17. Wilson JL, Jenkinson M, de Araujo I, Kringelbach ML, Rolls ET, Jezzard P. Fast, fully automated global and local magnetic field optimization for fMRI of the human brain. Neuroimage. 2002;17(2):967–76.
18. Deichmann R, Josephs O, Hutton C, Corfield DR, Turner R. Compensation of susceptibility-induced BOLD sensitivity losses in echo-planar fMRI imaging. Neuroimage. 2002;15(1):120–35.
19. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol. 2004;72(5):341–72.
20. Blood AJ, Zatorre RJ, Bermudez P, Evans AC. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat Neurosci. 1999;2(4):382–7.
21. Gottfried JA, O'Doherty J, Dolan RJ. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science. 2003;301(5636):1104–7.
22. Keller J, Young CB, Kelley E, Prater K, Levitin DJ, Menon V. Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. J Psychiatr Res. 2013;47(10):1319–28.
23. Epstein J, Pan H, Kocsis JH, et al. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. Am J Psychiatry. 2006;163(10):1784–90.
24. Keedwell PA, Andrew C, Williams SCR, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005;58(11):843–53.
25. Harvey P-O, Armony J, Malla A, Lepage M. Functional neural substrates of self-reported physical anhedonia in non-clinical individuals and in patients with schizophrenia. J Psychiatr Res. 2010;44(11):707–16.
26. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. Hashimoto K, ed. PLoS One. 2012;7(5):e35622.
27. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35(1):217–38.
28. Wolkin A, Sanfilipo M, Wolf AP, Angrist B, Brodie JD, Rotrosen J. Negative symptoms and hypofrontality in chronic schizophrenia. Arch Gen Psychiatry. 1992;49(12):959–65.
29. Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res. 2009;201(2):239–43.

30. O'Reilly RC. The What and How of prefrontal cortical organization. Trends Neurosci. 2010;33(8):355–61.
31. Zijlstra F, Veltman DJ, Booij J, van den Brink W, Franken IHA. Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males. Drug Alcohol Depend. 2009;99(1):183–92.
32. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage. 2009;46(1):327–37.
33. Germine LT, Garrido L, Bruce L, Hooker C. Social anhedonia is associated with neural abnormalities during face emotion processing. Neuroimage. 2011;58(3):935–45.
34. Harvey P-O, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry. 2007;12(8):703. 767–75.
35. Gabbay V, Mao X, Klein RG, et al. Anterior cingulate cortex γ-aminobutyric acid in depressed adolescents: relationship to anhedonia. Arch Gen Psychiatry. 2012;69(2):139–49.
36. Walter M, Henning A, Grimm S, et al. The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. Arch Gen Psychiatry. 2009;66(5):478–86.
37. Park IH, Kim J-J, Chun J, et al. Medial prefrontal default-mode hypoactivity affecting trait physical anhedonia in schizophrenia. Psychiatry Res Neuroimaging. 2009;171(3):155–65.
38. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol. 1954;47(6):419–27.
39. Yun IA, Wakabayashi KT, Fields HL, Nicola SM. The ventral tegmental area is required for the behavioral and nucleus accumbens neuronal firing responses to incentive cues. J Neurosci. 2004;24(12):2923–33.
40. Pizzagalli DA, Holmes AJ, Dillon DG, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166(6):702–10.
41. Blood AJ, Iosifescu DV, Makris N, et al. Microstructural abnormalities in subcortical reward circuitry of subjects with major depressive disorder. Bartolomucci A, ed. PLoS One. 2010;5(11):e13945.
42. Lee JS, Park H-J, Chun JW. Neuroanatomical correlates of trait anhedonia in patients with schizophrenia: A voxel-based morphometric study. Neurosci Lett. 2013;489(2):110–14.
43. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry. 2010;67(10):902–11.
44. Kringelbach ML, Berridge KC. The neuroscience of happiness and pleasure. Soc Res (New York). 2010;77((2):659–78.
45. Crespo-Facorro B. Neural mechanisms of anhedonia in schizophrenia. A PET study of response to unpleasant and pleasant odors. JAMA. 2001;286(4):427.
46. Kühn S, Gallinat J. The neural correlates of subjective pleasantness. Neuroimage. 2012;61(1):289–94.
47. Lanzenberger R, Hahn A, Windischberger C, et al. Serotonin-1A receptor binding and Reward-dependent Activation are associated within the Human Dorsal Raphe Nucleus as revealed by PET-fMRI. Neuroimage. 2009;47.
48. Gaillard R, Gourion D, Llorca PM. Anhedonia in depression. Encéphale. 2013;39(4):296–305.

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