Current Topics in Behavioral Neurosciences 58

Diego A. Pizzagalli *Editor*

Anhedonia: Preclinical, Translational, and Clinical Integration

Springer

Current Topics in Behavioral Neurosciences

Volume 58

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Anhedonia: Preclinical, Translational, and Clinical Integration

Springer

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ISSN 1866-3370 ISSN 1866-3389 (electronic)
Current Topics in Behavioral Neurosciences
ISBN 978-3-031-09682-2 ISBN 978-3-031-09683-9 (eBook)
https://doi.org/10.1007/978-3-031-09683-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

An avid painter for almost four decades, over the past five months Jamal has totally lost interest in painting. When asked by his wife about this abrupt change, Jamal explains that he derives no pleasure from painting anymore, and, in fact, this hobby has become a burden. At his wife's urging, Jamal eventually reaches back out to the psychiatrist who successfully treated his first episode of major depression seven years ago with a selective serotonin reuptake inhibitor (SSRI). In therapy, Jamal describes feeling "trapped in a web of stress" he cannot control, including his wife's chronic and deteriorating health problems, mounting financial hardship, and difficulties at work. Unfortunately, the SSRIs that his psychiatrist now prescribes no longer have much effect, and Jamal's disinterest in painting expands to include his other favorite pastimes of reading and cycling. In their place, he spends an excessive amount of time watching television even though he frequently complains that "there's never anything good on."

Over the past months, Lina has been isolating herself from her friends and is falling behind in middle school. Though she had always been a temperamentally shy child from early age, her parents felt this time was different. They reach out to their family doctor, who is unsure how best to help. When asked about these changes, Lina explains that she never feels like doing anything with friends, even when she admits she would probably have fun. She acknowledges that she does enjoy spending time with at least a few of her friends, but often relies on others to invite her to join. Most of the time, however, Lina does not feel sufficiently motivated to initiate social activities herself.

Jamal and Lina are both exhibiting anhedonic behaviors, but those behaviors are distinct from each other and may thus have different etiologies and pathophysiologies. Jamal exhibits anhedonia as it is classically understood (inability to experience pleasure), which might have been triggered by chronic, uncontrollable stressors. Lina, on the other hand, can still experience pleasure but has difficulty exerting effort to pursue possible rewards. As illustrated by chapters in this volume, these and other forms of anhedonic behaviors are subserved by partially non-overlapping brain circuits, raising the possibility that different therapeutic strategies might be needed to address them.

A volume on anhedonia is thus timely, and, we believe, clinically and scientifically important. Anhedonia does not "obey" current nosological systems (e.g., Diagnostic Statistical Manual, International Classification of Disease), but is instead a transdiagnostic phenomenon. Across neuropsychiatric disorders, anhedonia is invariably associated with a more challenging clinical course, including weaker response to treatment, more chronic illness, and – for several disorders such as major depressive disorder – increased risk of attempted and completed suicide. Critically, anhedonic phenotypes can be elicited in experimental animals, typically through chronic exposure to uncontrollable and unpredictable stressors. These phenotypes have been linked to dysregulation within corticostriatal pathways receiving dense projections from dopaminergic neurons and other neuromodulators. In humans, anhedonia can be observed early in life and can be triggered or exacerbated by polygenic risk factors and environmental factors (here too, mostly exposure to uncontrollable chronic stressors). Anhedonia may emerge as both cause or consequence of other related symptoms and thought patterns, including pessimism, hopelessness, and pervasive fatigue. When it manifests, anhedonia can be difficult to treat, a clinical conundrum that has prompted the search for new pharmacological and neurostimulation targets, as well as the development of more targeted psychological treatments that specifically attempt to ameliorate anhedonia. Over the past 10–15 years, progress in all these areas has been substantial but more work is clearly needed.

Progress has been spurred by the launch of the Research Domain Criteria (RDoC) initiative by the US National Institute of Mental Health in 2010. The so-called Positive Valence Systems, which are "primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning" (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/positive-valence-systems), are clearly relevant to anhedonia and can be decomposed into different domains and subdomains (see Table 1).

Table 1 Constructs and subconstructs within the Positive Valence Systems of the Research Domain Criteria. For formal definitions and recommended tasks to probe these subconstructs, the interested reader is referred to https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/positive-valence-systems

Construct	Subconstruct
Reward Responsiveness	Reward Anticipation
	Initial Response to Reward
	Reward Satiation
Reward Learning	Probabilistic and Reinforcement Learning
	Reward Prediction Error
	Habit
Reward Valuation	Reward (probability)
	Delay
	Effort

This framework is helping scientists and clinicians develop and launch new studies that target fundamental mechanisms underlying anhedonia. Nevertheless, anhedonia remains a formidable challenge, linked to substantial personal suffering, staggering societal costs (e.g., due to loss of productivity), chronicity and a worse clinical trajectory, and, at this stage, few good therapeutic options. Capitalizing on a burgeoning literature stemming from disparate fields (e.g., clinical psychology, neuroscience, psychopharmacology, computational psychiatry, genetics), this volume is intended to provide both specialists and readers new to this area with the most comprehensive evaluation of anhedonia to date. The authors enlisted here are leaders in their respective areas and have made major contributions toward a better understanding of anhedonia. The volume is organized in five parts:

Part I. Historical Aspects, Etiology, and Assessments
Part II. Anhedonia in Psychiatric and Neurological Disorders
Part III. Reward Processing Systems in Anhedonia
Part IV. Special Topics
Part V. Treatments

In *Part I*, the first chapter provides a comprehensive review of anhedonia assessments across "units of analysis" (e.g., self-report, behavior, physiology) and species (*Wang et al.*). This is followed by reviews that consider the origin and developmental trajectories of anhedonia in preclinical models (*Birnie et al.*) and human samples (*Prabhakar et al.*). Next, chapters reviewing evidence highlighting both genetics (*Bondy and Bogdan*) and environmental (*Harkness et al.*) contributions to anhedonia are presented. Building on these foundational literatures, *Part II* is devoted to the manifestation, epidemiology, and pathophysiology of anhedonia within distinct neuropsychiatric disorders, including depression and bipolar disorder (*Whitton and Pizzagalli*), schizophrenia (*Moran et al.*), substance use disorder (*Koob*), nicotine dependence (*Gilbert and Stone*), Posttraumatic Stress Disorder (*Vinograd et al.*), anxiety disorders (*Taylor et al.*), eating disorders (*Murray et al.*), autism and developmental disorders (*Dichter et al.*), and neurodegenerative disorders (*Turner and Husain*).

In *Part III*, the opposite approach is taken: instead of focusing on anhedonia in discrete neuropsychiatric disorders, the authors synthetize the literature that has probed distinct Positive Valence Systems subconstructs in a transdiagnostic fashion. Thus, Part III includes chapters discussing anhedonia with respect to pleasure, reward value, and prediction error (*Kieslich et al.*), reward anticipation (*Phillips and Ahn*), vigor and effort-related aspects of motivation (*Treadway and Salamone*), and probabilistic reinforcement learning (*Kangas et al.*).

In *Part IV*, several critically important topics are discussed, including historical and current perspectives on the transdiagnostic nature and importance of social anhedonia (*Gooding and Pflum*), the role of inflammation in the pathophysiology of anhedonia (*Bekhbat et al.*), the use of computational modeling to "dissect" anhedonia and improve its understanding (*Huys and Browning*), and links between anhedonia and suicide (*Auerbach et al.*).

The book concludes with important chapters in *Part V* that summarize and discuss progress in developing treatment approaches to tackle anhedonia. Specifically, pharmacological (*Klein et al.*), psychological (*Sandman and Craske*), and circuit-based neuromodulation (*Siddiqi et al.*) treatments are emphasized. These chapters discuss significant gains the field has made in treating anhedonia, but also challenges that remain and underscore the need for future research. A commonality across these treatment chapters is that progress has been accelerated by incorporating knowledge stemming from preclinical and clinical studies, as well as from neuroscience-based studies that have improved our understanding of biological and psychological mechanisms subserving hedonia and motivation.

Ultimately, the authors of each chapter are united in their desire to help people like Jamal and Lina, by integrating basic, translational, and clinical research targeting the manifestation, etiology, pathophysiology, and treatment of anhedonia.

I would like to thank several individuals who provided much valued help with this project. First, Dr. Andre Der-Avakian (University of California, San Diego), who provided invaluable initial input in developing the structure of the book and identifying possible contributors. He also served as a Guest Editor for the chapter on depression and bipolar disorder (which I co-authored). I am also grateful to Drs. Jonathan Roiser and Michael Browning for serving as Guest Editors on the chapter on reinforcement learning (which I co-authored). Second, each chapter was peer-reviewed by two reviewers, and I am grateful to 25 anonymous reviewers who evaluated a given chapter (in some cases, more than once). Third, I would like to thank Dr. Mark A. Geyer (University of California, San Diego) – Series Editor for Current Topics in Behavioral Neurosciences – who encouraged me to develop a book on anhedonia. Many thanks also to various Springer staff, in particular Susanne Dathe (Publishing Editor) and Alamelu Damodharan, for their guidance throughout the project. A huge expression of gratitude to my parents, Rita and the late Renzo, for supporting me in so many ways and encouraging me to pursue my path. Finally, this book is dedicated to my wife Michèle Candrian and our children, Mattia D. Pizzagalli and Lisa M. Pizzagalli, who have fueled and sustained my hedonic health for decades. With much gratitude and love for enriching my life.

Belmont, MA, USA Diego A. Pizzagalli
March 16, 2022

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Part I
Anhedonia – History, Etiology, and Assessments

Clinical and Preclinical Assessments of Anhedonia in Psychiatric Disorders

Shijing Wang, Francesco Leri, and Sakina J. Rizvi

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Abstract Anhedonia is a prevalent symptom across many psychiatric disorders. The contemporary scope of anhedonia across various models includes interest,

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Curr Topics Behav Neurosci (2022) 58: 3–22
https://doi.org/10.1007/7854_2022_318
Published Online: 19 April 2022

reward anticipation, motivation, effort expenditure, reward valuation, expectation, pleasure, satiation, and learning. In order to further elucidate the impact of anhedonia on treatment outcomes, quality of life, as well as brain function, validated tools to probe the various facets of anhedonia are necessary. This chapter evaluates assessment tools for anhedonia in clinical populations and in animals. Subjective clinical scales have been in use for decades, and as the construct of anhedonia evolved, contemporary scales were developed to integrate these new concepts. Clinical scales are useful for understanding the subjective experience of anhedonia but do not account for objective aspects of anhedonia, including implicit learning. Behavioral tasks that probe responses to rewarding stimuli have been useful to fill this gap and to delineate the specific brain processes underlying facets of anhedonia. Although there have been translational challenges in the assessments of anhedonia and reward deficits from preclinical to clinical (and vice versa), the multifaceted clinical scales and reward tasks provide valuable insights into the conceptualization of anhedonia and its neural basis across psychiatric disorders.

Keywords Anhedonia · Cross-species · Effort · Learning · Motivation · Positive valence system · Reward

1 Introduction

Anhedonia is prevalent in psychiatric and neurological disorders including major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ), substance use disorder (SUD), and Parkinson's disease (American Psychiatric Association 2013). Importantly, anhedonia has broadened from its initial definition (i.e., the loss of pleasure or interest) toward a spectrum of reward processing deficits (Berridge and Robinson 2016; Cooper et al. 2018). Current conceptualizations, such as the positive valence systems outlined by the Research Domain Criteria (RDoC) (Morris and Cuthbert 2012), encompass reward facets including interest, reward anticipation, motivation, effort expenditure, valuation, learning, pleasure, and satiation (NIMH 2016; Rizvi et al. 2016).

There has been a tremendous effort to develop tools, from clinical assessments that encompass different anhedonia facets to translational reward tasks in basic research (Young and Geyer 2015; Young and Markou 2015). Although there have been difficulties in translating the assessments of anhedonia and reward deficits across species, the effort to measure the neural basis of reward translationally has provided important information regarding the mechanisms and the treatments for anhedonia across psychiatric diagnoses (reviewed in Der-Avakian and Pizzagalli 2018). This chapter will evaluate the existing methods to assess anhedonia and reward processing in clinical populations and in animals, including clinical scales, as well as clinical and preclinical behavioral reward tasks.

2 Clinical Scales of Anhedonia and Reward Deficits: Beyond Pleasure and Interest

Early measures assessed anhedonia primary based on the traditional conceptualization of anhedonia as a lack of experienced pleasure of interest, while contemporary measures include facets of anhedonia beyond these subconstructs. The definition of anhedonia began to evolve on the basis of neurobiological and behavioral evidence from the year 2000 onwards. During this time, scale development methods also became more rigorous. Thus, clinical scales can be understood in the context of the time they were developed. The following will review these scales based on early (1970–2000) and contemporary (2001–2021) measures.

2.1 Early Measures (1970–2000)

The main measures developed during this time were the self-report *Chapman anhedonia scales (Revised Physical Anhedonia Scale and Revised Social Anhedonia Scale – CPAS and CSAS*, respectively; Chapman et al. 1976; Eckblad et al. 1982), *the Fawcett Clark Pleasure Scale (FCPS)* (Fawcett et al. 1983), and *the Snaith-Hamilton Pleasure Scale (SHAPS)* (Snaith et al. 1995). While the Chapman scales were developed for use in schizophrenia, the FCPS and SHAPS were designed for use in Major Depressive Disorder (MDD). This is reflected in the item content as the Chapman scales include experiences that can be related to negative or positive symptoms of schizophrenia (e.g., "my emotional responses seem very different from those of other people" in CSAS). Despite the content specificity, the Chapman scales have been psychometrically validated in schizophrenia, MDD, alcohol use disorder, and personality disorders (social scale only), while the FCPS and SHAPS are only validated in MDD. Of these scales, only the CPAS and CSAS tap into the facets of motivation, effort, as well as pleasure specific for physical and social rewards (Chapman et al. 1976). All four scales demonstrated moderate to strong reliability (Cronbach α: 0.74–0.85; Table 1). The SHAPS and FCPS also demonstrated good convergent and divergent validity, while the CPAS and CSAS relate strongly to personality and psychotic disorders. In addition to the above scales, *the Behavioral Activation System and Behavioral Inhibition System scale (BIS/BAS)* (Carver and White 1994) has also been frequently used in clinical studies and taps into personality traits of reward sensitivity, drive, seeking, as well as avoidance of reward.

Table 1 Early measures of anhedonia

Scales	Overview	Psychometric properties	Populations validated
Revised Chapman physical anhedonia scale (CPAS)	40-item, true-false scale *Reward facets*: Motivation/ effort/pleasure	*Reliability* $\alpha = 0.78–0.82$	HC, SCZ, MDD, personality disorder, SUD
Revised Chapman social anhedonia scale (CSAS)	61-item, true-false scale *Reward facets*: Motivation/ effort/pleasure	*Reliability* $\alpha = 0.79$	HC, SCZ, MDD, personality disorder, SUD
Fawcett–Clark pleasure capacity scale (FCPS)	36-item *Reward facets*: Pleasure	*Reliability* $\alpha = 0.85$	MDD, BD, HC
Snaith-Hamilton pleasure scale (SHAPS)	14-item *Reward facets*: Pleasure	*Reliability* $\alpha = 0.74$ (MDD)	HC, MDD, Parkinson's disease, SCZ, adolescents
Behavioral activation system and Behavioral inhibition system scale (BIS/BAS)	24-item *Reward facets*: Motivation, pleasure	*Reliability* $\alpha = 0.66–0.76$	HC, MDD, BD, SCZ, personality disorder, SUD, Parkinson's disease

2.2 Contemporary Measures (2001–2021)

As the conceptualization of anhedonia expanded, scales were developed to reflect facets beyond pleasure and interest. A review of the most common measures follows with additional scales reported in Table 2.

The Temporal Experience of Pleasure Scale (TEPS) (Gard et al. 2006) is an 18-item scale with two subscales distinguishing between anticipatory and consummatory pleasure in physical rewards. The TEPS demonstrates satisfactory psychometric properties; however, the consummatory subscale internal consistency was somewhat low. The TEPS interestingly showed that anticipation, but not pleasure differed between patients with schizophrenia and healthy controls (Gard et al. 2007). The factor structure has yielded conflicting findings, including yielding two subscales that were strongly correlated (Garfield et al. 2016; Simon et al. 2018). Therefore, further validation trials would be helpful to confirm the psychometrics and factor structure.

The Motivation and Pleasure Scale – Self-Report (MAP-SR) contains 15 items across reward facets of anticipation, motivation, effort, and pleasure primarily in the social domain (Llerena et al. 2013) and is only validated in populations with psychosis. The scale queries the intensity and frequency of pleasurable experiences. A recent study found that the MAP-SR has a 3-factor structure consisting of pleasure, social motivation, and motivation for work (Richter et al. 2019). However,

Table 2 Contemporary measures of anhedonia

Scales	Overview	Psychometric properties	Populations validated
Temporary experience of pleasure scale (TEPS)	18-item *Reward facets*: Anticipation, pleasure	*Reliability* $\alpha = 0.78$ (total scale), 0.72 (anticipation), 0.64 (pleasure). *Test-retest reliability* $r = 0.81$ (total), 0.80 (anticipation), 0.75 (pleasure)	HC, BD, SCZ/SCA, opiate dependence
Reward probability index (RPI)	20-item *Reward facets*: Interest, pleasure, reward probability, behaviors	*Reliability* $\alpha = 0.90$ *Test-retest reliability* $r = 0.69$	MDD, heavy alcohol drinkers, HC
Motivation and pleasure scale – Self-report (MAP-SR)	15-item *Reward facets*: Motivation/effort, pleasure	*Reliability* $\alpha = 0.87$ – 3-factor structure (pleasure, social and work motivation); motivation factors need to be reconstructed *Test-retest reliability* $r = 0.63$	SCZ/SCA
Specific loss of interest scale (SLIPS)	23-item *Reward facets*: Interest/pleasure	*Reliability* $\alpha = 0.94$	Undergraduate students, community sample, MDD
Anticipatory and consummatory interpersonal pleasure scale (ACIPS)	17-item *Reward facets*: Anticipation, pleasure	*Reliability* $\alpha = 0.86$–0.91 *Test-retest reliability* $r = 0.78$ – Anticipation/pleasure not separate factors	Students, community sample, HC (adolescents and adults)
Dimensional anhedonia rating scale (DARS)	17-item *Reward facets*: Pleasure, interest, motivation, effort	*Reliability* $\alpha = 0.91$–0.96 (total), 0.75–0.92 (subscales)	Community sample, HC, MDD or BD, mixed psychiatric sample
Rewarding events inventory (REI)	58-item *Reward facets*: Anticipation of enjoyment, frequency of rewards in past week	*Reliability* $\alpha = 0.94$–0.95 (total score), 0.70–0.90 (subscales) *Test-retest reliability* $r = 0.89$ (total score), 0.83–0.89 (subscales)	Past and current smokers
Beliefs about pleasure scale (BAPS)	22-item *Reward facets*: Valuation, expectation	*Internal consistency reliability* $\alpha = 0.92$–0.93 (total), 0.73–0.90 (subscales) *Test-retest reliability* $r = 0.82$ (total), 0.63–0.76 (subscales)	College students, SCZ, patients with high social anhedonia, HC

(continued)

Table 2 (continued)

Scales	Overview	Psychometric properties	Populations validated
Positive valence systems scale (PVSS)	21-item with 7 subscales based on reward domain. *Reward facets*: Anticipation, motivation, expectation, valuation, pleasure	*Internal consistency reliability* $\alpha = 0.91–0.95$ (total), 0.66–0.89 (subscales) *Test-retest reliability* $r = 0.83$ (total), 0.55–0.91 (subscales)	Community sample, college students, MDD, HC
Anhedonia scale for adolescents (ASA)	14-item with 3 subscales *Reward facets*: Interest/anticipation/pleasure, effort/motivation	*Internal consistency reliability* $\alpha = 0.93–0.94$ (total), 0.79–0.92 (subscales) *Test-retest reliability* $r = 0.73$ (total), 0.74–0.78 (subscales)	High school and college students from 11 to 18 years old

only the pleasure subscale demonstrated high reliability and convergent validity. The authors recommended the motivation factors be reconstructed.

The Specific Loss of Interest and Pleasure Scale (SLIPS) is a 23-item scale that probes changes in reward interest for social and recreational reward over a 2 week period (Winer et al. 2014). The scale demonstrated strong psychometric properties in college and community samples, as well as individuals with MDD. The SLIPS yielded a 1-factor structure representing social anhedonia. Importantly, it predicted anhedonic depression over the SHAPS and TEPS.

The Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) (Gooding and Pflum 2014a, b; Gooding et al. 2015) is a 17-item self-report questionnaire that examines social anhedonia in terms of deficits in anticipation and consummatory pleasure. This distinction builds on the CSAS. Items also avoid age bias and so can be used in youth groups. The scale showed high internal consistency and convergent validity with the TEPS subscales and good test-retest reliability. However, the scale demonstrated a 3-factor solution based on social interactions rather than reward anticipation and pleasure. A similar factor structure has been observed in French and Chinese populations (Chan et al. 2016; Chaix et al. 2017).

The Dimensional Anhedonia Rating Scale (DARS) (Rizvi et al. 2015), a 17-item self-report scale that includes items of interest, motivation, effort, and pleasure across four reward domains (hobbies, food/drink, social, and sensory). To increase item sensitivity, subjects provide their own examples of rewarding experiences in each domain and answer standardized questions about how they feel "right now." The scale demonstrated high internal reliability, convergent and divergent validity in community populations and MDD patients. Importantly, the scale yielded a 4-factor component mapping onto reward domain rather than facets. The DARS is validated in Spanish (transdiagnostic sample; Arrua-Duarte et al. 2019) and German (young adults; Wellan et al. 2021) with confirmed strong psychometric properties and factor structure.

The *Positive Valence Systems Scale (PVSS)* was developed to cover the reward facets specified in the positive valence systems (PVS) within RDoC and to be used transdiagnostically. It is a 21-item self-report scale that probes anhedonia over the past 2 weeks and contains seven subscales based on reward domain (food, physical touch, outdoors, positive feedback, social interactions, hobbies, goals) (Khazanov et al. 2020). The scale demonstrated strong internal reliability, test-retest reliability, and good convergent and divergent validity in MDD patients and healthy controls. Similar to other scales, the PVSS did not yield a factor structure that distinguishes reward facets.

2.3 Other Measures of Anhedonia

Some scales were not specifically developed to assess overall anhedonia, but they measure motivational deficits, personality traits, or other aspects of anhedonia. *The Apathy Evaluation Scale (AES)* (Marin et al. 1991) mainly evaluates amotivation and apathy, but it also contains a subfactor of reward interest. *The Motivation and Energy Inventory (MEI)* is a scale developed for MDD to specifically assessing motivation and energy deficits (Fehnel et al. 2004). It includes three subscales of social motivation, physical energy, and mental energy. *The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)* (Torrubia et al. 2001) specifically measures sensitivity to punishment and reward in 2 subscales. *The Reinforcement Sensitivity Theory of Personality Questionnaire (RST-PQ)* includes BIS and BAS, but also includes a fight-flight-freeze system (FFFS) (Corr and Cooper 2016). Items related to goal planning to obtain reward in addition to motivation and effort were included. These motivation and personality scales have been utilized in clinical studies to assess reward and especially motivational deficits.

2.4 Gaps in Existing Anhedonia Clinical Scales

There has been a tremendous effort to refine clinical scales. Data clearly demonstrate a consistent deficit in anhedonia across psychiatric disorders compared to healthy controls and support the use of some scales as being sensitive to change over time or with treatment. However, evidence also suggests that it is challenging to reliably differentiate reward facets even among scales where this was the goal. Instead, items tend to map onto reward domain. Consequently, it is not presently possible to differentiate which specific reward facet might be impaired in a given psychiatric diagnosis based on self-report scales. While this may initially be considered problematic, it makes theoretical sense that levels of interest, motivation, and pleasure would vary based on the reward domain. Future studies should explore this idea more comprehensively. Next, although scales specified different timeframes, the distinction between acute symptom scales and personality inventories remains to be

explored. Interestingly, studies show moderate convergence between reward scales that evaluates aspects of personality (e.g., BIS/BAS) and anhedonia scales. This speaks to whether there are aspects of anhedonia that are trait-based and other aspects that are sensitive to change. It is also not clear how anhedonia or facets of anhedonia fluctuate acutely and over time. This necessitates further research in order to determine the optimal timeframe for questionnaires. Moreover, there are aspects of anhedonia experience, like reward learning, that cannot be measured with clinical scales and instead require behavioral assessments. Finally, many different reward domains have been targeted in scales, including primary rewards like food, social reward, sexual rewards, as well as more human-specific types of rewards such as recreational rewards, and work-related motivation. Therefore, not all reward types assessed in clinical studies have preclinical correspondence, leading to difficulties in translational research. The subjective nature of these assessments also adds to the difficulty in translational research.

3 Preclinical and Clinical Reward Tasks

Although clinical scales are important for measuring subjective aspects of anhedonia, behavioral tasks provide objective measurement and may be more likely to translate across species. We will review how different tasks have been translated to evaluate reward facets in preclinical (laboratory animals) and clinical (human) subjects.

3.1 Anticipation

3.1.1 Preclinical

Reward anticipation occurs during the waiting period before the delivery of a reward, which is usually tested in animals with a reward acquisition protocol (reviewed in Der-Avakian et al. 2016; Phillips and Ahn 2022). For neurophysiological studies, the neural activity can be measured during the time preceding a cue of reward or the delay to receiving a reward. Several measures have been used to quantify reward anticipation in animals in response to different types of reward (food, drug, sexual rewards) including locomotor activities (e.g., food-anticipating activity, approach behaviors, and reward-related speeding). Anticipation is consistently impaired in animal models of depression and schizophrenia (Kamal et al. 2010; Barnes et al. 2014).

3.1.2 Clinical

Behavioral paradigms that have a delay before receiving rewards make it possible to observe reward anticipation neurocircuitry using techniques such as functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG). The Monetary Incentive Delay (MID) task disentangles the anticipation and outcome periods of reward processing (Knutson et al. 2000) and has been frequently used in neuroimaging studies *across psychiatric populations* (Oldham et al. 2018). An adaption of the MID, the Social Incentive Delay (SID) task, examines social reward anticipation (Spreckelmeyer et al. 2009). While less studied, it has been utilized in mood and anxiety disorders (Martins et al. 2021). Preliminary evidence suggests that the SID is more sensitive than the MID in identifying deficits in reward anticipation and consummatory pleasure in patients with MDD (Zhang et al. 2020).

3.2 Motivation and Effort Expenditure

3.2.1 Preclinical

Motivation is a complex construct that includes a range of behaviors directed toward rewarding stimuli, initiation of reward acquisition, as well as persistence of effortful behaviors to obtain a reward (Salamone et al. 2016). In tests of motivation and effort, animals are trained to perform effortful behaviors (*such as poking with nose, turning a wheel*) to receive a small amount of reward (reviewed in Salamone et al. 2016; Treadway and Salamone 2022). In addition, effort-related choice paradigms provide animals with choices between high-effort/high-reward and low-or-no-effort/low-reward options (Salamone et al. 1991, 2016). Choices can be modeled to assess individual differences in reward motivation and willingness to expend effort in exchange for reward.

3.2.2 Clinical

Several motivation and effort tasks from preclinical studies are adapted to assess the willingness to exert effort for monetary rewards in clinical populations (reviewed in Der-Avakian and Pizzagalli 2018). There are some variations among human effort tasks, such as using humorous cartoon clips as reward types, the grip force task that involves squeezing a hand grip for money, and the cognitive effort that is tested in monetary reward discounting protocols (Reddy et al. 2015; reviewed in Rizvi et al. 2016). The Effort Expenditure for Reward Task (EEfRT) provides subjects with choices between high-effort/high-reward and low-effort/low-reward options (Treadway et al. 2009), developed based on the rodent paradigm of effort-related choices mentioned above. Compared to other physical, perceptual, and cognitive effort discounting tasks, the EEfRT showed the best psychometric properties,

including internal consistency reliability, stability as a repeated measure, and ability to detect between-group differences (Reddy et al. 2015). Impairment of effortful choices using the EEfRT has been reported in patients with MDD and schizophrenia (Gold et al. 2015).

3.3 Valuation of Reward

3.3.1 Preclinical

For optimal reward functioning, it is necessary to assess the relative value of a single reward or across multiple reward options to make approach behavior choices. Valuation of reward can be tested using the outcome devaluation task (Adams and Dickinson 1981), where animals are presented with two reward stimuli with different values (usually food reward or sucrose pellets). The animals are trained to devalue one of the two reward stimuli by either satiating it or using instrumental conditioning to pair it with a noxious stimulus. In animals with normal reward functioning, the choice of the reward that has not been devalued is usually preferred. In addition, the Delay Discounting task used widely in clinical studies was adapted to laboratory animals to assess reward valuation with different delays (Abela and Chudasama 2013). Subjects are required to decide between receiving a smaller reward magnitude at a shorter delay versus a larger reward magnitude at a longer delay.

3.3.2 Clinical

The outcome devaluation task was translated from animal studies to clinical studies using stimuli such as food items, food pictures paired with neuroimaging, and monetary rewards (reviewed in Der-Avakian et al. 2016). This task has been used in the context of OCD, eating disorders, substance use, and Parkinson's disease. Similarly, a sensory-specific satiety paradigm has been tested in schizophrenia (Waltz et al. 2015). This task assessed devaluation by measuring pleasantness ratings before and after satiation of a food stimulus compared to another stimulus that has not been satiated. As mentioned, the Delay Discounting task has been commonly implemented to assess reward valuation in clinical studies. Although the task varies, the common paradigm is that participants are asked to evaluate their preference for receiving smaller monetary reward immediately or larger rewards after a delay (reviewed in Rizvi et al. 2016). Other aspects of discounting for reward have also been tested in clinical studies. For example, the discounting rate of ambiguity (reward probability) and risk (potential of losing) of a reward is tested in the Probability Choice Task. Studies using the delay discounting task found impaired reward valuation in individuals with mood, schizophrenia, borderline personality disorder, and eating disorders (Amlung et al. 2019).

3.4 Expectation and Prediction Error

3.4.1 Preclinical

In a reward task, animals expect a reward value or probability based on previous experiences. Reward expectation is often tested using paradigms that probe prediction error, the discrepancy of anticipated and received reward (Schultz 1998). The prediction error signal in the brain associated with reward outcomes that are unexpectedly greater or less can be discerned very consistently (Schultz 1998). Prediction error can be assessed within a number of reward probabilistic learning or gambling tasks where there is an initial learning about a reward probability that changes in subsequent trials (for reviews and links to clinical disorders, see Kieslich et al. 2022).

3.4.2 Clinical

In clinical studies, prediction error can also be assessed with reward gambling paradigms using computational modeling to estimate the amount of reward encoded and/or neuroimaging to examine neural activity to unexpected reward outcomes. Reward learning paradigms where participants acquire the initial reward contingencies of a cue, which then change, have traditionally been used to assess prediction error (reviewed in Rizvi et al. 2016). Abnormal neural responses to prediction error within dopamine-rich regions have been implicated in depression and schizophrenia, which may be associated with impairment in reward valuation as well as learning (Gradin et al. 2011).

3.5 Outcome and Consummatory Pleasure

3.5.1 Preclinical

The consummatory aspect of reward has been widely measured by the sucrose preference test, where the animal is given the choice between plain water and sucrose solution (Willner et al. 1987). Hedonic taste reactivity after consumption of a reward can also be measured (reviewed in Berridge 2000). For example, animals with normal reward functioning have affective orofacial reactions toward reward such as licking.

3.5.2 Clinical

The sucrose preference task has been translated to clinical populations to assess consummatory pleasure (reviewed in Rizvi et al. 2016). However, the rating of this

task has not been able to distinguish between individuals with MDD or schizophrenia vs. healthy controls (Berlin et al. 1998; Dichter et al. 2010). Many reward tasks can be used to assess pleasure or reward outcome following reward feedback. For example, the MID and SID task introduced in Sect. 3.1.2 has a reward outcome phase to assess the neural response to reward, punishment, and neutral outcomes. Reward gambling paradigms can also be used to assess consummatory pleasure/outcome. However, these tasks use limited forms of reward (e.g., hypothetical monetary gain, a human face showing approval), so they may not fully characterize the reward one experiences in life.

3.6 Reward Learning and Feedback Integration

3.6.1 Preclinical

Several forms of reward learning have been assessed in animal models of psychiatric disorders. The initial reward learning associates a stimulus and a rewarding outcome (i.e., through Pavlovian conditioning), so the preference of reward cues over neutral cues can indicate reward learning. In addition, animals can also learn the probability of reward stimuli associated with cues from feedback using probabilistic learning tasks, where two stimulus choices have different probabilistic schedules (e.g., 80% reinforcement rates for one stimulus, and 20% for the other). Probabilistic learning paradigms can also be combined with a signal-detection task, where animals distinguish between ambiguous stimuli to receive a reward. A resulting association of one of the ambiguous stimuli with a higher probability for reward leads to a response bias toward one stimulus over the other. The probabilistic reward task (PRT) is designed to assess this response bias, a task adapted from clinical studies (Der-Avakian et al. 2013). In animal versions of the PRT, correct identification of ambiguous tone durations, odor stimuli, and more recently visual stimuli, are associated with different probability of food rewards (reviewed in Der-Avakian et al. 2016; Kangas et al. 2020).

In uncertain reward decision-making tasks, reward learning also involves updating of existing reward contingencies based on feedback. Feedback integration can be assessed through the probabilistic reversal learning task (PRLT), a task adapted from human studies (Bari et al. 2010; Ineichen et al. 2012), where animals initially learn the reward probabilities of the stimuli, and then the reward contingency reverses. Performance of reversal learning can be quantified with win-stay and loss-shift behaviors (the change of response after a winning or losing feedback), which was impaired in animal models of anhedonia (Tran et al. 2016). Furthermore, gambling paradigms such as the preclinical Iowa Gambling Task (IGT) can assess neurocircuitry involved in reward learning in rats under neuroimaging conditions (Rivalan et al. 2009).

3.6.2 Clinical

Similar to preclinical tasks, different forms of reward learning can be assessed in clinical reward learning and gambling tasks. The Pavlovian conditioning task has been used clinically to assess initial association of neutral cues and reward stimuli (O'Doherty et al. 2004). As in the preclinical studies, the probabilistic learning paradigms are common in clinical research to assess reward- and punishment-based learning, such as the probabilistic stimulus selection task (PSST) (Frank et al. 2004). In addition, the PRT assesses reward response bias in human using a smiley face with different mouth lengths as the ambiguous stimulus (Pizzagalli et al. 2005). The PRT has been combined with neuroimaging techniques such as EEG to examine neural responses to feedback (Whitton et al. 2016). Feedback integration can be assessed via reward learning (e.g., PRLT) and gambling paradigms (e.g. IGT). Impaired reward feedback integration has been found in individuals with depression and schizophrenia (Schlagenhauf et al. 2014; Mukherjee et al. 2020).

3.7 Translational Difficulties in Behavioral Assessments of Anhedonia

Preclinical and clinical assessments of reward have inevitable methodological differences with respect to the task design and the forms of reward used (but see, e.g., Kangas et al. 2020 for an exception), which result in translational difficulties. First, the distinction of primary and secondary reward limits the translation of preclinical and clinical studies (Rizvi et al. 2016). Primary rewards are inherent, instinctual, and unconditioned rewards that are important for survival and reproduction, such as food, sex, drug, and social rewards. On the other hand, secondary rewards (e.g., money) are not inherently pleasurable, and learning is required to associate them with reward. Although there may be some overlapping neural basis with primary and secondary rewards, they also involve distinct neural basis (Sescousse et al. 2013). For example, the MID and SID were found to activate overlapping regions during reward anticipation (Gu et al. 2019), but distinct neural activation during the outcome period: while social reward was mainly associated with the amygdala, the thalamus was mostly activated during monetary outcome (Rademacher et al. 2010). This indicates that the study of different reward facets may be affected by the reward type to different extents. While preclinical paradigms predominantly use primary reward such as food, sexual, drug rewards and direct neural stimulation, clinical behavioral tasks mostly used monetary reward. Given the potential different neural basis primary and secondary reward stimuli involve, this limits the translation of studies probing the altered neural basis of reward in clinical populations. Some clinical studies have used olfactory, gustatory, or visual stimuli as well, but this brings its own issues such as deficits of basic olfactory and gustatory processing in

some clinical groups. Nevertheless, there is also an argument that many preclinical reward paradigms are also using secondary rewards since they usually require conditioned or learned reward responses (Huston et al. 2013). The distinction of reward type is not absolute, and more research is needed to elucidate the distinction of reward types to better inform the translation between preclinical and clinical research that use different types of reward.

For both preclinical and clinical paradigms, another common problem is that not all reward facets can be disentangled in a given task. For example, although the MID task separates reward anticipation and outcome, it does not differentiate reward outcome and reward expectation (prediction error). Furthermore, not all reward facets are associated with a measurable and quantifiable behavioral measure such as consummatory pleasure. Importantly, neuroimaging or physiological recordings with techniques such as fMRI, EEG, and positron emission tomography (PET) address the limitation of understanding of the neural mechanisms underlying non-behavioral aspects of reward. Computational parameter estimations make it easier to measure reward facets such as expectation (prediction error) as well as valuation (discounting rate). Using these novel techniques, future research should explore the development of tasks that encompass several reward facets in order to identify how reward facets are related to each other, as well as their distinct and overlapping neurocircuitry. This would provide data on how neurocircuitry maps onto the psychological and behavioral functions that may be impaired in psychiatric disorders.

Regardless of the challenges, there has been great effort in translating preclinical reward paradigms to clinical populations and vice versa with more comparable task designs and features. Future research in task development should create parallel versions for preclinical and clinical studies to increase generalizability across species while considering the translational challenges (see guidelines for developing trans-species tasks in Der-Avakian and Pizzagalli 2018).

4 Conclusions

In summary, clinical scales vary in their ability to assess multiple aspects of reward, with contemporary scales more likely to include multiple facets of anhedonia. Nevertheless, clinical scales are limited in their ability to disentangle deficits in one reward facet compared to another. Furthermore, clinical scales that require subjective ratings cannot be translated to animals. In terms of behavioral assessments of reward deficits in psychiatric disorders, tasks that have a preclinical to clinical translation are more within the anhedonia facets of motivation, effort, valuation, expectation, and learning. Other facets, such as reward anticipation and outcome, have less correspondence in terms of reward type and the design of preclinical and clinical behavioral paradigms. The development of tasks that assess several reward facets would be valuable to yield neurobiological data that is more consistent with the functional deficits observed in psychiatric disorders.

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Developmental Trajectories of Anhedonia in Preclinical Models

Matthew T. Birnie, Sophia C. Levis, Stephen V. Mahler, and Tallie Z. Baram

Contents

Abstract This chapter discusses how the complex concept of anhedonia can be operationalized and studied in preclinical models. It provides information about the development of anhedonia in the context of early-life adversity, and the power of preclinical models to tease out the diverse molecular, epigenetic, and network mechanisms that are responsible for anhedonia-like behaviors.

Specifically, we first discuss the term anhedonia, reviewing the conceptual components underlying reward-related behaviors and distinguish anhedonia pertaining to deficits in motivational versus consummatory behaviors. We then describe the repertoire of experimental approaches employed to study anhedonia-like behaviors in preclinical models, and the progressive refinement over the past decade of both experimental instruments (e.g., chemogenetics, optogenetics) and

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Curr Topics Behav Neurosci (2022) 58: 23–42
https://doi.org/10.1007/7854_2021_299
Published Online: 14 February 2022

conceptual constructs (salience, valence, conflict). We follow with an overview of the state of current knowledge of brain circuits, nodes, and projections that execute distinct aspects of hedonic-like behaviors, as well as neurotransmitters, modulators, and receptors involved in the generation of anhedonia-like behaviors. Finally, we discuss the special case of anhedonia that arises following early-life adversity as an eloquent example enabling the study of causality, mechanisms, and sex dependence of anhedonia.

Together, this chapter highlights the power, potential, and limitations of using preclinical models to advance our understanding of the origin and mechanisms of anhedonia and to discover potential targets for its prevention and mitigation.

Keywords Development · Early-life adversity · Rodent

1 The Concept of Anhedonia and Its Operationalization in Preclinical Models

Anhedonia denotes a transdiagnostic construct that necessitates understanding the role of the reward circuit and its altered function in the pathophysiology of mental illnesses (Bedwell et al. 2014; Lake et al. 2017). Thus, the Research Domain Criteria (RDoC) framework put forth by the National Institute of Mental Health (NIMH) in the USA suggests that the neurobiological basis of anhedonia, together with empirical behavioral measures in humans and animal models is key to understanding how specific conditions including genetic make-up or early-life adversity (ELA) might lead to mental health vulnerabilities. Indeed, the common presence of anhedonia as a herald or component of many psychiatric illnesses supports the notion that the disruption of reward-circuit function which characterizes anhedonia is a common mechanism for several neuropsychiatric disorders.

The concept of anhedonia and the diverse definitions of the term are well addressed in other chapters in this tome. Here we note that, in both humans and experimental models, there are multiple domains of anhedonic behaviors, and these may involve distinct neural mechanisms and processes (Der-Avakian and Markou 2012; Shankman et al. 2014; Zald and Treadway 2017). Preclinical studies have identified several behavioral components that are grouped within the concept of anhedonia (Berridge and Kringelbach 2015; Der-Avakian and Pizzagalli 2018; Levis et al. 2021). Some studies of anhedonia have focused on deficits in motivation or anticipatory reward (Sherdell et al. 2012; Bryant et al. 2017; Szczepanik et al. 2019), whereas others emphasize the importance of assessing consummatory reward (Kringelbach and Berridge 2016; Wright et al. 2020). In addition, the attenuation of reward-seeking behaviors observed in humans or preclinical models can be limited to some reinforcers but not others (e.g., social vs. food rewards), further complicating the definition of anhedonic behaviors. Yet, whereas there is a vibrant ongoing discussion of the definition and boundaries of the term anhedonia, a broad consensus is emerging regarding the brain circuitry that is involved, namely, the

reward circuitry. Indeed, human and experimental animal studies conclude that distinct deficits in reward-seeking behaviors which comprise specific aspects of anhedonia all arise from selective and yet overlapping disruption of the operations of specific nodes and connections within the reward circuit.

The facts above suggest that key insights into the nature and mechanisms of anhedonia require interrogation of the reward circuits, yet the ability to do so is limited in humans. Whereas the advent of structural and functional magnetic resonance imaging has proven invaluable to visualizing the human brain and its circuits, establishing causality, teasing apart the distinct roles of genetics and environment, and overcoming other uncontrolled confounders limit the capacity of human studies to fully uncover the issues revolving around anhedonia. Thus, the establishment of animal models with the goals of studying anhedonia and identifying salient projections, nodes, and circuits together with molecules and mechanisms that are disrupted are key to elucidating the origins and trajectories of anhedonia.

1.1 Novel Tools for the Study of Anhedonia in Preclinical Models

Across neuropsychiatric diagnoses, anhedonia can manifest as consummatory and/or motivational deficits (Sherdell et al. 2012; Kringelbach and Berridge 2016; Bryant et al. 2017; Szczepanik et al. 2019; Wright et al. 2020). These responses to rewarding stimuli are often relatively easy to study in rodents, yet historically, anhedonia has not been formally distinguished in rodent studies from measures of depression-like behaviors. Thus, often, repeated exposure to aversive conditions has been utilized along with reward specific tasks to model clinical depressive symptoms. Behavioral despair tests, such as the forced swim (FS) tail suspension (TS), and chronic stress (CS) and chronic mild stress (CMS) paradigms have been used to measure anhedonia and antidepressant-like behavior in rodents (Katz 1982; Willner et al. 1992; Cryan et al. 2005; Castagné et al. 2011). However, these tasks often lead to difficulties in interpretation and reproducibility and thus may not be optimal measures of the diverse facets of anhedonia. Therefore, more complex and nuanced behavioral tasks are currently used to measure aspects of anhedonia in preclinical models (Table 1), as described below.

Reward circuit dysfunction, which is thought to underlie aspects of anhedonia, is often studied using tasks involving motivated behavior, such as drug seeking, food seeking, and the seeking of sex-reward cues. Notably, reward consumption at low effort can be distinguished from highly motivated, effortful reward seeking. These two types of tasks have dissociable underlying neural processes (Berridge and Robinson 2003; Vanderschuren et al. 2005; Baldo and Kelley 2007; Bentzley et al. 2013; Berridge and Kringelbach 2015; Salamone et al. 2016; Volkow et al. 2017) that may therefore be differentially susceptible to disruption and the production of anhedonia. These distinct types of reward seeking behaviors can be individually measured using tasks such as taste reactivity assays (Smith et al. 2010),

Table 1 Preclinical models of anhedonia

Task	Behavioral component	Important circuits/ substrates	Reference
Forced swim, tail suspension, Chronic stress, Chronic mild stress	Behavioral despair; depression-like behavior; antidepressant actions	Prefrontal cortex, extended amygdala, hippocampus, nucleus accumbens, serotonin/ norepinephrine systems	(Katz 1982; Willner et al. 1992; Cryan et al. 2002; Castagné et al. 2011)
Taste reactivity	Motivational valence (appetitive/aversive); incentive "liking"; core hedonic process	Nucleus accumbens, ventral pallidum, amygdala, endogenous opioid, endocannabinoid systems	(Smith et al. 2010)
Social interaction, urine sniff test	Social, sexual motivation; motivational anhedonia	Nucleus accumbens, hypothalamus, amygdala, prefrontal cortex, olfactory circuits, oxytocin, dopamine, endogenous opioid, endocannabinoid systems	(Malkesman et al. 2010; Roberts et al. 2010; Trezza et al. 2010)
Sucrose preference	Hedonic capacity; incentive "liking"; consummatory anhedonia	Nucleus accumbens, amygdala, nucleus of the solitary tract, prefrontal cortex, paraventricular nucleus of the thalamus, endocannabinoid systems, CRH	(Mahler et al. 2007; Bolton et al. 2018a; Tan et al. 2020)
Conditioned place preference	Incentive motivation/ "wanting"; motivational learning; motivational anhedonia	Amygdala, striatum, hippocampus, mesolimbic dopamine	(Everitt et al. 1991)
Intracranial self-stimulation	Incentive motivation/ "wanting"; motivational anhedonia	Striatum, medial forebrain bundle, basal forebrain, mesolimbic dopamine	(Olds and Fobes 1981)
Economic demand	Discriminate hedonic set point (low-cost consumption) from essential value/motivation (high-effort consumption)	Striatum, pallidum, extended amygdala more critical for regulating hedonic set point; mesolimbic dopamine more critical for high-effort consumption	(Koob 1999; Bentzley et al. 2013, 2014; Salamone et al. 2016)
Reinforcement learning	Associate outcome with previous experience/ choice	Ventral tegmental area, amygdala, ventral striatum, hippocampus, prefrontal cortex, dopamine	(Der-Avakian et al. 2013; Huys et al. 2013; Costa et al. 2016; Kangas et al. 2021)

intracranial self-stimulation (Olds and Milner 1954; Carlezon and Chartoff 2007), drug or food self-administration and relapse (Berridge and Aldridge 2009), reinforcement learning (Der-Avakian et al. 2013; Kangas et al. 2021), and others.

In both humans and rodents, an eloquent behavioral tool for simultaneously studying both consummatory and motivational aspects of reward in the setting of

anhedonia capitalizes on behavioral economic theory, which stipulates that consumption of any commodity is sensitive to increasing price. Relative sensitivity to increasing price is referred to as "demand elasticity" (Hursh 1980). *Inelastic* demand, or relative *in*sensitivity to price, is a feature of the excessive reward seeking associated with substance use disorders (Bickel et al. 2014), whereas relatively high sensitivity to increasing price, or a lack of motivation to obtain a reward at high cost, may be a feature of anhedonia. This behavior is distinct from reward intake when required effort is very low. Specifically, while consumption that persists at high cost is more reliant on motivational processes, drug consumption when cost is low corresponds to hedonic value, or "liking" of the drug, governed by a so-called hedonic setpoint (Hursh and Silberberg 2008; Bickel et al. 2014; Strickland et al. 2019). Anhedonia may therefore manifest as reduced "liking," or decreased hedonic setpoint for a given reinforcer, independent of changes to demand elasticity. Thus, behavioral economic tasks allow for the dissociation of anhedonic behaviors resulting from *motivational deficits* from those resulting from deficits in the hedonic aspects of reward *consumption*. Indeed, the neural substrates of demand elasticity and hedonic setpoint for drug rewards appear to be distinct (Bentzley and Aston-Jones 2015; Bolton et al. 2018b; Salamone et al. 2018; Levis et al. 2019).

In rodents, demand elasticity and hedonic setpoint for rewards such as palatable food or abused drugs can be modeled by examining intake at different "prices," operationalized as the amount of effort required to receive one unit of the reward (e.g., a single drug infusion or a single food pellet) (Hursh and Silberberg 2008; Oleson and Roberts 2008, 2009; Bentzley et al. 2013, 2014; Newman and Ferrario 2020). For example, using this method, early-life adversity (ELA) leads to reduced hedonic setpoint for cocaine in male rats (Bolton et al. 2018b), suggestive of anhedonia. Strikingly, in ELA-reared female rodents there is a distinct *lack* of anhedonia. Rather, females have *enhanced* motivation (reduced demand elasticity) to obtain both opioid drugs and palatable food rewards, and no alteration in hedonic setpoint (Levis et al. 2019). Interestingly, in humans, there are no compelling data identifying sex differences in the prevalence and pathophysiology of anhedonia, although sex-specific effects have not been extensively probed. Yet, these disparate findings in preclinical models demonstrate the power of sophisticated tests to tease out distinct, sex-specific disruptions of reward circuits by ELA or other insults that are associated with vulnerability to anhedonia in humans.

1.2 The Reward Circuit and Its Study in Experimental Models

The reward circuitry is complex, encompassing nodes including the nucleus accumbens (NAc), prefrontal cortex (PFC), ventral tegmental area (VTA), ventral pallidum (VP), amygdala (Amyg), hippocampus (HPC), and paraventricular nucleus of the thalamus (PVT) (Fig. 1). These are engaged during reward processing and related choices. The NAc modulates the response to reward-related cues, as well as the value of expected versus actual reward outcomes. Studies to date have largely

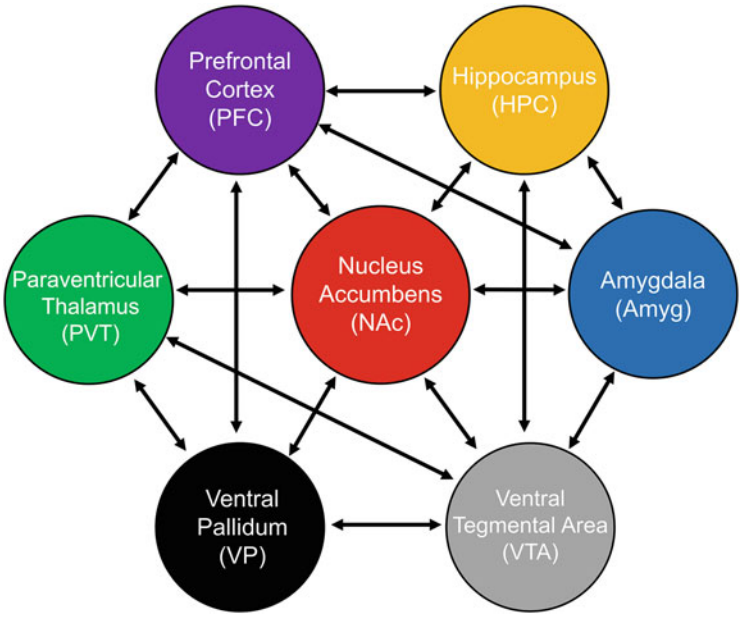

Fig. 1 Cross-species nodes and connectivity of the reward circuit

focused on glutamatergic and dopaminergic input pathways to the NAc and have demonstrated its role in integrating excitatory and inhibitory input to signal the salience of rewarding stimuli. These stimuli in turn are encoded via projections to and from limbic structures (Fig. 1) (Ballard et al. 2011; Tritsch et al. 2012; Britt et al. 2012; Bagot et al. 2015; Ferenczi et al. 2016; Robbins 2016).

Several neurotransmitters and neuromodulators convey information from and to the NAc (Fig. 1). Specifically, glutamatergic projections from cortical, thalamic, hippocampal, and amygdalar regions terminate in the NAc and mediate behavioral effects via AMPA, NMDA, and metabotropic glutamate (mGluR) receptors (Krystal et al. 2003; Cozzoli et al. 2012; Wang et al. 2012). For instance, reward seeking can be restricted via glutamatergic VP neurons increasing the activity of GABA VTA neurons (Tooley et al. 2018). Dopamine plays a role in motivation and reward and has been extensively studied. Dopamine influences incentive salience and instrumental behaviors in cue reward tasks (Peciña et al. 2003), and blocking dopamine receptors in the NAc reduces the effort expended to obtain a reward (Aberman et al. 1998). Serotonin also plays a role: dorsal raphe serotonin transporter (SERT) terminals, which synapse onto VTA dopaminergic neurons, increase rewarding behaviors (Wang et al. 2019).

Beyond the classically known neurotransmitters, several peptides and neuromodulators are expressed in reward circuit nodes to influence behaviors. Opioids and endocannabinoids are well-established major neurochemical mediators of reward responsiveness (Pecina and Berridge 2005; Mahler et al. 2007). Importantly, focusing on consummatory anhedonia, several peptides are expressed and function within the reward circuit. These include orexin and neuropeptide Y which

modulate food intake (Van Den Heuvel et al. 2015; Castro et al. 2016), and corticotropin-releasing hormone (CRH), a stress responsive peptide and its receptors (Peciña et al. 2006; Lemos et al. 2012; Walsh et al. 2014; Peng et al. 2017; Bolton et al. 2018a).

Whereas the complexity of the neuroanatomical and molecular interactions described above is daunting, animal models allow the use of novel and evolving instruments and techniques to address these intricacies. Specifically, they enable both mapping and cell-type-specific and projection-specific manipulation of select components of the reward circuit. Anterograde and retrograde tracers have been extensively used to visualize the connectivity between circuit nodes (Nassi et al. 2015; Tervo et al. 2016; Itoga et al. 2019; Engelke et al. 2021). These connections can be interrogated further, with the use of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) (Mahler et al. 2014, 2019) and channelrhodopsins (Miyazaki et al. 2014; Cole et al. 2018) to dissect brain region and cell type specific functional control of behavior. For instance, in rats and mice, anterograde and retrograde tracing has identified novel CRH expressing projection sources to the NAc from regions integrating reward and stress circuits (Birnie et al. 2020a), and optogenetic activation of a CRH+ PVT-NAc projection reduced food seeking behavior (Engelke et al. 2021), identifying a novel role for a stress-regulated peptide that influences reward behaviors.

2 Anhedonia and Early-Life Adversity (ELA)

2.1 Why Study ELA and Anhedonia? The Human Landscape

In humans, ELA is linked to several mental health disorders that indicate dysfunction of the operation of the reward circuit. Functional magnetic resonance imaging (fMRI) studies have probed the functional activation of components of the reward circuitry in individuals who have experienced early-life adversity and identified several deficits (Boecker et al. 2014; Corral-Frías et al. 2015). ELA and subsequent emotional problems differ in men and women, with women with a history of early-life trauma being more likely to crave comfort food and opioids (Mason et al. 2013). These differences between the sexes are a result of both intrinsic differences in the operation of the reward circuit and sex dimorphism in the response to ELA and to stress in general (Davis and Pfaff 2014; Walker et al. 2017).

2.2 What Is ELA and How Do We Model It?

Early-life adversity is a heterogenous concept. In humans, it typically denotes low socioeconomic level, poverty, parental depression, neglect or abuse and a violent, chaotic environment (Short and Baram 2019; Luby et al. 2020). These complex

contexts generate and convey numerous types of signals to the developing infant and child, including significant emotional and sometimes physical anguish. Yet, in humans and especially in experimental models, the rich array of signals from caretakers and the environment, which reach and activate selective brain regions and nodes of the stress and reward circuits are often simply summed up as "stress," and considered interchangeable with activation of the neuroendocrine stress response. Instead, ELA is a multidimensional construct, and simply looking at the activation of the hypothalamic-pituitary-adrenal system may not recapitulate its numerous effects on the different functions of the brain (Molet et al. 2016a; Bolton et al. 2018a). It is also likely that different types of ELA and even the same type of ELA generated at different developmental stages might exert distinct differences to mesolimbic structures which undergo significant growth, maturation, and plasticity throughout specific sensitive periods (Tottenham 2020; Marini et al. 2020; Birnie et al. 2020b; Luby et al. 2020).

The development of preclinical models for ELA provides basic and translational scientists with the opportunity to understand complex neural mechanisms using techniques and approaches that are not possible in humans (Baram et al. 2012). Indeed, several approaches have been used to generate adversity early in life. Maternal separation has been used extensively to study the effects of such adversity/stress, and several variants exist including daily short (3–4 h) separation or a single prolonged deprivation. These models have generally yielded deficits in cognitive abilities as well as anxiety-like, depression-like and addiction-like behaviors, yet the development of anhedonia has not been consistent (Matthews et al. 1996; Leventopoulos et al. 2009; Nelson et al. 2009; Andersen 2019). More recently, with the aim of generating a naturalistic, highly reproducible model for early-life adversity, a paradigm of simulated poverty, using cages with limited bedding and nesting material (LBN) in rodents, has been devised and used extensively around the world. This environment stresses the dams and leads to disruption of maternal caring behaviors (Ivy et al. 2008; Molet et al. 2016a). This translates into unpredictable and fragmented sensory signals received by the developing pups. Whereas the overall duration and quality of maternal care remain unaltered, the pattern of their signals to pups is aberrant. Sensory signals from the environment are required for normal maturation of brain circuits including visual and auditory systems (Espinosa and Stryker 2012; Short and Baram 2019). It is believed that aberrant patterns of tactile signals from the dam may interfere with the maturation of reward- and stress-related circuits in the pups (Short and Baram 2019; Birnie et al. 2020b; Luby et al. 2020). Indeed, aberrant brain circuit maturation is generated in the pups, evidenced with MRI (Molet et al. 2016b; Bolton et al. 2018a) and manifesting as impaired memory as well as deficits in emotional-like and reward-executed behaviors, measured by food consumption, social play, and hedonic setpoint for cocaine. A third model of ELA involves cross-fostering, aiming to model early postnatal instability in humans. Starting during the first 2 days of birth, pups are cross-fostered with a lactating dam. This intervention allows for distinguishing between relatedness and environment, thus allowing researchers to recognize how genes and environment interact to influence developmental processes and later adult behaviors (Hager et al. 2009;

Ventura et al. 2013; McCarty 2017). Comprehensive reviews of these preclinical models have been published (Molet et al. 2014; Walker et al. 2017).

2.3 *Anhedonia Following ELA Involves a Developing Reward Circuit*

In the context of the mechanisms by which ELA generates anhedonic behaviors, it is useful to consider that the reward circuity overlaps with nodes of the stress circuit, and that both are in a state of maturation and heightened plasticity during the developmental epochs comprising ELA (Avishai-Eliner et al. 2002; Birnie et al. 2020b).

Robust evidence exists for profound, likely permanent changes in brain reward and stress systems of individuals experiencing ELA, including mesolimbic and extended amygdala circuits, and neurotransmitter/neuromodulator systems including dopamine, endogenous opioids, and CRH. These enduring changes may promote vulnerability to anhedonia. At the circuit level, amygdala-PFC structural connectivity was augmented in adult male rats that had experienced ELA relative to controls (Bolton et al. 2018a). Pre-weaning LBN males, but not females, have reduced BLA-PFC and altered PFC-striatum resting state functional connectivity (Guadagno et al. 2018a, b), a finding that persists into adulthood and is accompanied by reduced sucrose preference and social interaction (Yan et al. 2017). Disruption of the early maturation of BLA-PFC connections has been reported after maternal separation as well (Brenhouse et al. 2013; Honeycutt et al. 2020; Nieves et al. 2020), further implicating this circuit in the effects of ELA. Notably, human studies suggest that ELA's impact on amygdala development is critical for the resulting depression and anxiety (Callaghan and Tottenham 2016; Fareri and Tottenham 2016), and potentially for anhedonia as well.

Changes in neurotransmitter and neuromodulators in both reward and stress circuitries result from ELA. For example, endogenous opioid systems are enduringly altered by ELA, a fact that may impact pleasure or other reward-relevant processes (Peciña et al. 2019). Maternal separation persistently alters endogenous opioid peptides, as well as opioid and dopamine receptor expression in reward and stress-related areas, including striatum, midbrain, hippocampus, and hypothalamus in both a sex- and ELA timing-dependent manner (Ploj et al. 1999, 2001, 2003; Gustafsson et al. 2008; Chang et al. 2019). The development of the mesolimbic dopamine system is also strongly impacted by ELA (Rodrigues et al. 2011; Ventura et al. 2013; Peña et al. 2014; Bonapersona et al. 2018), thereby potentially disrupting dopamine-dependent incentive motivation and learning.

ELA leads to enduring changes in the expression levels of the stress-sensitive neuropeptide CRH in the amygdala central nucleus (CeA) (Dubé et al. 2015) and hippocampus (Ivy et al. 2010), and is associated with major changes in circuit functions (Brunson et al. 2005; Ivy et al. 2010). Such changes in circuit function

are apparent from both neuronal activation and from performance in tasks probing the reward circuits and specifically anhedonia. For example, palatable food, social play, and acute cocaine reward induce a stronger Fos response in CeA of ELA males than of control males, an effect accompanied by anhedonia-like behavioral responses to those same rewards (Bolton et al. 2018a, b). These findings suggest that ELA promotes aberrant activation of stress-circuit nodes during tasks that typically engage the reward circuit exclusively.

2.4 Anhedonia After ELA: Manifestations and Sex Specificity

The expression of anhedonia following ELA in preclinical models appears to involve interactions among the timing and nature of the ELA paradigm, biological sex, and the nature of the behavioral tests (Matthews and Robbins 2003; Rüedi-Bettschen et al. 2005; Der-Avakian and Markou 2010; Leussis et al. 2012; Molet et al. 2016a; Lukkes et al. 2017; Di Segni et al. 2019; Luby et al. 2020). For example, in male rodents, ELA imposed via rearing for 1 week in cages with limited bedding and nesting materials leads to enduring anhedonia for both natural and drug rewards. This includes blunted sucrose and palatable food preference, and reduced interest in social play (Molet et al. 2016a; Rincón-Cortés and Sullivan 2016; Yan et al. 2017; Bolton et al. 2018a, b). Using a behavioral economic assay of cocaine seeking, ELA does not change motivation to obtain drug at high effort (demand elasticity), but leads to reduced hedonic setpoint for cocaine in male rats when the drug is "free" (Bolton et al. 2018b). This suggests that, in addition to anhedonia for natural rewards (Bolton et al. 2018a), these animals are anhedonic for drug rewards. Such anhedonia is not observed in female rats after LBN (Levis et al. 2019), however others have identified an age-dependent reduction of sucrose preference and depressive-like behaviors in female mice following LBN (Goodwill et al. 2019). Using a maternal separation model of ELA, both male and female rats have reduced sucrose preference later in life (Matthews et al. 1996; Leventopoulos et al. 2009; Coccurello et al. 2014). Anhedonia has also been reported in nonhuman primates exposed to maternal deprivation and maltreatment (Rosenblum and Paully 1987; Paul et al. 2000; Pryce et al. 2004; Kaufman et al. 2007; Glynn and Baram 2019), including reduced sucrose preference (Paul et al. 2000) and lack of interest in social interaction (Coplan et al. 1996). However, others have found increased sucrose drinking in juvenile males following ELA (Nelson et al. 2009).

Together, the findings in rodents and nonhuman primates suggest the manifestations of reward circuit disruption by ELA may vary by the timing, duration, and nature of the ELA, and may be further modulated by sex. Whereas deficits in reward seeking behaviors are observed in males, such deficits are not as commonly found in females. Rather, in females, the prevailing phenotype includes the enhanced consumption palatable food and drugs of abuse. Furthermore, the variable consequences of ELA on distinct assays of reward-seeking behaviors in animal models (e.g., reduced "hedonic setpoint" but unchanged "demand elasticity") demonstrate that

reward processing is not a singular entity; rather, individuals may express different and dissociable anhedonia phenotypes that suggest potentially discrete mechanisms of reward circuit disruption. Thus, further investigation into how ELA alters specific aspects of reward processing, and the underlying neural substrates will be critical for understanding the biological processes that contribute to the risk anhedonia, a key harbinger and component of several psychiatric disorders.

3 General Conclusions

Anhedonia is a transdiagnostic construct which is both a herald and a core component of several mental illnesses, yet the identification and characterization of the neural mechanisms that contribute to its emergence remain challenging. Strides have been made in understanding the origins of anhedonia through both human studies and the use of preclinical animal models. In rodents, researchers can induce anhedonia-like behaviors, enabling the identification and characterization of individual reward-circuit nodes and projections that influence these behaviors, and further characterize them at the cellular and molecular level. The study of the emergence of anhedonia-like behaviors following experimental ELA is an exciting avenue for two reasons. First, it recapitulates the human association, allowing delineation of trajectories and life-long progression. Second, it enables the use of powerful modern technologies including chemo- and optogenetics for the interrogation and functional identification of neural projections and molecules that may mediate anhedonia. Critically, with the use of animal models and asking the right questions, clinical queries can be translated to lab-based mechanistic studies, which in turn can lead to novel discoveries for the prevention of anhedonia or its mitigation.

Funding and Disclosures The authors' work was supported by National Institute of Health Grant Nos. P50 MH096889, MH73136, F30 DA051137, T32 GM008620; and the Hewitt Foundation for Biomedical Research.

The authors thank Dr. Annabel Short for excellent discussions.

MTB, SCL, SVM, and TZB report no biomedical financial interests or conflicts of interest.

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Origins of Anhedonia in Childhood and Adolescence

Janani Prabhakar, Dylan M. Nielson, and Argyris Stringaris

Contents

Abstract Anhedonia reflects a reduced ability to engage in previously pleasurable activities and has been reported in children as young as 3 years of age. It manifests early and is a strong predictor of psychiatric disease onset and progression over the course of development and into adulthood. However, little is known about its mechanistic origins, particularly in childhood and adolescence. In this chapter, we provide a socio-cognitive model of the development of anhedonia. This model is substantiated by past literature presented in this chapter to account for how the individual trajectories of emotion knowledge, autobiographical memory, and self-

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Curr Topics Behav Neurosci (2022) 58: 43–60
https://doi.org/10.1007/7854_2022_356
Published Online: 19 May 2022

concept representations contribute to the onset, persistence, and progression of anhedonia from early childhood through adolescence.

Keywords Emotion knowledge · Episodic memory · Self-concept development

1 Introduction

Anhedonia symptoms are one of the most common presentations of depression across the lifespan (Pelizza and Ferrari 2009). They reflect a reduced ability to engage in activities that were previously pleasurable and/or a difficulty in feeling and expressing joy (Husain and Roiser 2018). In this definition, joy and pleasure reflect dimensions of positive emotion differentiated only by the experiential nature of pleasure and the internal feelings of joy (Mortillaro et al. 2011). Anhedonia may present early in life in depression (Luby et al. 2002, 2003, 2004, 2006) and is associated with worse disease course and treatment response in youth and adults (Luby 2010). Recent literature has indicated a high prevalence of anhedonia over the course of development. For example, in a relatively small sample of preschoolers, more than half of the depressed preschoolers presented with anhedonia (Luby et al. 2004). In adolescent population samples, anhedonia presents in approximately 10–15% of adolescence, with or without psychiatric illnesses (Pornpattananangkul et al. 2019; Stringaris et al. 2015). The large incidence of anhedonia in developmental populations underscores the importance of understanding the nature of anhedonia presentation from a developmental context.

This chapter will provide a developmental socio-cognitive account of mechanisms that may give rise to anhedonia and specifically, to the difficulty individuals face in feeling and experiencing joy. This account proposes that anhedonia and anhedonic behaviors are the outcome of an interactive relationship, over the course of development, of emotion knowledge (the set of emotion representations instantiated in a person's memory arsenal), autobiographical memory (one's memory for their own past, personal experiences), and self-concept representations (one's set of beliefs about who they were, are, and will be). This interactive relationship is a result of an individual's inherent desire to make choices and decisions that allow them to maintain a coherent sense of self, that is, remain internally consistent with their beliefs about who they are (Coughlin and Robins 2017; Howe and Courage 1997). As such, this account suggests that an ideal state is to ensure that the set of choices one allows for themselves overlaps with their self-concept beliefs (Fig. 1a). However, as the overlap between one's set of self-concepts and allowable choices diverge (Fig. 1b), individuals are placed in a position of discomfort to resolve the discrepancy. A resolution to reduce the distance between the sets of self-concept beliefs and allowable choices can be made through a process of discounting, either discounting the self-belief as not truly being reflective of self, or the choice as not relevant or of interest to the self. One's capacity to reduce this distance may, thus, be dependent on

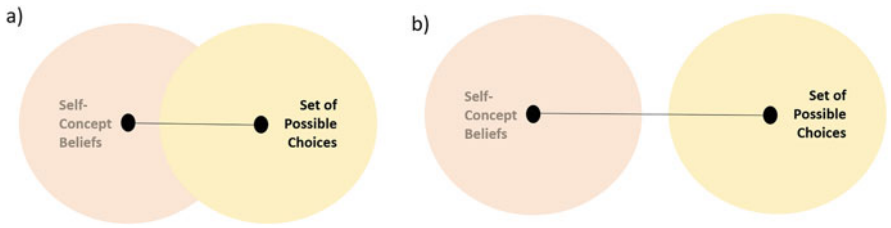

Fig. 1 This figure represents a graphical depiction of the socioemotional hypothesis of anhedonia proposed in this manuscript. Individuals strive to select choices from what is possible (yellow circle) that cohere with their self-concept beliefs (red circle). The length of the lines in these figures reflects the degree of discordance one might feel when their choice or choices are not consistent with their self-concept beliefs. As such, an ideal place is when the distance between one's self-concept beliefs and set of possible choices is not exceedingly distant (**a**). When choices begin to diverge from one's set of beliefs and the distance between them begins to increase (**b**), the discrepancy may generate feelings of discomfort and unease. To reduce this distance, one needs to either alter their set of beliefs to overlap with the choice that was made or select options that are more in line with one's self-beliefs

the strength of self-representations ingrained in one's memory (or, how well one has determined their own self-beliefs), and the extent to which one has made choices, over time, that are repeatedly consistent with these self-representations. In essence, self-concepts allow individuals to select or choose activities that maintain a level of coherence with who they are, and the choices individuals make help strengthen those self-concept beliefs. For example, prior work has shown that adolescents with higher self-concept clarity (i.e., notion of who they are) make personal choices about college and their future with greater confidence (van der Aar et al. 2019), suggesting that choices help reinforce one's personal views. This notion is supported by models of depression that suggest that pervasive negative processing of one's self-identity may generalize to influence how one processes incoming information and selects appropriate actions (Clark et al. 2000). We propose that anhedonia may be a means of avoiding the uncomfortable feeling of being incoherent with one's internal sense of self. A built sense of self can result from one's efforts to make meaning out of past experiences or find meaning in the present. Past experiences that reflect a high frequency of negative events or a low frequency of positive events may lead to self-concept representations that skew less positive and more negative. For example, repeated experience of social exclusion may result in an individual building a representation of self as "shy" or "awkward." This self-concept representation provides an explanatory framework for negative experiences and supports choices, like avoiding social gatherings, that may cause undue distress. Continuing efforts to avoid these feelings lead to greater avoidance of social gatherings, strengthening self-concept representations as "shy" or "awkward."

These negative self-representations can also drive personal daily behaviors outside the context of social gatherings. A lack of motivation to engage in personally beneficial activities, such as routine activities like taking a hot shower or cooking a delicious meal, can result from a reduced capacity to derive positive satisfaction

from these activities on a daily basis. Indeed, prior research indicates that individuals who report lower anticipation of pleasure also engage less frequently in usual, daily activities, and report lower positive self-concept and emotion (Rosebrock et al. 2021). These authors suggest that this relationship may result from individuals' perceived notions of difficulty engaging in routine activities and a lack of motivation, as a result, to do so. It is important to consider that the process of building self-concepts relies on meaning making (Conway and Pleydell-Pearce 2000) and when one lacks motivation or perceives activities as too burdensome, these activities may then hold lesser positive value within one's identity. As such, if decisions to engage in a routine activity are impacted by the perceived low emotional value it holds, then these activities will be routinely avoided.

Neurobiological data support this notion that individuals with anhedonia may place less value on personally rewarding activities. Individuals with anhedonia show a blunted neural response to future rewards in delay discounting tasks (Kang et al. 2020), suggesting that these types of typically rewarding items do not hold the same personal value in individuals who fail to derive satisfaction from them. In pre-adolescence, altered connectivity, specifically during reward anticipation, in children with anhedonia was reported between the ventral striatum and cingulo-opercular network, indicating a lack of intrinsic arousal to a potential reward (Pornpattananangkul et al. 2019). Other evidence in patients with Major Depressive Disorder (MDD) suggests that abnormal activation of structures within this network and in the subcortical-cortical midline system more broadly (e.g., the dorsomedial prefrontal cortex, the anterior cingulate cortex, and the precuneus) correlates with increased focus on negative self-related judgments as well as anhedonia (Grimm et al. 2008, 2009; Greicius et al. 2007; Phillips et al. 2003). These abnormalities in structures and networks typically involved in self-processing and reward anticipation suggest that anhedonia may reflect not only a diminishment of a potential reward but also an increased level of negative emotion to rewards or positive events, as well.

Taken together, the extent to which one's memory systems respond to emotionally laden input, construct self-beliefs, and use those self-beliefs to inform actions is dependent on the reciprocal and dynamic nature as well as the individual trajectories of emotion knowledge, autobiographical memory, and self-concept development. This chapter interprets prior literature in the context of how anhedonia may arise from disruptions in developing emotional concepts of positive emotion during infancy, in memory processes that build knowledge structures regarding joy-inducing experiences during childhood, and in developing a sense of self, during childhood and beyond, as (or not as) one who experiences joy. Altogether, the chapter will provide the foundation for an integrative model of how conceptual development of positive and negative emotions, memory processes, and self-concept formation can perpetuate anhedonic symptoms and the avoidance of positive experiences through a need to maintain coherence with oneself and avoid feelings of distress.

2 Impact of Positive Caregiving During Infancy

Infancy is a highly flexible and dynamic period for emotion concept formation (Gelman and Kalish 2006). During this time, caregivers learn to identify infant cues to respond to their emotional and physiological needs. These interactions help children build emotion concepts that are functionally useful to signal a need to the caregiver. The foundations of this dyadic relationship between caregiver and infant come from early characterizations of attachment theory (Ainsworth and Bowlby 1991). In this theory, the strength of caregiver-infant attachment rests on the extent to which caregivers respond to infants seeking security and comfort. Infants seek attachment figures for safety and security, but caregiver response can reflect differing levels of maternal responsiveness to infant cues and needs that range from positive and emotionally responsive to negative and hostile. Lack of early attachment or maternal deprivation, as noted in early human (Bowlby 1965) and non-human primate development (Harlow and Zimmerman 1958), can result in significant detachment issues in infancy and childhood. Furthermore, other evidence shows that positive emotional synchrony between parent and child in early childhood contributes to less negative behaviors and greater self-regulation exhibited by the child later (Lunkenheimer et al. 2020; Meyer et al. 2014; Eisenberg 2020). As such, missing this early opportunity to instantiate emotion knowledge in one's representational arsenal impacts the extent to which infants can continue to their emotional growth outside of the home.

Caregiver response to emotion cues during the first few months to years of life helps build a social contract between parent and child. This social contract aligns with a rational constructivist approach to emotion learning (Barrett 2006; Hoemann et al. 2019), a scientific framework suggesting that infants begin with proto-conceptual primitives and end with domain-specific intuitive theories of emotion knowledge and expression by engaging learning processes. Critically, this framework hypothesizes that the expression of "joy" or "pleasure" results from a distributed and integrated network of neural connections drawn from across different brain states and processes, including motor, perceptual, affect, and memory states (Hoemann et al. 2019; Phan et al. 2004), that act on top-down and bottom-up cues. That is, the ad hoc emotion concept and expression is capable of being stored and retrieved through predictive or top-down activation processes. This section will provide an overview of the early influences of caregiver support (e.g., responsiveness) on building strong emotion representations and how the absence of these influences may impact socioemotional growth and limit positive emotion development, specifically.

In neonates, smiles are a primitive index of joy and pleasure that result from a relaxation of cognitive tension in response to a stimulus (Sroufe and Waters 1976; Camras et al. 2017). Over the first few 10–20 weeks of life, infants begin to dynamically shift attention to environmental stimuli and form connections between primitive forms of smiling behavior and the responses they elicit. Infant smiles engender parental caregiving and cognitive processes help instantiate the functional

role of infant smiles to elicit desired outcomes, thereby establishing strong social bonds between the parent and child (Camras et al. 2017; Oster et al. 1992; Holodynski and Friedlmeier 2006; Bridges 1932; Messinger and Fogel 2007; Fogel and Thelen 1987).

With experience, children display a repertoire of discernable expressions in response to parental communications (Oster et al. 1992; Messinger and Fogel 2007). As such, increasingly complex representations of positive emotion come with greater experience and engagement, wherein the expression of joy and pleasure expands beyond these states of arousal into other features, like laughing. Ultimately, these dynamic processes allow infants to learn that their smiles elicit warmth from parents and parents consolidate cues from infants to prompt caregiving behaviors, establishing a reciprocal relationship that solidifies parent–child bonds and further strengthens neural connections associated with "joy" and "pleasure" (Kärtner et al. 2013). A dynamic system such as this underscores that emotion responses reflect an interactive relationship between real-time expression of affect and the social context in which they occur. In early infancy, this social context is based on the relationship with the parent during which time social contingencies and contagion between infant expression and parental response are established (Mireault et al. 2015; Shultz et al. 2018; Mundy and Jarrold 2010).

The strength of the reciprocal nature between child and caregiver is predicated on the approach, style, and sensitivity in the caregiver response (Parsons et al. 2017; Dollberg et al. 2010; Granat et al. 2017). In one study, authors found that infants of depressed mothers exhibited greater self-regulatory (e.g., self-soothing behaviors, like thumb sucking, during interaction with mothers) behaviors during positive emotion expression (Granat et al. 2017), suggesting that a lack of a positive reciprocal relationship with the caregiver reduces positive emotion expression. Relatedly, parental depression and anxiety have negative influences on infant smiling, possibly mediated by dysfunctional amygdala connectivity with cortical regions (Phillips et al. 2021; Weinberg and Tronick 1998). This is supported by further evidence showing that maternal stress about one's own ability to provide appropriate parental care is negatively associated with reductions in infant smiling and laughter behaviors over time (Bridgett et al. 2013; Legerstee and Varghese 2001), suggesting that one's beliefs about their own parenting capability can impact their child's positive emotion growth. In addition, low maternal affect mirroring, or emotion contagion (i.e., the maternal emotional response of warmth, sensitivity, and responsiveness to infant behaviors), results in lower amount of smiling, vocalizations, and prosocial behaviors in the infants (Harker et al. 2016).

These drawbacks in parental caregiving and responsiveness hinder the adaptive functionalities of early expression and behaviors that are designed to build children's emotional repertoire. This hindrance has reciprocal properties such that parents of insecurely attached infants display more negative emotions that likely hinder emotional growth and perpetuate further the insecure attachment (Radke-Yarrow et al. 1985). This underdevelopment further hinders normative trajectories of development of neural networks, particularly in the frontoparietal regions, that are engaged to store, retrieve, express, and coordinate internal representations associated with

emotion (Hanford et al. 2018). In mothers, network connectivity in similar regions that provide a coordinated response to infant joy is also affected (Laurent and Ablow 2013).

Essentially, a dearth of positive caregiver approaches (i.e., a lack of approach-oriented positive emotion from caregiver and use of a broad range of facial expressions) results in impoverished attentional and learning environments that hinder the establishment of emotion concepts and expression. This is supported by other work showing that lack of caregiving support in early childhood mediates effects of impoverished environments (e.g., low-income households) on lower hippocampal volume in middle childhood (Luby et al. 2013). These results suggest that nurturing environments have meaningful and significant impacts on brain development and emotion development, with likely implications for child psychosocial and emotional well-being, as well.

Of course, one cannot talk about the environment without discussing genetic and heritable features that may also disturb maternal reciprocation to infant emotion expression. Prior literature suggests that while negative emotion has a substantial heritable component, positive emotion is much more strongly dependent on the environment (Zheng et al. 2016; Baker et al. 1992; Luby et al. 2004). This notion is further supported by evidence showing that genetic attributes that result in anhedonia may be more connected to negative emotion and personalities than positive emotion and trait features (Luby et al. 2004). In several overlapping studies, authors found that a melancholic subtype or anhedonic depressed subtype in preschoolers was characterized by greater depression severity, alterations in stress cortisol reactivity, increased psychomotor retardation, and increased melancholic symptoms (Luby et al. 2004, 2009). Critically, the authors found that anhedonic preschoolers appeared "slowed down" or "restless," and these preschoolers compared to healthy controls showed greater negative overall affect. In another study, preschool-aged boys who exhibited lower trait sociability were more likely to exhibit anhedonia symptoms in middle childhood (Mumper et al. 2021). These data suggest that the dependency on a positive environment underscores the development of positive emotion and expression in infants and may serve as a protective and manipulable feature against the development of anhedonia.

Animal models align with these findings, showing a unique molecular profile of anhedonia specific to mice who are intrinsically vulnerable to chronic environmental stress (Couch et al. 2013). Vulnerability to stress was captured by measures of susceptibility (e.g., floating versus swimming during a forced swim task) or negative bias (e.g., providing more negative than positive responses to an ambiguous cue). These data suggest that inherent trait features may moderate the extent to which environmental stress is a risk factor for anhedonia, and that these traits may promote greater negative processing of environmental cues (Couch et al. 2013). Taken together, this evidence points to the role of trait by environment interactions in determining who is most susceptible (Rygula et al. 2013). These results are particularly important to consider in the context of the model presented in this review. If certain trait features predict an infant's susceptibility to anhedonia, then these features may also impact the quality of early caregiver interactions (e.g., how the

infant negatively processes cues from the caregiver). Our model underscores the importance of these interactions for positive emotion development and later positive self-concept formation. As such, early identification of inherent trait features associated with anhedonia and their influence on early environmental exposures would open the possibility for early intervention.

3 Impact of Memory Processes and Social Engagement During Early and Middle Childhood

Memory systems emerging in early childhood aid in establishing robust representations of emotion concepts (Nelson 2000). Children's experience of and response to positive experiences, such as positive feedback from caregivers or social engagement with the outside world, are encoded into memory. With repeated exposure, not only are these encoded representations strengthened within the memory system, but they are also more readily accessible for retrieval. As such, repeated exposure to positive input during early childhood, inside and outside the home, allows children opportunities to instantiate and strengthen representations of positive emotion knowledge and expression. In this section, we establish how memory processes provide the foundation upon which emotion representations are stored, retrieved, and used.

From early childhood onward, children experience a greater level of agency and control over their own behaviors. This occurs with the onset of language as well as greater interaction with individuals outside the home. The development of language during this time motivates a rapid emergence of concept development and as children engage to a greater extent with the environment, their own sense of agency within it allows them to make connections between new experiences and subjective feelings (Meltzoff and Kuhl 2016). The process rests on furthering the reciprocal nature of positive expression and positive feedback, and social engagement during early childhood allows children to build emotion representations and regulate them based on peer feedback and social response (Holodynski and Friedlmeier 2006; Marshall and Meltzoff 2011). While early displays of this reciprocal behavior between mother and child allows for the prototypical concepts of positive affect, dynamic engagement with the outside world allows children to exercise these concepts flexibly and engage in a more significant way with individuals outside their immediate context (Meltzoff and Kuhl 2016). These dynamic interactions lead to construction of schematic representations of affect expression, including joy and pleasure.

Schemas are cognitive frameworks that allow children to organize and categorize events and experiences in memory based on commonalities between them and can be used to make meaning of the world and select actions (Nelson 2019; Holodynski and Seeger 2019). Schematic representations of emotions developed during early childhood include feelings of anger, fear, joy, disgust, amusement, and guilt (Conway and

Pleydell-Pearce 2000). The ontogenesis of these emotions that include the dynamic relationship between the environment and internal cognitive processes reflects the significance of emotions as social cues and ways to engage with the social environment. Establishing schematic representations of emotion knowledge and expression allows for flexible and efficient use of these representations to reflect internal processes to the external world and guide behaviors within a social setting.

Functionally, establishing schematic representations occurs from a complex combination of attentional, memory, and control processes. As toddlers engage with their environment, they attach valence to events and stimuli they encounter, and these emotional features are encoded into memory. Repeated exposure to these valenced stimuli allows for repeated retrieval, re-consolidation, and strengthening of these stored emotional concepts in memory such that they develop into robust representations of emotion knowledge that can be accessed as semantic structures (or, schemas) when similar events are encountered once again (Weinberg and Tronick 1998). The more readily and frequently these are accessed through control processes that regulate the child's present motivations and drives, the stronger these emotion schemas are reflected within one's memory architecture. This interplay reflects the foundation of the relationship between the hippocampus and the amygdala, wherein increased attention to emotionally laden stimuli through amygdala activation prioritizes hippocampal encoding processes toward such stimuli and events (Holodynski and Seeger 2019; Phelps 2004; Barch et al. 2019).

Alison Gopnik's characterization of toddlers as social beings (Gopnik 1996) has value in establishing the functional role of schematic representations of emotions, particularly positive ones. The prevalence of positive experiences in childhood through play and exploration serves as the foundation for the establishment of robust representations of positive affect that has utility. When these opportunities for play and exploration are hindered, so then are the establishment of long-term, readily accessible schematic representations. Children signal intent and goal through display of emotion, but if they don't have the context within which these emotion displays are received and reciprocated, they do not build robust representations that can be retrieved later. That is, joyful activities no longer have predictive cues for an affect-based response (Alwaely et al. 2021).

Acknowledging the value of social engagement in positive emotion development, its availability or quality is highly affected by community and neighborhood factors (Cutrona et al. 2005; Ewing et al. 2019). Evidence shows that neighborhood factors and household support play a critical role wherein adverse home and neighborhood environments (including but not limited to economic or perceived stress, parental psychopathology, parenting techniques, and empathy) increase susceptibility to depression and anhedonia (Ewing et al. 2019; Simons and Steele 2020). Economic deprivation results in a disrupted ability to establish a social contagion within which schematic representations of emotions can be dynamically and reciprocally utilized (Gao and Han 2016; Bolger and Patterson 2001; Cicchetti and Aber 1998; Raver 2004). This serves as a potential opportunity for intervention in providing access to peer interaction within under-resourced environments.

4 Role of Self-Concept Development During Childhood and Adolescence on Anhedonia

Self-concept reflects a set of representations or knowledge base that encompass one's beliefs, desires, and goals (Conway 2005). These concepts emerge from a dynamic interaction between inherent traits and external experiences, wherein one's experience of the world is driven by knowledge of themselves ("what would I want to do?") and one's knowledge of themselves is influenced by their experience of the world ("how did that make me feel?"). This drive to know more about oneself is supported by memory processes that privilege self-related information.

Self-concept formation begins in middle childhood as children begin to generate self-beliefs by integrating across their own past experiences (Conway and Pleydell-Pearce 2000). The self-memory system (SMS) emphasizes the interconnectedness between the self and memory (Conway and Pleydell-Pearce 2000; Ross et al. 2020). This model defines the active construction of a self-concept as the "working self" that is comprised of one's present actions, goals, and self-images, and serves as the foundation upon which memory and regulatory processes emerge. The working-self coordinates and modulates control and memory systems in order to maintain consistency between one's past self, present self, and future self. Access to semantic knowledge structures, including schemas of emotion concepts, allows individuals to control how the working self operates within the world. A more effortful, top-down search (a generative search) can probe autobiographical memory structures for evidence from one's past that allows one to establish coherence with present drives and motivations (e.g., "I was shy when I went to that party, so I will avoid this party"). This interplay between control and memory systems allows individuals to make meaning of who they were and incorporate that into their knowledge base to regulate and coordinate present-day actions, thereby substantiating and perpetuating self-concept representations over time (Conway and Pleydell-Pearce 2000).

With a dearth of positive experiences instantiated into memory during early development, self-concept formation capacities are likely built on few examples of positive experiences. As such, integrating across a dearth of positive experiences may result in fewer positive self-concepts that, ultimately, influence the kind of choices children believe they have. Over time, fewer choices that elicit positive emotion or positive sense of self may result in general avoidance of pleasureful activities, or anhedonia. This section will provide an overview of how self-concept beliefs are built and can shape the extent to which a child may engage in pleasure-seeking activities.

Prior evidence shows that the SMS is active in preschool-aged children. In one study, authors found that preschoolers with a strong self-concept knowledge base showed stronger source memory for self-referential information and that this relationship was mediated by the quality of their autobiographical memory reports (Scheuplein et al. 2021; Ross et al. 2020). That is, children's ability to remember personal aspects of their own past (i.e., their autobiographical memory) explained their ability to use knowledge about the self to guide encoding and retrieval of self-

referential information in the present. This study underscores the foundational relationships between oneself and memory, and the extent to which a robust relationship between the two guides present behaviors and actions (Higgins 1987). Furthermore, normative development shows heightened sensitivity and memory bias to self-related information in adolescents, with this heightened sensitivity decreasing into adulthood, suggesting that childhood and adolescence is a particularly vulnerable period in which self-concepts shape goals and behaviors, as well as memory and identity (Ross et al. 2020).

While a primary role of the working self is to maintain consistency with one's sense of self, discrepancies can occur within this system wherein individuals perceive their current self to be different from their ideal self (Barry et al. 2006). This notion is reflected in the distance model we introduced at the beginning of this chapter (Fig. 1) wherein individuals strive to maintain consistency with who they are and reduce the distance between one's set of self-concept beliefs and the possible choices one considers. In the context of depression, reduction in the number of choices that provide positive outcomes can negatively impact the extent to which children both build and are motivated to retrieve positive self-perceptions (Jacobs et al. 2003). Furthermore, in order to return to a state of coherence in a void of positive social input, individuals with depression may be biased to negative past experiences and self-perceptions from memory and as a result, make choices that cohere with these negative self-beliefs, thereby perpetuating them in the present and future, and maintaining a close distance between choices and self-beliefs.

In the context of anhedonia, this may be manifest as a lack of desire or an unwillingness to engage in pleasureful or joyful activities (Jacobs et al. 2003). In the context of development, when children are still building an integrated self-concept, discrepancies can be more difficult to reconcile. Insufficient top-down regulatory processes may promote negative drives and input, and an emerging memory system may be unable to flexibly identify those self-beliefs that counteract the negative input, leaving children confused and distressed (Burrows et al. 2017). In support, prior work suggests that children with a strong self-concept, or knowledge of who they are, exhibit lower levels of internalizing symptoms and higher positivity biases (i.e., notions that the future will hold positive outcomes) (Hsieh and Stright 2012; Kraus et al. 2011). In essence, this work aligns with our hypothesis that a strong internal self-representation can help an individual maintain a sense of individual and personal authenticity, positive or negative (Cunningham et al. 2014).

An aspect critical to self-referential processing is that it is built on the combination of personal and social identities. Daily engagement and interaction with the social world help shape one's identity, and input from the external world helps individuals determine how they feel about themselves and how they want others to see them. As young as 3 years of age, children engage in social comparisons to inform their self-evaluations, resulting in dynamic changes and opportunities for disruption in the formation of a positive self-view (Ruble and Frey 1991; Calheiros et al. 2020a). Not surprisingly, positive youths' perceptions of their social images were associated with their positive self-representations, and negative youths' perceptions of their social image were associated with youth's negative self-

representation (Pfeifer et al. 2009). In adolescence – when social inputs become far more relevant a part of one's social experience, greater network activity is seen in the adolescent than adult brain in areas relevant to self-perception (medial prefrontal and parietal cortices) and social cognition (dorsomedial prefrontal cortex, temporal-parietal junction, subgenual anterior cingulate cortex, and posterior superior temporal sulcus). These latter findings suggest adolescent self-construal may rely more heavily on others' perspectives about the self and on the need for self-acceptance (Golde et al. 2019; Masten et al. 2009). As such, self-evaluation and an adolescent's evaluation of the world are tightly linked, supported further by evidence showing that perceived loneliness is associated with reduced neural processing in areas implicated in self-processing, including the vmPFC, and in reducing self-related processing (Van der Cruijsen et al. 2018).

These deficits in self-referential processing align with similar evidence from depressed adolescents, as well. For example, in one study, depressed female adolescents endorsed more negative than positive views of the self. These results were substantiated by neural evidence showing greater P1 amplitudes (i.e., early ERP modulation over parietal-occipital sites) in response to these negative self-views, suggesting that depressed adolescents may exhibit early and strong biobehavioral response to negative self-referential information (Auerbach et al. 2015). In the context of anhedonia, individuals actively dampen responses to statements that are positively self-focused (e.g., think about high achievement) and positively emotion-focused (e.g., think about happy feelings), potentially rooted in overactive self-regulatory processes associated with the frontostriatal system (Werner-Seidler et al. 2013; Joormann and Stanton 2016). These results suggest that individuals with anhedonia struggle to regulate appropriate responses to positive self-information. These deficits may be particularly felt in adolescence considering the high instance of social inputs and relationships prompting more frequent self-appraisals. It is, thus, not surprising that the prevalence of anhedonia and MDD increases through the course of adolescence (Bennik et al. 2014). In recognition of these challenges in the context of anhedonia, recent work has suggested utilizing metacognitive interventions to improve self-esteem and attenuate negative self-views (McLeod et al. 2021).

5 Conclusions and Future Directions

Altogether, this points to the important role of self-cohesion in driving positive actions and feelings throughout childhood. While there is generally a decrease in positive traits during adolescence (Calheiros et al. 2020b), a dearth of positive experience or input in the context of anhedonia can increase negative traits because of socially driven negative self-evaluations, resulting in children disengaging from social and pleasureful activities. A disrupted social environment can have multiple avenues of influence on anhedonia. First, a lack of social engagement could reduce the extent to which children engage in self-referential processing, resulting in a less

defined self-knowledge base. As a result, a self-memory system would struggle to identify relevant aspects of one's past self that might guide present choices and regulatory functions may struggle to identify a coherent path forward. For example, children with little social input may not readily know what to expect from themselves in a social event and avoid it altogether, thereby perpetuating feelings of loneliness and avoidance of typically pleasureful activities. Second, increased negative or decreased positive social engagement can increase negative traits that are perpetuated through the iterative self-memory system to maintain coherence. For example, negative self-evaluations such as "I am shy" may be used to protect against the possibility of negative social evaluations. It is also important to note that environmental and social inputs are constantly in flux. As such, self-evaluations are dynamic and shift over time based on changes in positive or negative experiences or feedback, potentially resulting in the present avoidance of what was previously pleasureful activities.

This is particularly critical when thinking about an adverse life event that may set children on a path toward negative self-representation and the cyclical nature in which this perpetuates avoidance of joyful activities. Prior work shows that maltreatment in the form of sexual abuse increases negative self-representations in youth, and physical and psychological abuse, emotional maltreatment, and neglect decrease positive self-reflections (Rygula et al. 2013). In this context, negative self-representations serve as protective factors in reducing externalizing symptoms because of physical and psychological abuse.

It is also important to note that the relationship between negative self-representations and memory, as outlined in this paper in the context of anhedonia, may also play a role in maintaining other psychiatric disorders, including social anxiety disorder (Anderson et al. 2008; Hulme et al. 2012; Aymerich-Franch et al. 2014), obsessive compulsive disorder (Aardema and O'Connor 2007; Aardema et al. 2013), and eating disorders (Amianto et al. 2016). Neurobiologically, prior work has shown abnormalities in the adolescent hippocampal volume because of current and past depression, deficits in emotion regulation and episodic memory processes, and early childhood adversity, suggesting a strong link between development of memory systems, deficits in cognitive functions, early environment, and a host of psychiatric outcomes (Meyer et al. 2014).

Altogether, the model presented here delineates a dynamic, interactive relationship between the central role of self-concept in regulating and moderating emotionally laden choices. The overview of prior literature outlines the value of early experience in establishing emotion representations in memory. It further outlined the role of memory processes in maintaining representations of emotionally laden memories and concepts for flexible retrieval and use. Finally, it establishes how emotion representations and memory processes interact to establish a self-concept that drives what choices individuals believe they have and what choices they make. In particular, the work presented here provides a possible developmental perspective of how a dearth of positive experiences and emotion concepts in early memory might impact, over time, the extent to which an individual makes choices that appear pleasure-seeking and joyful. To validate this perspective, future work would benefit

from longitudinal designs that can account for how early exposures impact the development of emotion memory processes and how the type of meaning making that must occur to generate one's set of self-beliefs might draw from impoverished memory networks related to positive content. Future work would also benefit from focusing on treatment and intervention. Parent–child interactions in early development are important for emotion development, and a focused intervention on parental caregiving and emotion expression may help scaffold emotion learning during this vulnerable period. Reappraisal, regulation, and metacognitive strategies later in adolescence may help alter the persistence of negative self-concept beliefs in defining one's identity and actions.

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Understanding Anhedonia from a Genomic Perspective

Erin Bondy and Ryan Bogdan

Contents

Abstract Anhedonia, or the decreased ability to experience pleasure, is a cardinal symptom of major depression that commonly occurs within other forms of psychopathology. Supportive of long-held theory that anhedonia represents a genetically influenced vulnerability marker for depression, evidence from twin studies suggests that it is moderately-largely heritable. However, the genomic sources of this heritability are just beginning to be understood. In this review, we survey what is known about the genomic architecture underlying anhedonia and related constructs. We briefly review twin and initial candidate gene studies before focusing on genome-wide association study (GWAS) and polygenic efforts. As large samples are needed to reliably detect the small effects that typically characterize common genetic variants, the study of anhedonia and related phenotypes conflicts with current genomic research requirements and frameworks that prioritize sample size over precise phenotyping. This has resulted in few and underpowered studies of anhedonia-related constructs that have largely failed to reliably identify individual variants. Nonetheless, the polygenic architecture of anhedonia-related constructs identified in these studies has genetic overlap with depression and schizophrenia as well as related brain structure (e.g., striatal volume), providing important clues to

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Curr Topics Behav Neurosci (2022) 58: 61–80
https://doi.org/10.1007/7854_2021_293
Published Online: 14 February 2022

etiology that may usefully guide refinement in nosology. As we await the accumulation of larger samples for more well-powered GWAS of reward-related constructs, novel analytic techniques that leverage GWAS summary statistics (e.g., genomic structural equation modeling) may currently be used to help characterize how the genomic architecture of anhedonia is shared and distinct from that underlying other constructs (e.g., depression, neuroticism, anxiety).

Keywords Anhedonia · Brain · Depression · Gene · GWAS · Reward · Striatum

1 Introduction

It has long been speculated that psychiatric heterogeneity hinders the identification of etiologic mechanisms and stalls treatment advances (Gottesman and Gould 2003; Kotov et al. 2017). Plausibly, amalgamations of symptoms that define psychiatric disorders may reflect shared and/or unique complex pathophysiologies that are obfuscated in traditional case/control studies. This is further complicated by common psychiatric comorbidity as well as symptoms, characteristics, and correlates that are often shared across diagnoses (Cross-Disorder Group of the Psychiatric Genomics Consortium 2019; Radonjić et al. 2021). Concerns that within-disorder heterogeneity and across-disorder similarity have hindered research progress in psychiatry has led to research conceptualizations (e.g., endophenotype, intermediate phenotypes) advocating for the study of more homogenous quantifiable phenotypes whose pathophysiologies and genomic architecture will be presumably less heterogenous and hence more scientifically tractable (Gottesman and Gould 2003; Hasler et al. 2004; Meyer-Lindenberg and Weinberger 2006). These conceptual frameworks have inspired a variety of efforts to refine nosology (e.g., hierarchical taxonomies, machine learning-informed approaches; Feczko and Fair 2020; Kotov et al. 2017) and promoted funding for studies of fundamental dimensions of behaviors such as the U.S. National Institute of Mental Health (NIMH)'s Research Domain Criteria (RDoC) initiative, which is a framework for investigating mental health within a comprehensive consideration of typical and atypical functioning. In particular, the RDoC research strategy focuses on major domains of human functioning and dysfunction within these domains associated with psychopathology (for more information on the U.S. NIMH RDoC initiative see: (Insel et al. 2010; Morris and Cuthbert 2012).

Anhedonia, which reflects reduced pursuit of reward and diminished reactivity to pleasurable stimuli, has long been heralded as a critical neuropsychiatric phenotype for in-depth study that is rooted in deficits across various subcomponents of the Positive Valence Systems (PVS) domain of the RDoC, including reward anticipation, response to reward, reward learning, habitual reward, reward delay, and reward effort (Hasler et al. 2004; Kendler 2017; Morris and Cuthbert 2012; addition information regarding RDoC PVS domains can be found at https://www.nimh.nih.

gov/research/research-funded-by-nimh/rdoc/constructs/positive-valence-systems). Anhedonia is a core clinical feature of depression that commonly presents across various other forms of psychopathology including schizophrenia, posttraumatic stress disorder, and substance use disorder. Highlighting its potential import, across psychopathologies, anhedonia has been associated with increased severity and comorbidity as well as reduced response to treatment (Destoop et al. 2019; Kasch et al. 2002; Kendler 1997). Despite evidence that anhedonia and related constructs are moderately-largely heritable (Hess et al. 2016), the genomic sources of this heritability remain poorly understood. In this chapter, we review contemporary genetic studies of anhedonia and related RDoC PVS components. We begin by broadly contextualizing current research frameworks in psychiatric genetics and how they are and are not consistent with RDoC. Next, we delve into the genetics of anhedonia by first providing a broad overview of heritability estimates derived from twin studies and briefly discussing initial candidate gene studies that have generally not been replicated. We then focus predominantly on emerging evidence from nascent genome-wide association studies (GWASs) of anhedonia and related constructs as well as polygenic scoring approaches. Finally, we discuss challenges associated with genetic work on anhedonia and how addressing them may broadly inform our understanding of anhedonia to ultimately influence psychiatric nosology, treatment, and prevention.

2 Contemporary Psychiatric Genetics Frameworks: Relevance to RDoC

In contrast to the study of fundamental dimensions of behavior (e.g., RDoC) that have largely eschewed disorder-guided investigation, the field of psychiatric genetics has predominantly focused on case/control studies and easily quantifiable, yet heterogeneous, psychiatrically-relevant phenotypes (e.g., dichotomous responses to "Would you describe yourself as someone who takes risks?"; Strawbridge et al. 2018) in an effort to bolster sample size (Sullivan and Geschwind 2019). Initial excitement that the mapping of the human genome would quickly identify clinically actionable mechanistic targets and usher in an era of personalized medicine in psychiatry (Craddock and Owen 1996) was met with largely unreplicable candidate gene research (with notable exceptions in the field of substance use disorders: e.g., *ADH1B* rs1229984 and alcohol use disorder, *OPRM1* rs1799971 and opioid use disorder; Gelernter and Polimanti 2021) and initial underpowered GWASs that largely produced null associations (e.g., Sullivan et al. 2009). Constrained by high initial costs of molecular genetic research, this early underpowered work attempted to confront these limitations by focusing on intermediate phenotypes (e.g., brain function, structure) consistent with an RDoC perspective (Bogdan et al. 2017); while many intermediate phenotypes (e.g., brain structure, circulating biomarkers) have proven to be characterized by larger genetic association estimates than psychiatric

diagnoses, effects overall are small and require large samples to reliably detect (Grasby et al. 2019; Ligthart et al. 2018). Following technological advancements and related cost reductions in genome-wide genotyping, as well as sober realizations that associations between single common genetic variation and complex behavioral and biological traits are small in magnitude, the pendulum in psychiatric genetics shifted away from fundamental dimensions of behavior (e.g., RDoC) to focus predominantly on easily assayed and widely available phenotypes (e.g., psychiatric diagnoses, brief widely used questionnaires) that enable the formation of large collaborative datasets and the generation of single large studies (Sullivan and Geschwind 2019). This transition has prioritized a top-down scientific approach wherein initial GWASs are conducted on higher-order heterogenous constructs with subsequent follow-up studies applying these results to more finely grained behavioral constructs by attempting to define functional consequences of these variants and their associations with intermediate phenotypes, as well as phenotypic associations with their polygenic architecture. While the focus of psychiatric genetics remains on heterogenous clinical constructs, more recently large-scale GWASs have begun to address heterogeneity by conducting GWASs of individual disorder symptoms and construct items (e.g., each item contributing to neuroticism) that have revealed both shared and distinct architectures (Mallard et al. 2021; Nagel et al. 2018b). Further, the establishment of large-scale studies that include deep phenotyping (e.g., UK Biobank, ABCD Study, All of Us) has begun to establish large datasets that have assessed RDoC-related constructs across levels of analysis (i.e., behavior, biomarkers, brain; Elliott et al. 2018).

3 Genetic Studies of Anhedonia and Related Constructs

3.1 Twin and Family Studies

Twin studies, which assume uniform additive effects of segregating loci, have been used for a century to estimate latent sources of genetic influence on psychiatrically-relevant traits. Overall, twin work suggests that the vast majority of complex psychiatric and related traits (e.g., brain structure, personality) have moderate to high heritability (Polderman et al. 2015; ~0.30–0.80). Despite long-held theory that anhedonia may be a genetically influenced vulnerability factor for depression (Loas 1996; Snaith 1993), there has been limited research on the heritability of anhedonia and related behavioral constructs, with the exception of self-reported impulsivity and broad spectrum externalizing behavior (Linnér et al. 2020), which will not be considered here. Much like the broader literature of complex psychiatrically-relevant traits, the heritability of self-reported anhedonia (Berenbaum et al. 1990; Berenbaum and McGrew 1993; Clementz et al. 1991; Dworkin and Saczynski 1984; Franke et al. 1993; Hay et al. 2001; Heath et al. 1994; Katsanis et al. 1990; Kendler et al. 1991; Thaker et al. 1993) as well as related RDoC-related PVS constructs (e.g., reward learning, delay discounting, corticostriatal brain structure, reward-related

ventral striatum activation; Anokhin et al. 2011, 2015; Bogdan and Pizzagalli 2009; Galimberti et al. 2013; Grimm et al. 2014; Guffanti et al. 2019; Li et al. 2019; Liu et al. 2016; Melhorn et al. 2016) ranges from moderate to large. As the heritability work on these constructs has predominantly been conducted in small samples that produce wide 95% confidence intervals overlapping with one another, it is unclear from this literature to what extent the heritability of distinct anhedonia-related constructs differs from one another, making it difficult to prioritize particular aspects of reward processing for further investigation based on heritability.

Due to aforementioned concerns about psychiatric heterogeneity, some studies have examined the heritability of specific subtypes of depression, based on symptom constellations, comorbid conditions, age of onset, and general outcomes (Harald and Gordon 2012). Melancholic depression, one of the most widely studied subtypes, is characterized by anhedonia, early morning wakening, weight loss, psychomotor disturbances (agitation or retardation), and excessive guilt (Angst et al. 2007; Parker et al. 2017). Findings regarding the heritability of melancholic depression largely suggest that melancholic depression is less uniquely heritable than other subtypes, such as atypical depression (Kendler 1997; Klein et al. 2002; Lamers et al. 2016; Maier et al. 1991), and is instead suggestive of higher familial liability for any form of depression.

3.2 Candidate Gene Studies

Similar to RDoC-like approaches, initial hypothesis-driven candidate gene efforts adopted a bottom-up scientific approach by studying single variants with putative functional consequences (e.g., 5-HTTLPR with *SLC6A4* (Caspi et al. 2003; Lesch et al. 1996), *COMT* rs4680 (Egan et al. 2001), *MAOA* promoter variant (Caspi et al. 2002), ADH1B rs1229984 (Thomasson et al. 1991)) within pathways (e.g., serotonin, dopamine, etc.) known to be associated with psychiatric phenotypes. While some of these variants have been validated using GWASs (e.g., ADH1B rs1229984; Gelernter et al. 2014), the vast majority have not been replicated in the extensive psychiatric genetics literature (Border et al. 2019; Duncan and Keller 2011; Johnson et al. 2017). Prior candidate gene investigations of single common variants in this context initially reported associations with anhedonia and related constructs (e.g., reward learning, delay discounting, reward-related brain function) in small samples (Corral-Frías et al. 2016; Dillon et al. 2010; Docherty and Sponheim 2008; Dreher et al. 2009; Grimm et al. 2014; Troisi et al. 2011); however, while some evidence of convergence emerged, there have been few replication attempts and given what has been learned in the broader field of psychiatric genetics, a high degree of skepticism exists.

Today, the vast majority of candidate gene research is done following the identification of variants from a GWAS, consistent with a top-down approach in which variants are first associated with heterogenous psychiatric constructs and then characterized according to their associations with intermediate phenotypes (Bogdan

et al. 2018). This work has linked variants associated with depression to anhedonia and related neural constructs (e.g., responsiveness to reward; Wetherill et al. 2019; Lancaster et al. 2019). However, the small effect sizes associated with common single genetic variants and extensive evidence that complex traits are undergirded by an extensive polygenic architecture, this work has largely transitioned to polygenic scores that allow for the non-specific aggregation of genomic risk (see Sect. 3.4 below). Further, much like studies of regional differences in neural phenotypes that account for global metrics, it will be important for single variant work to test whether such associations exist above and beyond the polygenic architecture.

3.3 GWAS

As the field of psychiatric genetics has prioritized large datasets of heterogeneous clinical constructs (see Sect. 2 above), it is unsurprising that there have been few GWASs of anhedonia and related constructs and that they have typically been conducted in small samples. Indeed, contrasting recent well-powered investigations of heterogeneous psychiatric constructs including depression (Howard et al. 2019), neuroticism (Nagel et al. 2018a), externalizing behavior (Linnér et al. 2020), and risk taking (Karlsson Linnér et al. 2019) that have begun to reliably identify single loci and characterize the broad polygenic architecture of these phenotypes, we are only aware of 11 GWASs assessing anhedonia and/or more precise PVS constructs (Jia et al. 2016; May-Wilson et al. 2021; Ortega-Alonso et al. 2017; Pain et al. 2018; Ren et al. 2018; Sanchez-Roige et al. 2018; Service et al. 2012; Tomppo et al. 2012; Verweij et al. 2010; Ward et al. 2019; Wingo et al. 2017), of which only 3 (Ward et al. 2019; Sanchez-Roige et al. 2018; May-Wilson et al. 2021) have more than 12,000 participants (Table 1), which we highlight here. These anhedonia-related GWASs may be divided into those assessing anhedonia directly in the context of depression or psychosis assessments as well as RDoC PVS domain components, and they have generally been conducted among those of European ancestry (primarily from the United States and United Kingdom), with one study conducted among those with African American ancestry.

In the largest GWAS of anhedonia ($n = 375{,}275$) to the best of our knowledge, Ward et al. (2019) identified 11 independent loci associated with state anhedonia assessed using the Patient Health Questionnaire-9 (i.e., "Over the past two weeks, how often have you had little interest or pleasure in doing things?") in the UK Biobank (middle – late adulthood). While several of these loci reside near genes that have previously been implicated in reward-related clinical constructs (e.g., *EPHB1* associated with antidepressant response, schizophrenia, and Parkinson's disease; *DRD2* well-characterized role in reward), none showed replicable associations with state anhedonia in an independent UK Biobank subsample ($n = 17{,}120$). Single loci did not replicate in this study, although genomic liability to state anhedonia was significantly shared with major depressive disorder ($r_g = 0.77$ [95% CI 0.71, 0.83]), schizophrenia ($r_g = 0.28$ [0.21, 0.35]), and bipolar disorder ($r_g = 0.12$ [0.05, 0.19]),

Table 1 GWAS studies of anhedonia and related positive valence systems constructs

Reference	N	Anhedonia/PVS phenotype	Significant loci (#)	Genes identified
Verweij et al. (2010)	5,117	Reward dependence	0	N/A
Service et al. (2012)	11,000	Reward dependence	0	N/A
Tomppo et al. (2012)	4,561	Revised social anhedonia scale, revised physical anhedonia scale	0	N/A
Jia et al. (2016)	1,544	Neural activity during reward anticipation	0	N/A
Ortega-Alonso et al. (2017)	4,269	Revised physical anhedonia scale, revised social anhedonia scale	0	N/A
Wingo et al. (2017)	2,522	Positive affect (PANAS)	1	*LINC01221*
Pain et al. (2018)	6,579	Psychotic-like experience domains	1	*IDO2*
Ren et al. (2018)	759	Composite measure of "interest-activity" generated from items on Montgomery-Asberg depression scale, Hamilton depression rating scale, and Beck depression inventory	18	*PRPF4B, TAOK3, NPAS3, EYS,LARP4, LOC153910, FAM19A2, COX16, CDH18, STAB2, NOTCH4, ADGRG6, FAM46A, NOX3, LOC105374974*
Sanchez-Roige et al. (2018)	23,217	Delay discounting	1	*GPM6B*
Ward et al. (2019)	375,275	Question from PHQ-9	11	*RGS1, RGS2 EPHB1, CTNNA3, GRM5, DISC1FP1 NCAM1, DRD2 PRKD1 SLC8A3 ISLR2, NRG4 DCC*
May-Wilson et al. (2021)	161,625	Food "liking" ratings	173	*ADH1B, TSNARE1, SLC39A8, PARP1, LINC01833, GDF15, OR4K17, TAS2R38, FGF21, among other*

but not Parkinson's disease or OCD. Simply put, these findings suggest that the overall genomic architecture that is associated with state anhedonia during mid-later life largely overlaps with depression has moderate overlap with schizophrenia, and a small, but significant, overlap with bipolar disorder. These genetic correlations with discrete psychiatric disorders highlight the potential utility of GWASs of specific symptoms shared across disorders and RDoC constructs to identify shared and unique genomic architectures that may ultimately aid in the characterization of pathophysiologies across various forms of psychopathology to refine nosology and treatments (see also Sect. 4 below).

The other 2 large GWASs of anhedonia-relevant reward-related behavioral traits also show intriguing genetic correlations. For example, Sanchez-Roige and colleagues conducted a GWAS of delay discounting using data from 23,217 23andMe (www.23andme.com) customers (Sanchez-Roige et al. 2018). This GWAS identified a single variant (rs6528024) in an intron of the gene *GPM6B* (which encodes membrane glycoprotein) on the X chromosome associated with delay discounting performance. Much like the GWAS of anhedonia by Ward et al. (2019), this study also showed genetic correlations with delay discounting across psychiatric disorders (ADHD $r_g = 0.37$ [0.15, 0.59], depression $r_g = 0.47$ [0.14, 0.80], schizophrenia $r_g = -0.22$ [−0.35, −0.08]), although the directionality of this relationship with schizophrenia (negative) differed from results found by Ward and colleagues. Sanchez-Roige et al. (2018) also found that delay discounting shared genomic liability with related constructs (e.g., lifetime smoking $r_g = -0.32$ [0.08, 0.56], neuroticism $r_g = -0.18$ [0.02, 0.34], cognition measures: college attainment $r_g = -0.93$ [−1.22, −0.64], years of education $r_g = -0.67$ [−0.85, −0.49], and childhood IQ $r_g = -0.63$ [−0.96, −0.45]). Finally, in a recent preprint GWAS of 161,625 UK Biobank participants, May-Wilson et al. (2021) identified 173 loci (61 showed nominal evidence of replication) associated with food liking and reported that the genomic architecture of liking highly palatable foods is associated with reduced striatal volumes, which have been previously associated with anhedonia and other brain metrics (Auerbach et al. 2017; Harvey et al. 2007); correlations with psychiatric diagnoses were, however, not examined.

The smaller and less well-powered studies of anhedonia-related phenotypes have largely identified individual loci that have as of yet not been replicated. In the smallest GWAS among them ($n = 759$), Ren and colleagues identified 18 partially-independent (i.e., linkage disequilibrium [LD] $R^2 < 0.50$) genome-wide significant variants associated with an interest-activity composite score derived from depression assessments in a treatment seeking sample of depressed individuals; however, none of these replicated in an independent treatment sample of 1,351, with some even showing nominally significant associations in the opposite direction. Of the three GWASs conducted on anhedonia in the context of psychosis assessments (Ns 4,269-6,297; Ortega-Alonso et al. 2017; Pain et al. 2018; Tomppo et al. 2012), only the study by Pain and colleagues identified a single genome-wide significant locus, which however did not replicate in an independent sample and was characterized by relatively low minor allele frequency (0.015). Along similar lines, two GWASs of reward dependence ($n = 5{,}117$; Verweij et al. 2010;

$n = 11{,}000$; Service et al. 2012), which were conducted prior to the development of now typical follow-up techniques (e.g., genetic correlation as estimated using LD score regression), failed to identify any significant loci. A GWAS of positive affect as assessed using the Positive and Negative Affect Schedule among 2,522 African American participants identified a single genome-wide significant locus (rs322931) associated with wellbeing; although there was convergent evidence in a small sample ($n = 55$) also linking this variant to ventral striatum reactivity to emotional stimuli, this variant has yet to be replicated in other GWASs of related constructs (Wingo et al. 2017). Finally, a GWAS of a coordinated network of brain activity to reward anticipation evoked by the monetary incentive delay task among 1,544 adolescents identified no genome-wide significant loci, though highlighted the potential role of VPS4A, which regulates catecholaminergic systems (Jia et al. 2016).

Initial GWASs of anhedonia and related RDoC PVS constructs have yet to reliably identify individual loci as a whole, with the exception of the recent GWAS preprint of food liking (May-Wilson et al. 2021). This may be attributable to the lack of power of these GWASs and/or heterogeneity of the anhedonia construct more generally. Despite the overall lack of association with single common genetic variation, these GWASs are beginning to characterize an extensive polygenic architecture that is shared with disorders characterized by anhedonia.

3.4 Polygenic Studies

The identification of single variants associated with psychiatrically-relevant phenotypes holds tremendous potential to identify novel pathways and molecular mechanisms of disease that may be leveraged for treatment; however, with few exceptions (e.g., APOE rs429358 & rs7412 haplotypes & Alzheimer's Disease; Corder et al. 1993), they do little to inform individual risk or represent individual differences in molecular function in follow-up studies. Indeed, the vast majority of single loci associated with psychiatrically-relevant traits are characterized by small effects (e.g., odds ratios <1.1; Bogdan et al. 2018). Nonetheless, the additive effects of common variants, when weighted by their association with a phenotype of interest in an adequately powered GWAS, are reliably predictive of variance in the same and related traits (Bogdan et al. 2018; van Rheenen et al. 2019; Wray et al. 2021). These additive scores, which we refer to as polygenic scores (PGSs) have been applied to independent samples to explore how the polygenic architecture for a given trait is correlated with other phenotypes. Notably, the effect size of PGSs is small (typically predicting 0.01–3% of variance), although new techniques (e.g., PRS-CS [polygenic risk scores – continuous shrinkage]; Ge et al. 2019) using a Bayesian continuous shrinkage (CS) prior on SNP effect sizes and more strongly powered discovery GWAS have increased effect size estimates (Bogdan et al. 2018). Optimistically, current PGSs are typically most predictive of phenotypes most proximal to the phenotype in the original GWAS as opposed to intermediate phenotypes; for

example, educational attainment PGSs are most predictive of educational attainment and less predictive of more homogenous constructs such as cognitive performance (Lee et al. 2018), highlighting the need for additional GWAS of intermediate phenotypes (e.g., Grasby et al. 2019). Further, because PGSs rely on LD patterns, which much differ ancestrally, a PGS derived from a discovery GWAS in one ancestry is a less informative predictor in other ancestral groups, though novel approaches integrating GWAS data, CS priors, and external panels from multiple ancestries are showing promise (e.g., PRS-CSx, an extension of PRS-CS; L. Duncan et al. 2019; Peterson et al. 2019; Ruan et al. 2021). Importantly, the phenotypic presentation of depressive symptoms, including anhedonia, can vary cross-culturally (Chentsova-Dutton et al. 2015); as such, cultural variations in the experience of anhedonia will be important to consider in future PGS studies that include data from multiple ancestries. PGS studies require samples of 300 for adequate power and in all likelihood require samples much larger to reliably detect effects (Ge et al. 2019). Here, we summarize studies that have evaluated how PGSs of anhedonia-related constructs generated from the GWASs reviewed above are correlated with anhedonia and other related phenotypes, as well as how genomic liability to other phenotypes (i.e., depression, schizophrenia, and C-reactive protein [CRP]) is associated with anhedonia.

We are aware of only two studies that have evaluated associations between polygenic risk for anhedonia in an independent sample form the original discovery GWAS (but see also Ren et al. for the application of a polygenic risk score within the sample from which it was derived). These two studies have shown that polygenic risk for state anhedonia (derived using the Ward et al. 2019 discovery GWAS in UK Biobank) is associated with brain structure in an independent UK Biobank imaging sample ($n = 17{,}120$ in Ward et al. 2019; $n = 19.952$ in Zhu et al. 2021). More specifically, these studies found that polygenic risk for state anhedonia was associated with state anhedonia ($R^2 = 0.004$) as well as smaller total gray matter volume and larger total white mater volume, consistent with many studies linking polygenic risk for psychiatric phenotypes to global brain metrics. Interestingly, these global brain metrics were also associated with reported anhedonia. There was less evidence that anhedonia polygenic risk was associated with regional variability in gray matter structure; anhedonia polygenic risk was associated with thinner cortex in the insula, parahippocampal cortex, and superior temporal gyrus. Although significant associations were observed with white matter integrity, none of these were robust to the inclusion of potential confounds (e.g., stress, socioeconomic status, alcohol use). Collectively, these studies suggest that associations between global brain metrics and anhedonia may be partially genomic in origin.

In contrast to limited studies evaluating polygenic risk for anhedonia, several studies have investigated whether polygenic risk for related phenotypes (i.e., depression, schizophrenia, bipolar, inflammation) is associated with reported anhedonia and related behavioral and neural indices. For example, building upon the genetic correlations showing the genomic architecture of anhedonia is shared with clinical diagnoses characterized by anhedonia, Pain et al. (2018) found that polygenic risk

for schizophrenia and depression, but not bipolar disorder, is associated with anhedonia at nominal levels of significance in a sample of 6,579.

In an RDoC-inspired study among 83 participants, Guffanti et al. (2019) reported that polygenic risk for depression was not associated with self-reported anhedonia or behavioral reward learning, but it showed nominally significant stress-related reduction in reward prediction errors in the ventral striatum and putamen, as well as reductions in ventral striatum and putamen volume (the association with putamen volume would survive correction for multiple testing). These findings are consistent with theoretical speculation that intermediate phenotypes such as neural measures would be more closely associated with genetic architecture than more homogenous distal phenotypes such as self-reported anhedonia, although prior PGS studies suggest that they are typically most predictive of the most proximal phenotype to the original GWAS (e.g., in this case depression or depression symptoms), even if that phenotype represents a more heterogenous construct. Nonetheless, in another study of 478 college students, Mareckova and colleagues found that a transcriptomically-informed PGS based on 76 genes was not directly related to anhedonia but showed an indirect association through neural responses to neutral faces (Mareckova et al. 2020).

Finally, Kappelmann and colleagues examined associations between anhedonia and PGSs of immune-metabolic markers (Kappelmann et al. 2021), supported by widespread evidence of elevated inflammatory signaling across psychopathology (Baumeister et al. 2014). Inflammatory markers act upon several neural systems, and consequences include a reduction in the availability of dopamine in the basal ganglia (Felger 2017), plausibly implicating it in anhedonia symptomatology. Supportive of a potential etiologic mechanism, administration of proinflammatory cytokines in humans and non-human animals induces an anhedonic-like phenotype, alters the structure of the striatum, and reduces dopamine signaling capacity and striatal responses to reward (Felger et al. 2013; Harrison et al. 2016; Treadway et al. 2019). Interestingly, across samples (Ns = 1,058–1,100,101), higher polygenic risk for CRP was associated with reduced anhedonia, while the PGS for TNFα was correlated with higher levels of anhedonia (Kappelmann et al. 2021). Although immune pathways act on reward-related neural circuits implicated in anhedonia, these contradictory findings suggest that it remains unclear to what extent genetic liability to immune signaling is a contributing mechanism.

4 Conclusions and Future Directions

In contrast to a strong theoretical history highlighting the importance of anhedonia to psychopathology, studies of its genomic architecture remain uncommon and largely underpowered. While specific loci remain elusive, the polygenic architecture of anhedonia is showing expected correlations with related disorders and phenotypes (e.g., depression, striatal brain volume). Initial hopes that leveraging intermediate phenotypes would generate large boosts in power that would permit the use of

smaller samples have not been empirically demonstrated (e.g., Grasby et al. 2019). However, it remains plausible that loci identified by intermediate phenotype approaches may be more tractable for understanding psychiatric etiology and treatment. As is now clear in psychiatric genetics, larger samples are needed to be able to reliably estimate expected small effects, even for intermediate phenotypes and aggregate polygenic risk score approaches. Large-scale nationwide data collection projects (e.g., UK Biobank, Adolescent Brain Cognitive Development [ABCD] Study, HEALthy Brain and Child Development [HBCD] Study, All of Us) that incorporate deep phenotyping (e.g., neuroimaging, biomarkers, behavioral assessments) are importantly contributing to the genomic investigation of intermediate phenotypes and increasing sample sizes available to investigators. In the meantime, as we wait for larger samples to accumulate, we may leverage currently available GWAS summary statistics from studies of reward processing phenotypes and combine them with larger efforts characterizing related constructs that are more heterogeneous. For instance, we recently used genomic structural equational modeling, which identifies the shared and unique genetic architectures of multiple GWAS phenotypes, to show that genomic risk for specific forms of substance use disorders is largely shared and independent of the genomic architecture associated with substance use (Hatoum et al. 2021). Moreover, we found that this shared genomic risk for addiction was also shared with trait vulnerability to neurobehavioral stages of addiction (i.e., impulsivity, neuroticism, executive function), which mediates associations between substance psychopathology and non-substance psychopathology. A similar approach could be used to characterize the shared and distinct genomic architecture of anhedonia, and depression as well as depression related traits not typically characterized by reward deficits (e.g., neuroticism, and anxiety). This may bolster the genomic signal and allow for anhedonia-related and non-anhedonia-related genomic risk for depression to be estimated as we continue to accumulate larger samples needed for the genomic study of anhedonia. It is the hope that the replicated results emerging from genomic studies of anhedonia will uncover novel treatment targets for this condition that has been linked to poor disease course, treatment failures, and increased suicide risk.

Acknowledgments This work was supported by F31 MH123105 (EB) and R01 AG061162 (RB). EB and RB report no conflicts of interest.

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Environmental Contributions to Anhedonia

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Contents

Abstract Anhedonia is a core feature of psychopathological conditions that have recent exposure to stress and trauma as central to their etiology. Indeed, evolutionary accounts of depression suggest that decreased motivation to pursue reward may be an adaptive strategy in the face of social stress, in particular, as it may serve to defuse interpersonal conflict. Through a review of rodent models and research with humans, we show that exposure to stress, particularly when it is chronic, repeated, and/or involves themes of social rejection or defeat, is consistently associated with reduced hedonic capacity ("liking"), motivation to pursue reward ("wanting"), and ability to learn from reward ("reward learning"). Further, across rodent and human research, there is evidence that females show greater stress-induced blunting of reward

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Curr Topics Behav Neurosci (2022) 58: 81–108
https://doi.org/10.1007/7854_2021_289
Published Online: 12 December 2021

processing than males. In humans, this sex difference emerges most strongly when examining individual differences in the stress *response* rather than group differences in stress *exposure*. We discuss the implications of these findings for understanding the etiology of, and sex differences in, stress-related psychopathology, including depression and addiction.

Keywords Anhedonia · Childhood adversity · Reward · Stress

1 Introduction

Stress is a ubiquitous experience and has been throughout evolution. Mammals, in general, have evolved adaptive strategies for surviving acute, predictable dangers in the environment (e.g., predator attack). Such stress exposures initiate a cascade of neurobiological processes, including activation of mesolimbic and mesocortical dopamine (DA) pathways, that promote behavioral activation and coping (Pani et al. 2000). These systems did not evolve, however, to address the sorts of chronic, unpredictable, and/or uncontrollable stressors that are common in our human context and central to the etiology of numerous chronic medical and psychiatric illnesses (McEwen 2013). In this chapter we review evidence from rodent models and studies with humans showing that chronic and/or severe stress has a general blunting effect on hedonic capacity, motivation to pursue reward, and reward learning. Further, we illustrate that this general relation is moderated by important characteristics of the stressor and individual. The ultimate goal of this discussion is to further understand alterations in reward processing as a crucial mechanism underlying anhedonia in stress-related illness.

2 Definitional Issues: Consummatory vs. Motivational Anhedonia

Anhedonia is characterized by deficits in the capacity to experience pleasure (consummatory anhedonia, "liking") and in the motivation to pursue reward (motivational anhedonia, "wanting"; Treadway and Zald 2011). Briefly, the perception of hedonic experiences is largely mediated by endogenous opioids, which function by binding to opioid receptors in distinct regions of the ventral striatum and medial prefrontal cortex (mPFC; Liberzon et al. 2002). Affective pleasure responses are most strongly mediated by mu-opioid receptors in the medial shell of the nucleus accumbens (NAc) (Peciña and Berridge 2005) and the ventral pallidum (Smith and Berridge 2007), known as the "hedonic hotspots." The hedonic value of a stimulus alone does not motivate goal-directed actions (MacAulay et al. 2014). Instead,

DA-mediated associative learning processes link the pleasurable aspect of a stimulus to its motivational value. Thus, motivational anhedonia primarily reflects disruptions in midbrain DA. At the same time, DA modulation alone does not affect consummatory reward processing. For example, sucrose preference – a measure of hedonic capacity – is preserved in mice following DA depletion (e.g., Cannon and Palmiter 2003).

Stress has effects on both consummatory and motivational reward processes, thus interfering with the integration of these processes. Acute stress generally activates DA neurons in the ventral tegmental area (VTA), thereby initiating DA release in VTA-projection sites, namely mesolimbic (e.g., NAc) and mesocortical (e.g., mPFC) pathways (Holly and Miczek 2016). In contrast, chronic stress is associated with marked reductions in extracellular DA in the NAc (Pothos et al. 1995), which has been attributed to reduced activity of DAergic neurons within the NAc (Gambarana et al. 1999) (see Fig. 1). Chronic stress also reduces opioid receptor binding in the NAc (Dantas et al. 2005). Relatedly, chronic stress reduces NAc enkephalin levels (Nam et al. 2019) and down-regulates its receptor expression in the NAc shell (Poulin et al. 2014).

3 Definitional Issues: Stress Exposure and Response

The term "stress" can refer to external environmental exposures (e.g., stressful life events) or to the behavioral, emotional, and/or physiological responses to these environmental exposures (i.e., the feeling state of "stress"). Certainly, stress exposures elicit stress responses, but the relation between exposure and response is not perfect. In addition to environmental exposures, stress responses are influenced by several other factors that vary across individuals (e.g., sex, genetic vulnerability, prior experience/exposure; Harkness and Monroe 2016). As such, even in animal models, there can be wide differences in responses to the same level of stress exposure, both across individuals and even within individuals over time. For this reason, "stress exposure" and "stress response" should be conceptually and methodologically distinguished.

The literature addressing stress exposures includes naturalistic stressors and laboratory stress paradigms. Naturalistic exposures refer to stressful experiences that occur in individuals' natural environment (e.g., major life events, daily hassles, childhood trauma). The primary advantage of examining naturalistic stressors is high ecological validity. However, an important disadvantage is poor experimental control. All of these exposures vary within category, and across people, in terms of their severity, chronicity, time period of exposure, and so on. Laboratory-based stress exposures, in contrast, are tightly controlled and homogenous. Importantly, they are homogenous in terms of the *exposure,* which means that any individual differences are due to the differences in the stress *response.* Laboratory stressors in human studies are typically either physical (e.g., cold water immersion, mild electric shock) and/or social-evaluative (e.g., social exclusion, public speaking, performance

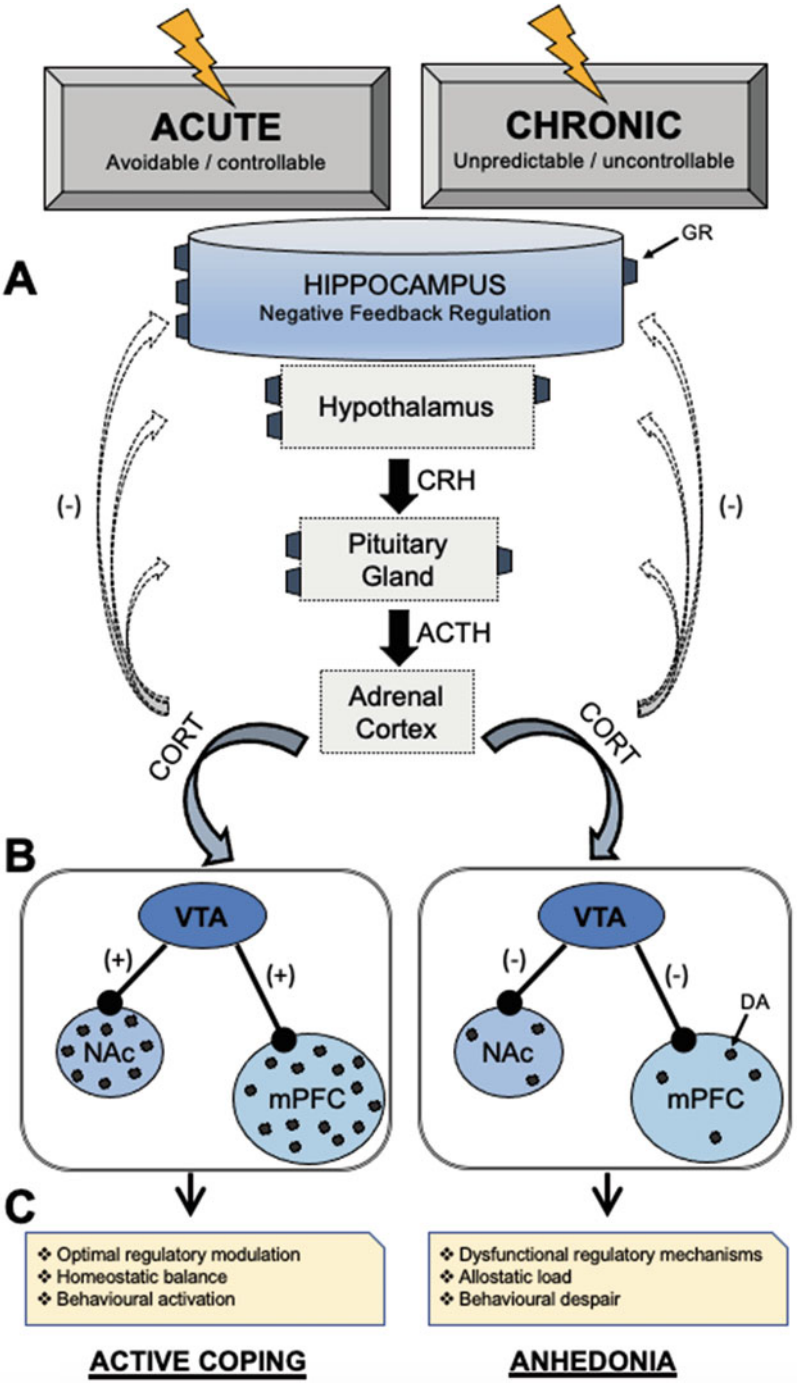

Fig. 1 Mesocorticolimbic dopamine (DA) output is differentially modulated by acute and chronic stress in rodents. (**a**) Prolonged cortisol (CORT) secretion, as shown during chronic stress, impairs negative feedback modulation of the hypothalamic-pituitary-adrenal (HPA) axis via glucocorticoid

evaluation) in nature (e.g., Kirschbaum et al. 1993; Lovallo 1975; Smeets et al. 2012; Williams and Jarvis 2006). Of course, much of the preclinical literature involves exposure to stress in the lab. In some cases, these stressors have been developed as analogues to naturalistic exposures in humans (early maternal separation as an analogue to parental neglect; resident-intruder paradigm as an analogue to assault; chronic mild stress as an analogue to uncontrollable and unpredictable chronic stressors in humans; e.g., Katz 1982; Koolhaas et al. 2017; Lehmann et al. 1999). Others are identical to laboratory exposures in humans (e.g., mild electric shock). Within laboratory studies, individual differences in the stress response have been examined most often in the human literature in terms of reactivity of the stress hormone cortisol (Zorn et al. 2017).

Distinguishing between stress exposure and stress response allows us to pose two distinct questions. The first is a between-group question: Are there differences in reward processing between stress-exposed vs. non-exposed groups? The second is an individual differences question: Is the magnitude of the stress response correlated with response to reward? Importantly, laboratory studies provide a unique opportunity to compare results across these two questions because the characteristics of the exposure are controlled. In the sections that follow, we review the state of the literature examining the association of stress exposures and response to consummatory and motivational aspects of reward processing.

4 Relation of Stress to Reward Processing in the Preclinical Literature

4.1 Chronic Mild Stress

Historically, hedonic capacity has been evaluated in rodents by measuring sweet solution consumption (sucrose or saccharin) relative to plain water, with lower intake denoting a reduction in the perceived hedonic value of reward. This protocol, known as the sucrose preference test (SPT), became the gold standard preclinical

Fig. 1 (continued) receptor (GR) down-regulation in the hippocampus, hypothalamus, and pituitary gland. (**b**) Exposure to acute, avoidable, and/or controllable stress typically activates the ventral tegmental area (VTA), thereby increasing dopamine (DA) in the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC). By contrast, exposure to prolonged, unavoidable, and/or uncontrollable stress inhibits DA projections from the VTA, leading to decreased DA in the NAc and mPFC. (**c**) Whereas acute stress promotes adaptive coping, chronic stress leads to dysregulated HPA functioning, behavioral despair, and motivational deficits that characterize anhedonia. Notably, the depicted framework reflects the majority of preclinical literature in adult male rodents, but emerging findings show opposing patterns in female animals (e.g., Bryce and Floresco 2021), where impairments in motivated behavior are observed following acute stress. Relatedly, the type of stressor and timing of exposure (including developmental period) differentially affect DA output patterns and reward-related behaviors

assessment of consummatory anhedonia. Beginning in the early 1980s, Katz (1982) discovered that sweet solution consumption could be curtailed by continuously exposing animals for several weeks to a series of severe stressors (e.g., intense footshock, immersion in cold water). This regime was subsequently changed to a series of micro-stressors (e.g., soiled bedding, overnight illumination). Though each stressor is mild in nature, the totality of the revised protocol, known as the chronic mild stress (CMS) paradigm, is considered moderately stressful (Willner et al. 1987). Sucrose preference decreases with CMS exposure and can be restored by chronic (but not acute) treatment with antidepressants (e.g., Muscat et al. 1992; Willner et al. 1987).

However, as the SPT became widely implemented, major flaws were identified (Matthews et al. 1995). In particular, group differences in sucrose consumption may disappear when controlling for group body weight differences (Matthews et al. 1995). Accordingly, it was recommended to report consumption as a percentage of body weight (i.e., *absolute sucrose consumption (g)/body weight (g)*) to account for the reduced caloric demands of smaller animals, which might affect intake. Nevertheless, current studies commonly report changes in absolute sucrose consumption, or percentage of sucrose consumption relative to water, without controlling for (or reporting) body weight changes (e.g., Rossetti et al. 2016). Importantly, several studies have determined that antidepressant treatment restores sucrose preference regardless of body weight changes, which offers a strong rebuttal to concerns surrounding the construct validity of this task (Willner et al. 1996). Nevertheless, the SPT remains controversial and there is wide variability in SPT findings from different labs.

Based on the limitations of the SPT, investigators have developed multi-parametric measurements in conjunction with the task. The Sweet Drive Task, for instance, measures animals' preference for sweet pellets while recording ultrasonic vocalizations (USVs). CMS suppresses 50 kHz USVs (which are associated with positive emotional valence; Borges et al. 2013) in response to sweet pellets, and the number of 50 kHz USVs positively correlates with sweet preference (Mateus-Pinheiro et al. 2014). Interestingly, Riaz et al. (2015) also found an attenuation of USVs in response to social interaction, implicating a broad influence of CMS on positively valenced emotions.

Similar effects of CMS are observed in tasks that probe other facets of hedonic capacity. For instance, CMS increases intracranial self-stimulation (ICSS) thresholds (Willner 2005), such that a significantly greater intensity of stimulation is required for reinforcement in CMS-exposed vs. non-exposed animals. Conditioned place preference (CPP) paradigms are also commonly used as animal tests of anhedonia by measuring reward sensitivity toward food or drugs (e.g., Papp et al. 1991). Specifically, CPP interferes with consummatory reward processing (Scheggi et al. 2018) based on an animal's preference for an environment that was previously paired with a reward (typically food or drug). CMS reduces time spent in a compartment previously paired with food rewards (Benelli et al. 1999) or addictive drugs (Valverde et al. 1997), and this effect has been documented in both males and females (Mathews et al. 2008). In direct contrast, in adolescent rats, CMS *increases*

CPP for certain drugs (e.g., alcohol; Song et al. 2007), and this effect is more pronounced in females relative to males (e.g., amphetamine; Mathews et al. 2008). These latter results may be particularly relevant for highlighting adolescence as a key sensitive period for the development of addiction in humans (Jordan and Andersen 2017). An important limitation surrounding the CPP is that the animal's hedonic capacity can only be inferred by the amount of time spent in the reward-paired environment (Scheggi et al. 2018). Interpretations are thereby restricted to this behavioral response, offering little insight into the animal's interest or willingness to work for a reward.

Although CMS produces fairly consistent effects on hedonic capacity, far less research has examined its effects on an animal's goal-oriented actions that bring them into contact with a reward (motivational anhedonia). The Probabilistic Reward Task (PRT), which was originally validated in humans (Pizzagalli et al. 2005), assesses an animal's ability to modulate decision-making as a function of reinforcement history (Der-Avakian et al. 2013) and taps both the consummatory (hedonic) and motivational aspects of reward. CMS disrupts preferential responding for a stimulus with a high reward probability (Der-Avakian et al. 2017; Lamontagne et al. 2018). However, these effects are only observed in a subset of rats, implicating resiliency factors.

4.2 Acute Stress

As noted above, exposure to acute, avoidable, and/or controllable stress (e.g., short-term immobilization, mild footshock, mild to moderate tail shock, or tail pinch) activates the mesolimbic pathway, thereby increasing extracellular DA in the NAc and mPFC (see Holly and Miczek 2016, for review). Such mesoaccumbens dopamine release in response to acute stress is an adaptive response that enhances incentive-triggered motivation, promoting active coping as well as behavioral activation against threats. The termination of stress then acts as a negative reinforcer (Holly and Miczek 2016).

However, mesolimbic dopamine release is inhibited when stressors are prolonged, unavoidable, and/or uncontrollable, leading to reduced reward sensitivity, as well as behavioral helplessness and despair (Cabib and Puglisi-Allegra 2012). For example, while brief physical restraint increases NAc dopamine release, this effect dissipates after the fourth consecutive day of exposure (Imperato et al. 1992). Corticotropin-releasing factor (CRF) is an important mediator of the above contrasting stress response. Through coactivation of CRF receptor 1 (CRFR1) and CRFR2, CRF increases dopamine in the NAc of mice in response to mild (but not severe) stressors; however, severe stress switches the behavioral response from appetitive to aversive (Lemos et al. 2012). In adolescent rats, a single exposure to footshock facilitates acquisition of CPP to nicotine; however, pre-stress treatment with a CRFR1 antagonist blocks this effect (Brielmaier et al. 2012).

A similar dissociation in motivation for reward is observed depending on the duration of exposure. For example, acute (1 h) restraint stress reliably decreases rats' preference for a high effort/high reward option, indicating lower motivation to work for reward (Bryce and Floresco 2016; Shafiei et al. 2012). In male rats, however, this acute stress does not affect progressive ratio responding, preference for larger rewards, or tolerance for delays to reward delivery (Shafiei et al. 2012). That is, acute restraint stress reduces effort-related decision-making, but does not affect general motivated behavior, reward valuation, or delay discounting. By contrast, longer-term (6 h per day for 28 days) restraint stress produces expansive impairment across multiple reward processing domains, spanning from the acquisition of instrumental conditioning to goal-directed learning (Xu et al. 2017). However, recent research with female rats suggests that even short-term, acute stress exposure may result in generalized motivational deficits that interfere with optimal decision-making. Acute restraint stress, for instance, reduces motivation and feedback sensitivity in a probabilistic reversal learning task in female rats, as evidenced by higher omission rates, increased choice latencies, greater error commission, and reduced win-stay lose-shift tendencies (Bryce and Floresco 2021). Some research has attributed acute stress-induced reward dysfunction to aberrant phasic mesolimbic DA release (e.g., decreased phasic DA signaling likely due to presynaptic autoreceptor activation; Kumar et al. 2014), which disrupts the encoding of positive prediction errors needed for reward learning (e.g., Anstrom et al. 2009; Carvalheiro et al. 2021). This might explain domain-specific deficits in reward processing depending on the task; however, it remains unclear whether sex differences in phasic DA burst-firing explain these diverging effects seen in male and female rats. This suggests, again, that further inclusion of females in animal models and further investigation of sex differences in the effects of stress on reward processing are required to allow a translation to understanding sex differences in the development of stress-related psychopathology in humans.

4.3 Social Stress

Ethologically-relevant stressors, particularly those that emerge during social interactions between conspecifics, produce robust effects on reward processing. In a naturalistic setting, the study of dominance hierarchies shed light on competition-induced activation of the stress response. Factors such as social status and rank, which impact preferential access to resources, produce intense conflict among conspecifics, leading to the emergence of stress-related pathology (e.g., hypercortisolism; Abbott et al. 2003). In a laboratory setting, social status conflicts are commonly induced using a resident-intruder paradigm. In this model, a subordinate (intruder) rat is placed in the home territory of a same-sex dominant (resident) rat, prompting an attack (defeat) of the intruder. Social defeat, which potently activates the HPA axis, is commonly implemented as a chronic stressor; however,

a single exposure sensitizes animals to subsequent mild, nonsocial stressors (Keeney et al. 2006).

Repeated social defeat produces mixed effects on hedonic capacity. Chronic social defeat increases ICSS thresholds in rats (Der-Avakian et al. 2014), implicating its role in diminishing reward sensitivity. However, while some studies have shown reduced sucrose preference following social defeat (Miczek et al. 2011), others show no effect (Hollis et al. 2010; Riga et al. 2015). These differences may be attributable to concerns regarding the reliability and validity of the SPT, as discussed above. In tasks that probe motivated behavior, however, results are more consistent. Repeated social defeat impairs reward learning in the PRT (Der-Avakian et al. 2017), reduces motivation to work for a higher value reward (Dieterich et al. 2020a, b), and attenuates anticipatory behavior in response to reward (Von Frijtag et al. 2002). Given that each of these constructs (i.e., reward learning, effort-related choice, and appetitive behavior) is strongly mediated by DA, these more reliable findings are likely attributable to a robust effect of chronic social defeat on the DAergic system. A major drawback to the social defeat paradigm is its reliance on innate inter-male territorial aggression, necessitating the exclusive use of male subjects in this research. A female social defeat model was recently established (Takahashi et al. 2017), which will help shed light on sex differences in reward sensitivity using an ethologically relevant paradigm.

In direct contrast to the above effects, *witnessing* social defeat (i.e., vicarious social stress) has been found to *increase* sucrose preference (Pijlman et al. 2003). Vicarious stress also significantly enhances cocaine self-administration (Ramsey and Van Ree 1993). The precise reasons for this paradoxical effect are unclear. One possibility is that in the vicarious social stress paradigms, stress exposure is relatively acute, whereas in the social defeat paradigm, reward insensitivity is seen with chronic and/or repeated exposure. Indeed, *chronic* witness stress is associated with decreases in sucrose preference (Warren et al. 2013).

4.4 Maternal Separation

Maternal separation has emerged as a potent stressor that has broad and persistent effects on brain development and behavior. In the typical rodent maternal separation paradigm, pups are separated from dams and isolated for 3–4 h per day on post-natal days (PD) 1–14. Pups are then weaned at PD21 and tested in adulthood (~4–-6 months of age). In studies of male animals, maternal separation results in heightened reward sensitivity to amphetamine (Der-Avakian and Markou 2010) and sucrose (Chocyk et al. 2015), as well as increased proliferation of VTA neurons (Chocyk et al. 2015), thus suggesting that maternal separation increases consummatory reward processing. In contrast, maternal separation is associated with *decreases* in the motivation to pursue rewarding stimuli (Leventopoulos et al. 2009). More recently, studies using the Limited Bed Nesting (LBN) procedure found *reduced* sucrose preference and aberrant pleasure-reward functional connectivity in

adolescent animals exposed to LBN immediately after birth (Bolton et al. 2018). Although the LBN protocol is not directly analogous to maternal separation, the sparsely distributed nesting material in the home cage causes abnormal and fragmented maternal behaviors, resulting in heightened stress responses in pups (Molet et al. 2014). Thus, findings from the LBN procedure could help parse the effects of erratic and unpredictable maternal environments from outright maternal neglect or abandonment (i.e., separation).

In female animals, maternal separation, as well as repeated cross-fostering, also results in heightened CPP for nicotine (Dalaveri et al. 2017) and cocaine (Di Segni et al. 2019), as well as heightened sucrose preference and increased c-fos expression in the NAc, caudate, and putamen (Di Segni et al. 2019). In direct contrast, however, maternal separation plus social isolation into adolescence has been found to result in *decreased* CPP for chocolate and down-regulation of D1 receptors in NAc specifically in female, but not male, rats (Sasagawa et al. 2017). These latter results might suggest a switch from reward sensitivity to reward insensitivity through the adolescent transition particularly for females. This is intriguing given that adolescence is the period in humans during which the gender gap in rates of depression is at its highest, with females evidencing 3.5 times the rate of new depression onsets relative to males during this period (Salk et al. 2017). However, even in male animals, maternal separation potentiates the anhedonic response observed following repeated (but not acute) social defeat (Der-Avakian and Markou 2010). This result suggests that exposure to maternal separation may sensitize animals of both sexes to developing anhedonic behaviors when exposed to social stressors later in life.

4.5 Stress Response and Reward

Exogenous administration of the stress hormone corticosterone is consistently associated with decreased hedonic capacity, indexed by reduced food seeking and reduced sucrose preference, as well as decreased motivation to expend effort for reward (Dieterich et al. 2020a, b; Peng et al. 2021). However, whether differences across animals in the *endogenous* neuroendocrine response to stress predict reward behaviors is less clear, and this is an area where more research is needed. A small number of studies have addressed this question with knockout paradigms, in which responsivity to stress is experimentally manipulated. A full review of this literature goes beyond the scope of the current chapter. A couple of examples from the literature suggest, however, that animals genetically engineered for heightened neuroendocrine response to stress show blunted reward processing. Nicotinic acetylcholine receptors (nAChRs) are expressed in endocrine cells in the pituitary and adrenal glands, implicating their role in the HPA axis stress response. Male α9-nAChR knockout mice showed an exaggerated corticosterone response when exposed to both acute and sub-chronic stress (Mohammadi et al. 2017). Further, in this same study they showed reduced sucrose preference relative to wild-type mice.

Relatedly, α5-nAChR knockout mice show reduced CPP for ethanol compared to wild-type mice (Dawson et al. 2018).

4.6 Summary

Preclinical studies reveal differential effects of stress on reward processing depending on the modality, duration, and severity of the stress exposure. Chronic and/or prolonged stress (i.e., CMS, social defeat, chronic footshock) broadly disrupts both consummatory and motivational reward processing. These effects are likely driven in part by the unpredictable and uncontrollable nature of these stressors. In contrast, acute stress exposure, as well as certain forms of emotional stress (e.g., vicarious stress), at least in males, lead to mesoaccumbens activation and enhancement of reward sensitivity. These processes may be adaptive in terms of heightening behavioral activation and adaptive coping to prepare for, and/or avoid, potential harm. However, maternal separation and other potent chronic stressors early in life are also associated with heightened sensitivity to substances of abuse well into adulthood, suggesting a strong role for early stress exposure in the development of addiction. Future research is needed examining sex differences in the relation of stress exposure to reward processing. Emerging evidence suggests that female animals show greater chronic stress-induced reward dysfunction and, contrary to their male counterparts, reduced motivation after acute stress and reduced reward sensitivity in adolescence following maternal separation. As such, these findings have important implications for understanding higher rates of depression and internalizing psychopathology in the face of stress in women compared to men. Further, male animals show *heightened* approach motivation in response to acute stress and do not show the switch from reward sensitivity to insensitivity in adolescence following maternal separation. These findings may be relevant in understanding higher rates of addiction in the face of stress in men than women.

Future research is also needed to elucidate the developmental timelines of stress effects on reward. Several studies have highlighted adolescence as a period during which the effect of stress in *heightening* reward sensitivity is particularly strong. Further, and importantly, as reviewed above, the effects of stress on reward in adolescence are in some cases completely opposite to the effects of stress on reward in adulthood (e.g., Mathews et al. 2008; Sasagawa et al. 2017; Song et al. 2007). Finally, elucidating the neurobiological mechanisms underlying the role of early stress in sensitizing animals to the effects of stress later in development will help in understanding the similar sensitizing effect of childhood adversity in stress-related psychopathology in humans (Stroud 2020).

5 Relation of Stress to Reward Processing in Humans

Consistent with findings from the preclinical literature reviewed above, exposure to stress across the lifespan in humans is associated with disruptions in hedonic capacity and pursuit of reward. Research is reviewed separately for exposure to recent, proximal stressful life events and exposure to stress early in development.

5.1 Proximal Stressful Life Events

Anhedonia is a core feature of psychopathological conditions that have recent exposure to stress and trauma as central to their etiology. The diagnostic criteria for post-traumatic stress disorder (PTSD), for example, include blunted affect and loss of interest in people and activities, and the severity of anhedonia immediately following trauma exposure is the strongest symptom predictor of the development of full-blown PTSD (Feeny et al. 2000). Further, in laboratory reward tasks, individuals with PTSD expend less effort for reward, and display lower expectancy for, and satisfaction with, rewarding stimuli relative to healthy individuals. Neuroimaging findings confirm these behavioral studies, suggesting lower ventral striatal activation during reward tasks in individuals with vs. without PTSD (see Fonzo 2018 for review).

Similarly, recent life stress exposure is central to the etiology of major depression and major depression is characterized by reward deficits at multiple levels of analysis. Central to the current discussion, patients with the endogenous subtype of depression, which includes anhedonia as a criterion symptom, are especially sensitive to stressful life events, such that they require a lower level of recent stress to trigger their depression than do patients whose depression syndrome is not characterized by anhedonia (Harkness and Monroe 2002).

The first empirical evidence that stressful life event exposure may cause anhedonia even in the absence of psychopathology was provided in a study of army cadets and healthy university students by Berenbaum and Connelly (1993). Army cadets reported lower levels of pleasure when viewing rewarding stimuli on training days relative to rest days. Similarly, students reported lower pleasure in daily life during final exams relative to baseline. Intriguingly, these effects were strongest among participants with a family history of depression, suggesting that stress-related deficits in hedonic capacity may represent an endophenotypic vulnerability.

Since the early work reviewed above, a number of studies have found support for the effect of recent stress exposure on behavioral, neurophysiological, and neuroimaging indices of reduced reward function. Most intriguingly, prospective, longitudinal work with children has shown, for example, that greater exposure to stressful life events at age 7 predicts lower striatal response to reward anticipation at age 10 (Vidal-Ribas et al. 2019). Much of the recent work on stressful life events has focused on reward positivity (RewP), which is a component of the event-related

brain potential that indexes reward sensitivity. In two studies of youth, recent exposure to peer bullying was associated with lower amplitude of the RewP in response to laboratory tasks designed to elicit responses to social (i.e., peer acceptance; Ethridge et al. 2018) or monetary (Rappaport et al. 2019) reward. In particular, Ethridge et al. (2018) reported this association for relational bullying, but not for physical victimization. Subsequent longitudinal work showed that lower RewP prospectively predicted the emergence of depression symptoms in youth, but particularly in those with higher levels of exposure to stressful life events during the prospective follow-up period (Goldstein et al. 2020). Further, lower RewP has been associated with the *generation* of stressful life events over an 18-month prospective period, even when controlling for baseline depression (Mackin et al. 2019). Collectively, these findings suggest that low RewP may provide a "double-threat" vulnerability to depression by heightening individuals' generation of, and sensitivity to, stressful life events.

Neuroimaging work has confirmed the above findings and extended them to the DA-mediated motivational aspect of reward processing. For example, in a sample of healthy adults, those who reported greater proximal stress exposure showed blunted neural responses in the mPFC following both monetary gain and loss feedback (Treadway et al. 2013). Further, healthy adults who reported greater levels of perceived stress showed a blunted adaptive glutamate response in the mPFC to an acute stressor (Cooper et al. 2021). Similarly, in a sample of adolescent boys with alcohol use disorder, higher stressful life event load accumulated from ages 15–18 was associated with lower mPFC activity during monetary reward anticipation and post-reward receipt, and these neurofunctional indices significantly mediated the relation of stress exposure to the severity of alcohol dependence (Casement et al. 2016). Similarly, in a study that combined positron emission tomography (PET) with ecological momentary assessment of daily life stress, Kasanova et al. (2017) found that higher levels of daily stress exposure were significantly associated with lower reward-induced dopamine activation in the right ventral striatum, and this association was stronger in participants with a family history of psychosis compared to those without this history. Therefore, across a variety of samples, greater exposure to stressful life events has been associated with greater severity of anhedonic symptoms and lower self-reports of pleasure; lower amplitude of the RewP to reward receipt; lower striatal response to reward; and lower striatal DA activation in response to reward, as well as lower response in DA-mediated mesocortical regions (mPFC) in anticipation of, and response to, reward.

5.2 Early Adversity and Maltreatment

Early adversity is a broad category of stress exposure during childhood and adolescence that includes experiences of physical, sexual, or emotional abuse or neglect, witnessing domestic and neighborhood violence, poverty, and parent

psychopathology and substance use, among other exposures. A history of early adversity has been associated with reduced hedonic capacity. For example, in a sample of women with major depressive disorder (MDD), Harkness and Monroe (2002) reported that those with a history of severe childhood maltreatment, and particularly histories of sexual or emotional abuse, were more likely than those without to receive a diagnosis of endogenous depression, which includes anhedonia as a cardinal feature. Similarly, in a small sample of young adults, Dillon et al. (2009) reported that those with documented abuse histories presented with higher levels of anhedonia symptoms, rated reward cues less positively, and exhibited lower basal ganglia responses to reward cues, than those without this maltreatment history. Similarly, Mehta et al. (2010) reported that adolescents with histories of severe institutional deprivation (Romanian adoptees) showed blunted striatal responses to reward cues relative to comparison adolescents. Even in samples of individuals in remission from depression, those with a history of maltreatment (in this case, sexual abuse) are less likely than those without to integrate previous reinforcement to optimize future learning (Pechtel et al. 2013).

Prospective, longitudinal research has generally confirmed the above findings. In a sample of 673 adolescents followed for 6 years, Cohen et al. (2019) reported that emotional neglect, but not physical, sexual, or emotional abuse, specifically predicted the emergence of anhedonia symptoms over that time period. Similarly, in a sample of 106 11–15-year-olds, Hanson et al. (2015) reported that emotional neglect significantly predicted lower (or blunted) change in ventral striatal activity when processing monetary reward over a two-year period. Further, blunted ventral striatal reward-related activity significantly mediated the relation of neglect to the emergence of depression symptoms over that time period. Dennison et al. (2019) found similar results in a sample of children and adolescents, indicating the primacy of neglect in predicting blunted reward performance (lower number of stars earned on a reward task).

The above changes to the reward system as a result of early adversity appear to persist into adulthood. For example, in a sample of 92 men followed for 3 decades, Hanson et al. (2016) reported that higher cumulative early life stress exposure, particularly in middle childhood, predicted lower monetary reward-related ventral striatal activity at age 26, even controlling for symptoms of psychopathology (see also Birn et al. 2017). Further, integrating the above two lines of inquiry, Corral-Frías et al. (2015) reported, in a large and diverse sample of 820 adults, that lower ventral striatal activity in a reward-related task was significantly associated with higher symptoms of anhedonia specifically, but only among those with a history of early adversity.

To date, the majority of studies investigating the relation of childhood maltreatment to reward and anhedonia have focused on a composite "childhood adversity/maltreatment" variable; however, distinctions based on maltreatment type have general prognostic significance. For example, emotional abuse and neglect are more strongly associated with the onset and clinical characteristics of depression than are sexual and physical maltreatment (Valatti et al. 2020). Consistent with this, the evidence above appears to implicate childhood neglect as a preferential risk

factor for anhedonia and disrupted reward processing, particularly in the context of depression. In contrast, physical maltreatment more strongly predicts externalizing psychopathology, including addiction (Keyes et al. 2012). Therefore, it is possible that the disruptions in reward processing that characterize these disorders may have their origins in these different forms of early adversity.

5.3 Acute Laboratory Stress

As noted at the outset of this chapter, an important limitation of studies examining naturalistic stress exposure is the lack of experimental control. Those with a history of early adversity, for example, are likely to differ from those without on a whole host of variables that could be related to their likelihood of developing symptoms of anhedonia and disruptions in reward processing (e.g., a family history of psychopathology). Further, as noted above, such exposures are very heterogenous on a large number of dimensions (e.g., chronicity, severity, domain) that may also differentially affect these reward-related outcomes. Laboratory stress paradigms allow for strict control over the nature of the stressful exposure, and allow experimenters to randomly assign participants to stress vs. non-stress conditions, thereby enabling causal inferences. Typical acute stressors implemented in these paradigms include nonsocial stressors, such as threat of shock or cold water immersion ("cold pressor task"), as well as social-evaluative stressors, such as sham peer rejection (e.g., the Cyberball task; Williams and Jarvis 2006) or the presentation of a speech in front of a panel followed by a difficult arithmetic test (e.g., the Trier Social Stress Test; Kirschbaum et al. 1993). All of these stress manipulations reliably elicit a stress response in healthy individuals, as indexed through psychological (e.g., affect), neuroendocrine (e.g., cortisol release), and psychophysiological (e.g., heart rate variability) measures.

In contrast to the preclinical literature, acute stress manipulations generally impair reward-related behaviors in humans. In healthy individuals, exposure to acute laboratory stress is significantly associated with reduced reward learning (Bogdan et al. 2011; Bogdan and Pizzagalli 2006), blunted RewP (Burani et al. 2021; Ethridge et al. 2020; Zhang et al. 2020), and lower anterior cingulate and orbitofrontal cortical activation in a probabilistic reward task (Bogdan et al. 2011), as well as lower striatal activation in response to rewarding cues (e.g., sexual stimuli; Oei et al. 2014) and during a monetary guessing game (Lincoln et al. 2019). These effects were consistently seen in samples of men and women, and across adolescent and adult age groups.

A small study of 15 healthy individuals specifically distinguished between the relation of laboratory stress exposure to the anticipation phase vs. the consummatory phase of reward processing within the same paradigm. Compared to a no-stress condition, exposure to a social-evaluative laboratory stressor was associated with blunted striatal and amygdalar activity during reward *consumption* (consistent with the results reported above), but greater striatal activity during reward *anticipation*

(Kumar et al. 2014). The dissociable stress-induced effects on "wanting" and "liking" might reflect differential effects on reward-related circuitry. While some brain regions respond during both the consumption and anticipation processes (e.g., striatum, amygdala), others respond more predominantly to reward consumption (e.g., mPFC) (Knutson et al. 2001). These findings are consistent with studies reviewed in the preclinical literature that acute, controllable stress may potentiate incentive motivation and approach but blunt the "liking" of rewarding stimuli.

5.4 Stress Response and Reward

As noted at the outset of this chapter, there are wide individual differences in responsivity to stress, even when the stress exposure is controlled. Altered stress reactivity is a strong correlate of, and risk factor for, stress-related psychopathology, most notably depression and PTSD. Greater cortisol awakening response (CAR), for example, is a significant prospective predictor of the first onset of depression in adolescence (Adam et al. 2010). Further, compared to healthy individuals, the syndrome of MDD presents with higher CAR and greater cortisol release in the face of laboratory stress (Boggero et al. 2017). In contrast, chronic depression, as well as both depression and PTSD in the context of a history of childhood maltreatment, is significantly associated with blunted CAR and blunted cortisol release in laboratory stress paradigms (Boggero et al. 2017; Bunea et al. 2017). Reduced output of cortisol in response to awakening and acute stress is believed to result from resistance (i.e., desensitization) of glucocorticoid receptors due to chronic stress exposure that promotes chronic release of cortisol (Harkness et al. 2011). This literature also highlights the strong effect of childhood stress in dysregulating the stress response system and heightening the risk of onset of psychopathology in the face of future stress well into adulthood.

The small number of studies that have examined the relation of cortisol reactivity to stress and processing of reward reveal intriguing evidence of sex differences. In the samples of healthy men in these studies, greater release of cortisol, either chronically (i.e., hair cortisol) or during laboratory stress, has been associated with *greater* NAcc activation in response to rewarding sexual cues (Oei et al. 2014), *higher* reward learning over blocks of a Probabilistic Reward Task (Cunningham et al. 2021), *greater* difference in effort expended to consume rewarding vs. non-rewarding sexual cues (Chumbley et al. 2014), and *greater* striatal activation in a reward-related decision-making task (Lighthall et al. 2012). In direct contrast, in the two studies reviewed above that included women, no relation between cortisol reactivity to stress and reward processing was found in this group (Cunningham et al. 2021; Lighthall et al. 2012). Further, in a study that only included women, Berghorst et al. (2013) found that greater cortisol release and higher negative affect in the face of laboratory stress were significantly associated with *decreased* sensitivity to reward. Similarly, in their sample of 88 healthy women, Treadway et al. (2017) found that greater increases in interleukin-6 in response to the

TSST significantly predicted *lower* ventral striatal reward prediction error signaling. Interestingly, in this study, *exposure* to the TSST (vs. a control condition) was not significantly associated with striatal RPE signaling.

An intriguing interpretation of the above findings in humans is that men who mount a greater glucocorticoid response to stress may also be those most sensitive, and most motivated, to approach rewards. On the one hand, these findings may help in understanding higher rates of addictive behaviors in men than women and increases in rates of such maladaptive behaviors during periods of stress (Becker et al. 2017). Additionally, stress-related *blunting* of reward processing in women may help in understanding higher rates of depression and other internalizing conditions in women than men (Salk et al. 2017). However, evidence from the addictions literature reveals that the relation of gender to stress-related reward processing is complex. While rates of addictive behaviors are higher in men than women (Becker et al. 2017), women nevertheless are at greater risk for relapse than men, and their use appears to progress more quickly to addiction (Becker and Hu 2008). One explanation for these gender differences in the *course* of substance use may be stress *exposure*. For example, in studies of nicotine- or cocaine-dependent adults, women show greater craving, arousal, and corticostriatal-limbic hyperreactivity in response to stress cues than men (Potenza et al. 2012; Saladin et al. 2012). In contrast, men only showed corticostriatal-limbic hyperreactivity in response to drug cues (Potenza et al. 2012).

Further, in the absence of addiction, men may be more likely than women to engage in adaptive, approach-related coping behaviors when faced with stress. Intriguing evidence for positive tuning together of the stress and reward systems comes from evidence that higher reward reactivity buffers men to the effects of stress. Specifically, in a recent imaging study of healthy men, Ethridge et al. (2020) reported that men who had a higher RewP during a guessing game with monetary reward showed significantly lower cortisol responses to a subsequent social-evaluative laboratory stressor. Even stronger experimental evidence for the stress-*buffering* effects of reward comes from a study of 45 heterosexual men showing that those randomized to view erotic images showed significantly lower cortisol responses to a subsequent social-evaluative laboratory stressor than those assigned to the neutral imagery condition (Creswell et al. 2013).

5.5 Summary

A summary of the primary findings of the relation of stress to reward processing in the clinical and preclinical literatures is provided in Table 1. Exposure to stress in humans is consistently associated with blunted reward processing. This relation is seen with exposure to naturalistic stressors in childhood and adulthood, as well as exposure to tightly controlled stress in the laboratory. Further, this relation is consistent across symptom-based, behavioral, neurophysiological, and neuroimaging measures of reward processing. There is suggestive evidence that social stress,

Table 1 Summary of preclinical and clinical research findings on the relation of stress exposures and the stress response to consummatory anhedonia (reward sensitivity) and motivational anhedonia

	Consummatory anhedonia		Motivational anhedonia	
	Preclinical	Clinical	Preclinical	Clinical
Ecologically-relevant stressful life events	*Chronic social defeat* Male • reduced sucrose preference (Miczek et al. 2011; c.f. Hollis et al. 2010; Riga et al. 2015) • increased ICSS thresholds (Der-Avakian et al. 2014)	*Recent stressful life events* • reduced levels of pleasure (Berenbaum and Connelly 1993) • reduced RewP (Ethridge et al. 2018; Rappaport et al. 2019) • reduced striatal DA activation in response to reward cues (Kasanova et al. 2017)	*Chronic social defeat* Male • reduced reward learning in the PRT (Der-Avakian et al. 2017) • reduced motivation to work for reward (Dieterich et al. 2020a, b) • reduced reward anticipation (Von Frijtag et al. 2002)	*Recent stressful life events* • reduced neural responses in the mPFC following reward feedback (Casement et al. 2016; Treadway et al. 2013)
Laboratory stress paradigms	*Chronic mild stress* Male • reduced sucrose preference (Katz 1982; Mateus-Pinheiro et al. 2014) • increased ICSS thresholds (Willner 2005) • reduced CPP for food/drug (Benelli et al. 1999; Valverde et al. 1997) Female (adolescence) • greater *increases* in CPP for drug reward relative to males (Mathews et al. 2008)	*Laboratory stress challenge* • reduced striatal activation in response to reward (Kumar et al. 2014; Lincoln et al. 2019; Oei et al. 2014) • reduced RewP (Ethridge et al. 2020; Zhang et al. 2020)	*Chronic mild stress* Male • reduced bias to respond to reward in PRT (Lamontagne et al. 2018) *Uncontrollable stress (e.g., prolonged footshock/ restraint)* Male • reduced effort-related decision making, motivated behavior (Xu et al. 2017) Female • greater and more generalized motivational deficits than males (Bryce and Floresco 2021)	*Laboratory stress challenge* • reduced reward learning (Bogdan et al. 2011; Bogdan and Pizzagalli 2006) • reduced anterior cingulate and orbitofrontal cortical activation in a probabilistic reward task (Bogdan et al. 2011) • reduced striatal activation in anticipation of reward (Kumar et al. 2014; Lincoln et al. 2019; Oei et al. 2014)

(continued)

Table 1 (continued)

	Consummatory anhedonia		Motivational anhedonia	
	Preclinical	Clinical	Preclinical	Clinical
Childhood stress	*Maternal separation* Male and Female • increased reward sensitivity to sucrose and drug (Chocyk et al. 2015; Dalaveri et al. 2017; Der-Avakian and Markou 2010; Di Segni et al. 2019) • increased proliferation of VTA neurons (Chocyk et al. 2015) • increased c-fos expression in the NAc, caudate, putamen (Di Segni et al. 2019) Female (adolescence) • *reduced* CPP for chocolate and down-regulation of D1 receptors in NAc (Sasagawa et al. 2017) *Limited bed nesting* Male (adolescence) • reduced sucrose preference (Bolton et al. 2018) • aberrant pleasure-reward functional connectivity (Bolton et al. 2018)	*Childhood maltreatment* • greater severity of symptoms of anhedonia (Cohen et al. 2019; Harkness and Monroe 2002; Dillon et al. 2009) • reduced striatal responses to reward cues (Birn et al. 2017; Corral-Frías et al. 2015; Dillon et al. 2009; Hanson et al. 2015, 2016; Mehta et al. 2010)	*Maternal separation* Male • reduced motivation to pursue reward (Leventopoulous et al. 2009)	*Childhood maltreatment* • reduced ability to integrate previous reinforcement to optimize future learning and performance (Dennison et al. 2019; Pechtel et al. 2013)

(continued)

Table 1 (continued)

	Consummatory anhedonia		Motivational anhedonia	
	Preclinical	Clinical	Preclinical	Clinical
Neuroendocrine stress response	*Endogenous corticosterone (α9-nAChR knockout mice)* Male • reduced sucrose preference (Mohammadi et al. 2017). • reduced CPP for ethanol (Dawson et al. 2018)	*Cortisol hyperreactivity* Men • *greater* NAcc activation in response to rewarding sexual cues (Oei et al. 2014), Lighthall et al. 2012) Women • *Reduced* sensitivity to reward	*Exogenous administration of corticosterone* Male • reduced motivation to expend effort for reward (Dieterich et al. 2020a, b; Peng et al. 2021)	*Cortisol hyperreactivity* Men • *increased* reward learning (Cunningham et al. 2021) • *increased* effort to obtain reward (Chumbley et al. 2014) • *increased* striatal activation in reward-related decision-making (Lighthall et al. 2012) Women • No significant relation

and particularly stressors with themes of neglect, social defeat, and/or rejection, may be particularly strongly associated with anhedonia and blunted reward (e.g., Cohen et al. 2019; Dennison et al. 2019; Mehta et al. 2010); however, studies specifically comparing social and nonsocial (e.g., physical) stress exposures are needed. Further, the load of stress required to cause alterations in neurophysiological and behavioral reward processing has yet to be determined. Are major, or traumatic, events necessary, or can there be a cumulative impact of minor stressors as seen in the CMS paradigms in rodent models? Relatedly, research in both humans and rodent models suggests that stress exposure early in development is associated with heightened sensitization to stress in adolescence and adulthood (Der-Avakian and Markou 2010; Stroud 2020). Therefore, research is needed that integrates across lifetime periods of exposure to determine (a) sensitive developmental periods of first risk, and (b) additive or interactive models of cumulative risk, for disrupted reward processing. There does not appear to be a gender difference in the relation of stress *exposure* to reward processing in healthy individuals. However, the relation may be more complex in special populations, such as those with addiction. Specifically, stress exposure is more likely to *heighten* reward sensitivity in drug-dependent women relative to men, which may account for the more pernicious course of substance use disorder in women, with greater risk of escalation of use and relapse over time.

Heightened *response* to stress, however, is consistently associated with *increased* reward sensitivity in men and *blunted* reward sensitivity in women. At the most basic level, these findings highlight the importance of clearly distinguishing between stress exposure and the stress response. In particular, they suggest that gender differences in stress-related reward dysfunction are driven primarily by differences in the neurophysiological and psychological stress response systems. Hypothalamic-Pituitary-Gonadal (HPG) hormones – particularly testosterone and estradiol – have been shown to amplify sex and gender differences in the effects of stress exposure on the HPA axis stress response (Juster et al. 2016). Therefore, these hormone markers may similarly modulate sex and gender differences in the effects of stress on reward processing (Taylor et al. 2014).

Neurophysiological systems, however, are tuned throughout development in a gendered context based on social systems that perpetuate women's lower social status relative to men (Duchesne et al. 2020). Therefore, in moving this important area of research forward, more attention should be paid to understanding how environmental contexts may differentially tune stress and reward responses for individuals of intersecting gender and cultural identities. There is strong evidence, for example, that relative to men, girls and women are exposed to higher levels of the sorts of severe stressors that may sensitize neurophysiological responses to stress (Mazurka et al. 2017) and, consequently, bias reward responding to a "better safe than sorry" approach (Badcock et al. 2017). Therefore, integrating multiple levels of analysis has the greatest potential for both understanding the etiology of stress-related illness, and developing novel and personalized pharmacotherapeutic and psychological targets for intervention.

6 Disclosures

The authors have no disclosures to report.

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Part II
Anhedonia in Psychiatric and Neurological Disorders

Anhedonia in Depression and Bipolar Disorder

Alexis E. Whitton and Diego A. Pizzagalli

Contents

Abstract Anhedonia is a hallmark feature of depression and is highly prevalent among individuals with mood disorders. The history and neurobiology of anhedonia has been most extensively studied in the context of unipolar Major Depressive Disorder (MDD), with converging lines of evidence indicating that marked anhedonia heralds a more chronic and treatment-refractory illness course. Furthermore, findings from neuroimaging studies suggest that anhedonia in MDD is associated with aberrant reward-related activation in key brain reward regions, particularly blunted reward anticipation-related activation in the ventral striatum. However, the ongoing clinical challenge of treating anhedonia in the context of Bipolar Disorder (BD) also highlights important gaps in our understanding of anhedonia's prevalence,

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Curr Topics Behav Neurosci (2022) 58: 111–128
https://doi.org/10.1007/7854_2022_323
Published Online: 10 April 2022

severity, and pathophysiology along the entire mood disorder spectrum. In addition, although current theoretical models posit a key role for reward hyposensitivity in BD depression, unlike studies in MDD, studies in BD do not clearly show evidence for reduced reward-related activation in striatal or other brain regions. Although further research is needed, the evidence to date hints at a divergent pathophysiology for anhedonia in unipolar and bipolar mood disorders, which, if better understood, could lead to significant improvements in the diagnosis and treatment of MDD and BD.

Keywords Anhedonia · Bipolar disorder · Epidemiology · Major depressive disorder · Neuroimaging · Phenomenology · Reward processing

1 Introduction

Although anhedonia is present across many psychiatric conditions, depression is perhaps its most paradigmatic disorder. This chapter provides a historical overview of the role of anhedonia in depression and its prevalence across Major Depressive Disorder (MDD) and Bipolar Disorder (BD). Complementing these epidemiological studies, we highlight qualitative studies describing the phenomenology of anhedonia, focusing on how the subjective experience of anhedonia in individuals with mood disorders extends beyond the loss of pleasure described in current diagnostic classification systems. Drawing upon these separate lines of evidence, we also highlight quantitative and qualitative differences in anhedonia in unipolar and bipolar mood disorders. Next, we provide a critical review of studies outlining the clinical significance of anhedonia, focusing on whether anhedonia and markers of its underlying neural circuitry hold utility for predicting mood disorder trajectory and treatment response. Finally, we briefly outline the current understanding of the neurobiological underpinnings of anhedonia in the context of mood disorders, focusing on how functioning in neural reward pathways goes awry in MDD and BD. Importantly, we comment on the degree to which a shared or distinct pathophysiology may underpin anhedonia in unipolar relative to bipolar mood disorders. Taken together, this overview will provide the reader with a broad knowledge of where the field stands in terms of our ability to better understand, identify, and treat anhedonia in the context of mood disorders.

2 History, Epidemiology, and Phenomenology of Anhedonia in Mood Disorders

2.1 Anhedonia as a Diagnostic Criterion for Depression

Descriptions of anhedonia have featured prominently in clinical texts on depression (or "melancholia"), dating back to the nineteenth century. In 1889, English physiologist William Bevan Lewis published *A Text-Book of Mental Diseases* (Lewis 1889), which included an analysis of 4,000 cases of mental illness treated at the West Riding Asylum, where he worked as Medical Director. In describing states of depression, he noted that "The patient exhibits a growing indifference to his former pursuits and pleasures: the ordinary duties of life and business become irksome and devoid of interest." (pp. 143–144). Around this time, the term anhedonia was formally defined by French psychologist Théodule-Armand Ribot as the "inability to experience pleasure," and proposed as a state antithetical to analgesia (i.e., the absence of pain; Ribot 1896). The marked impact of anhedonia on patients' quality of life is also evident in these early texts. In 1934, prominent psychiatrist Aubrey J. Lewis published a detailed analysis of 61 cases of mental illness treated at the Maudsley Hospital in London, where he was an Assistant Medical Officer. He observed how frequently depressed patients who had traveled from picturesque regions across Europe "...mention this failure to enjoy the sight of their fields, the sky and the trees and the flowers as one of the most distressing of their symptoms, a deprivation most keenly felt." (Lewis 1934 p. 331).

Although anhedonia was common in accounts of depression, several prominent clinicians noted the marked variability in how anhedonia manifested from patient to patient. In the early twentieth century, there was a growing interest in describing "subtypes" of depression that were more homogeneous in their clinical presentation. In *The Varieties of Religious Experience,* American psychologist William James described a particular form of depression characterized by a "passive joylessness" and "loss of appetite for all life's values." (James 1902). The notion of depressive subtypes was later formalized by American psychiatrist Donald F. Klein, who proposed the existence of "endogenomorphic depression," a unique type of depression characterized by a "sharp, unreactive, pervasive impairment of the capacity to experience pleasure or to respond effectively to the anticipation of pleasure" (Klein 1974, p. 449).

Despite descriptions of anhedonia featuring prominently in early psychiatric texts, it was not until Klein's work on endogenomorphic depression that anhedonia was included in the formal diagnostic criteria for depression. The symptom first appeared in the DSM-III (APA 1980), where it was listed among the diagnostic criteria for melancholia. With the release of the DSM-IV (APA 1994), a specifier was added to denote a subtype of depression "With Melancholic Features," which described individuals with a "near-complete absence of the capacity for pleasure, not entirely diminution." In the current DSM-5 (APA 2013) the melancholic specifier has been retained, with the intended purpose of identifying a more homogeneous

subgroup of depressed individuals who experience marked impairments in hedonic capacity. However, the degree to which this specifier serves its intended purpose remains a topic of debate. Using criteria from the DSM-5, Fried et al. (2020) calculated 10,377 unique symptom combinations that could yield a diagnosis of MDD. However, they found that there were as many as 341,737 different symptom combinations that could yield a diagnosis of MDD with Melancholic Features, challenging the notion that the melancholic specifier identifies a more homogeneous subgroup of depressed individuals.

In contrast to the rich descriptions of anhedonia documented in accounts of individuals with unipolar MDD, much less is known about the history of anhedonia in the context of BD. This may in part reflect an emphasis on the unique qualities of BD mania, as well as an assumption that depressive episodes across unipolar and bipolar mood disorders are of the same nature and kind. However, research into the neurobiology of mood disorders highlights several important points of divergence between unipolar and bipolar mood pathology. Accordingly, although the DSM criteria for a Major Depressive Episode is identical across MDD and BD, more thorough descriptive accounts of BD depression may yield important insights into the degree to which hedonic disturbances overlap and diverge across the mood disorder spectrum.

2.2 Epidemiology of Anhedonia in Mood Disorders

2.2.1 Prevalence of Anhedonia in Mood Disorders

Anhedonia is highly prevalent among individuals with mood disorders. When defined using the cut-off for clinical anhedonia on the Snaith-Hamilton Pleasure Scale ($\geq$3), anhedonia prevalence is approximately 70% in individuals with MDD (Cao et al. 2019) and 52% in individuals with BD depression (Mazza et al. 2009). Anhedonic symptoms often persist when other symptoms remit, contributing to increased inter-episode functional impairment. For example, in a study comparing the prevalence of anhedonia in euthymic individuals with BD, individuals in remission from MDD, and healthy controls, Di Nicola et al. (2013) found that one fifth of individuals with BD and one quarter of individuals with MDD had clinically significant anhedonia, despite scoring in the non-clinical range on measures of depression and mania. Although current diagnostic criteria conceptualize anhedonia as a state-like feature of a Major Depressive Episode, evidence of significant inter-episode anhedonia in individuals with mood disorders suggests that it may have a more enduring, trait-like quality.

2.2.2 Severity of Anhedonia Across Distinct Mood Disorder Diagnoses

To date, the findings from studies comparing self-reported or clinician-assessed anhedonia severity in MDD and BD samples have been mixed. Some studies report equivalent levels of anhedonia in individuals with BD and MDD in either depressed (Mula et al. 2010; Perlis et al. 2006) or euthymic (Di Nicola et al. 2013) states. In contrast, others have reported more severe anhedonia in adults with MDD than in adults with BD (Souery et al. 2012), whereas others report more severe anhedonia in youth with BD than in youth with MDD (Diler et al. 2017). The findings from studies comparing different forms of anhedonia across BD and MDD samples are also inconsistent, with some showing differences in anticipatory pleasure (Mitchell 2001), and others showing differences in consummatory pleasure (Zou et al. 2020) between the two disorders.

An important factor that likely underpins these discrepant findings is that MDD and BD samples are rarely matched on overall illness severity. Studies demonstrating more severe anhedonia in youth with BD compared to youth with MDD may reflect the fact that younger-onset BD tends to be a more severe form of the illness (Perlis et al. 2004). Similarly, evidence of more severe anhedonia in BD type II compared to BD type I (e.g., Dimick et al. 2021) may reflect the more pervasive depressive symptomatology observed in BD type II (Karanti et al. 2020). Studies using MDD and BD samples that are matched in terms of illness severity are needed to better understand differences in anhedonia severity between the two conditions.

2.3 Anhedonia Phenomenology

In the DSM-5, anhedonia is defined as a "Markedly diminished interest or pleasure in all, or almost all, activities" (APA 2013). Although this definition has changed very little since the term was first introduced by Ribot (1896), findings from phenomenological studies suggest that the actual experience of anhedonia likely encompasses a broader array of hedonic impairments, as well as their sequelae. Phenomenological studies focus on the lived experience of individuals with mental illness and provide rich insights into the features of psychiatric disorders that are most salient and/or disabling. In addition to loss of pleasure, phenomenological studies highlight the important role of loss of drive, connection, and purpose in the subjective experience of anhedonia. Watson et al. (2020) recently highlighted four key themes related to anhedonia, which emerged from a series of interviews with depressed adolescents. Two primary themes centered on the loss of joy and flattening of emotions, and difficulty with motivation and active engagement. Specifically, participants described feelings of boredom, monotony, and indifference to events happening around them. Two secondary themes also emerged: losing a sense of connection and belonging, and questioning sense of self and purpose. In particular, participants noted feeling disconnected from their social world and losing their sense

of what was important in life. Similar themes were described in a recent qualitative study in depressed adults, where "...inertia, the lack of motivation, the lack of meaning in life..." was identified as one of the most distressing aspects of living with depression (Chevance et al. 2020).

Findings from phenomenological studies are interesting for several reasons. First, they illustrate the breadth of anhedonic experiences that may need to be addressed in the clinical management of mood disorders. In particular, they demonstrate that reductions in motivational drive are a salient feature of depression that have marked impacts on daily functioning. Whether reductions in motivational drive are a consequence of reduced capacity for pleasure or reflect a primary disturbance distinct from other aspects of hedonic functioning remains an important unanswered question. Furthermore, themes emerging from phenomenological research highlight important links between loss of pleasure and other aspects of depression that, despite having a significant impact on quality of life, do not feature prominently in the modern discourse on mood disorders. One such example is depersonalization, a common feature of depression characterized by a sense of detachment from oneself and the world. Individuals experiencing depersonalization often describe themselves as functioning on autopilot without purpose, and as if the world and those around them have taken on an unfamiliar quality. Watson et al.'s (2020) findings hint at the important links between anhedonia and an individual's feelings of connection to their physical and social world, and the impact this may have on their sense of meaning and purpose in life. Gaining a better understanding of these links may help to shed light on the processes that underpin some of depression's more complex and nebulous features.

3 Clinical Significance of Anhedonia in Mood Disorders

3.1 Association with Illness Course

Converging lines of evidence suggest that anhedonia is associated with a more severe and recurrent illness course in the context of mood disorders. Cross-sectional studies show that increasing levels of anhedonia in adolescents with MDD are associated with a greater number of prior depressive episodes, longer depressive episode duration, and greater overall illness severity (Gabbay et al. 2015). Similarly, longitudinal studies in adults with MDD indicate that more severe levels of anhedonia predict a greater likelihood of depression still being present 12 months later (Spijker et al. 2001). These effects are not limited to unipolar MDD. For example, in youth with BD, severe lifetime anhedonia has been found to predict more severe lifetime mania (Dimick et al. 2021). These studies indicate that the presence of marked anhedonia may herald a more severe illness course across the mood disorder spectrum.

Anhedonia has also been linked to greater risk for suicidality, rendering it a potential indicator of patients who may require more intensive treatment and

monitoring. Heightened levels of anhedonia have been found to be associated with increased suicidal ideation cross-sectionally (Ballard et al. 2017; Ducasse et al. 2018) and longitudinally in mood disordered samples (Ducasse et al. 2021), with some studies showing that associations also extend to increased risk for suicide attempts (Fawcett et al. 1990; Sagud et al., 2021). Importantly, these associations remain significant when controlling for overall depression severity, suggesting that anhedonia may be a risk factor of suicidality independent from depression more generally.

3.2 Association with Treatment Response

Studies examining anhedonia's links with treatment response typically focus on one of two questions: (1) Does pre-treatment anhedonia severity predict treatment responsiveness? (2) Does treatment improve anhedonic symptoms? Here we review studies addressing the first of these questions, while the second is addressed in detail in Part V "Treatments".

Several studies have shown that in individuals with MDD, greater levels of anhedonia at the outset of treatment predict poorer responsiveness to a range of interventions, including antidepressant pharmacotherapy (Dunlop et al. 2020; Uher et al. 2012), cognitive behavioral therapy (Craske et al. 2016), and repetitive transcranial magnetic stimulation (Downar et al. 2014). The most consistent findings have emerged for selective serotonin reuptake inhibitors (SSRIs), where pre-treatment anhedonia predicts longer time to remission and fewer depression-free days following SSRI treatment (McMakin et al. 2012). These findings are corroborated by studies showing that behavioral and neural indices of reward processing predict treatment response in individuals with MDD. For example, studies using behavioral reward learning tasks have found that poorer pre-treatment reward learning or reward sensitivity is associated with poorer response to psychotherapy and/or pharmacotherapy (Ang et al. 2020; Vrieze et al. 2013; Whitton et al. 2020). Similarly, studies examining patterns of reward-related brain activation either using electroencephalography or fMRI have observed associations between blunted pre-treatment neural reward responsiveness and poorer response to psychotherapy (Webb et al. 2021) and pharmacotherapy (Whitton et al. 2020). Similar patterns have been observed for studies examining functional connectivity of corticostriatal circuits (An et al. 2019; Downar et al. 2014; Walsh et al. 2017). An important caveat is that few studies have included multiple active treatment arms, making it difficult to determine whether pre-treatment anhedonia/reward processing predicts response to a specific treatment or the persistence of depressive symptoms more generally. One of the few studies that has used multiple comparator treatments provides initial evidence that anhedonia/reward processing measures may predict responsiveness to dopaminergic pharmacotherapy (e.g., Ang et al. 2020), consistent with the critical role that dopaminergic abnormalities are thought to play in reward processing. Specifically, this study showed that more

normative pre-treatment reward learning and resting state corticostriatal functional connectivity predicted better response to the atypical antidepressant bupropion after failing 8 weeks of SSRI treatment (Ang et al. 2020).

In contrast, little is known about the relationship between pre-treatment anhedonia and response to BD-specific psychotherapy or pharmacotherapy (e.g., interpersonal and social rhythm therapy or mood stabilizers). The majority of the studies examining anhedonia as a predictor of treatment response have focused solely on samples with unipolar MDD, or mixed MDD and BD depression samples (e.g., Downar et al. 2014), and comprehensive studies of treatment response indicators in BD have not examined anhedonia and/or reward processing as separate predictors (e.g., Hui et al. 2019; Kleindienst et al. 2005). To date, the literature in BD has focused more closely on other clinical features, such as increased emotional reactivity and lability, as being predictive of treatment outcomes. For example, in a recent multisite study examining predictors of response to lithium in individuals with BD, Lin et al. (2021) found that treatment responsiveness was most closely related to pre-treatment anxiety and the presence of mixed episodes (i.e., mood episodes characterized by both depression and (hypo)manic symptoms). It is possible that distinct aspects of affective dysfunction relate to treatment outcome in MDD and BD, with anhedonia playing a prominent role in MDD and mood lability being more relevant in the case of BD. However, given the paucity of studies examining anhedonia as a predictor of treatment response in BD, future studies comparing distinct predictors in the same cohort are required to confirm this.

4 Neurobiology of Anhedonia in Mood Disorders

Research into the neurobiology of anhedonia in mood disorders has focused most closely on dysfunction in the domains of reward anticipation, reward consumption, and reward learning. Reward anticipation describes the ability to represent future incentives, while reward consumption captures the ability to compute the value of a reward as a function of its magnitude, predictability, time to expected delivery, and the effort required to obtain it. Reward learning integrates anticipatory and consummatory processes and encompasses mechanisms involved in learning about reward-predictive cues and how outcomes shape subsequent behavior.

Each of these processes maps onto overlapping yet partially distinct neural circuitry (for reviews, see Der-Avakian and Markou 2012; Husain and Roiser 2018). Although a comprehensive review of the neural circuitry implicated in various reward subdomains is beyond the scope of this chapter (for reviews, see Borsini et al. 2020; Haber and Knutson 2010; Höflich et al. 2019; Russo and Nestler 2013), it is important to emphasize the key role of the dopaminergic mesolimbic pathway. This pathway originates in the ventral tegmental area (VTA) and projects to the ventral (e.g., nucleus accumbens) and dorsal (e.g., caudate, putamen) striatum, and subsequently the prefrontal cortex (PFC), including the medial PFC and anterior cingulate cortex (ACC), among other regions. Relevant to our discussion, ventral

striatal regions have been found to be critically implicated in incentive motivation and reward prediction errors (RPEs; i.e., evaluating that an outcome is different than expected), whereas dorsal striatal regions have been involved in stimulus-response-reward learning (i.e., linking incentives to actions); medial PFC and orbitofrontal cortex (OFC) regions have been implicated in stimulus-reinforcement representations, including updating such representations to guide behavior; finally, the dorsal ACC has been involved in integrating reward probabilities over time.

4.1 Neural Correlates of Reward Processing in MDD

4.1.1 Blunted Anticipation-Related Activation in the Ventral Striatum as a Trait-Like Feature of MDD

Reduced striatal activation during reward anticipation is one of the most common findings in neuroimaging studies of reward processing in MDD. Meta-analyses show that compared to healthy controls, individuals with MDD exhibit blunted activation in the ventral striatum during anticipation of reward (Keren et al. 2018). Similar findings have been observed in asymptomatic individuals who are at increased familial risk for MDD (Olino et al. 2014), suggesting that blunted anticipation-related striatal activation may be a trait-like vulnerability marker for MDD. In adolescents, blunted anticipation-related ventral striatum activation has also been found to predict increases in depressive symptom severity over 2 years (Morgan et al. 2013), as well as new depression onset and concurrent anhedonia longitudinally (Stringaris et al. 2015), suggesting that this marker is associated with depressive illness course. Finally, changes in anticipation-related ventral striatal activation during SSRI treatment have been found to be associated with changes in depressive symptom severity (Takamura et al. 2017), suggesting that normalizing aberrant anticipation-related activation in the ventral striatum may be important for the clinical effectiveness of antidepressant treatments.

4.1.2 Disrupted Corticostriatal Activation to Reward Outcome (Consumption) in MDD

Reduced activation in ventral (nucleus accumbens) and dorsal (caudate, putamen) striatum, ACC, and OFC, as well as potentiated activation in various PFC regions (medial PFC, ventromedial PFC, and dorsolateral PFC) has emerged in tasks probing consummatory anhedonia (Borsini et al. 2020; O'Callaghan and Stringaris 2019; Zhang et al. 2016), with PFC over-recruitment thought to reflect over-compensation for reduced striatal activation (Forbes et al. 2009; O'Callaghan and Stringaris 2019; Pan et al. 2017). Blunted reward consumption-related ventral striatal activation has also been dimensionally linked to anhedonia severity (Epstein et al. 2006). Functional connectivity between reward hubs (nucleus accumbens,

VTA, OFC) and the ventromedial PFC while listening to pleasant music correlated negatively with anhedonia (Young et al. 2016). Finally, although striatal responses to rewards normalize after depression remission (Geugies et al. 2019), other abnormalities persist, including blunted OFC activation to reward receipt (Dichter et al. 2012) and reduced maintenance of ventral striatal responses to positive cues (Admon and Pizzagalli 2015).

4.1.3 Disrupted Reward Prediction Errors in MDD

Studies using computational modeling to quantify expected value and RPEs in MDD have generally reported reduced RPE in the ventral and dorsal striatum (Gradin et al. 2011; Kumar et al. 2008, 2018), ACC (Rupprechter et al. 2020; Ubl et al. 2015) and medial OFC (Rothkirch et al. 2017), although null findings have emerged (Rutledge et al. 2017). In a study using an instrumental reinforcement learning task, MDD was characterized by reduced medial OFC and ventral striatal RPE, which correlated with anhedonia severity (Rothkirch et al. 2017). Of note, larger ventral striatum RPE has also been found to predict reductions in anhedonia 6 months later (Eckstrand et al. 2019). In addition, although individuals in remission from MDD show normative ventral striatum RPE, VTA RPE remained upregulated, indicating that some reward-related abnormalities persist after remission (Geugies et al. 2019). Collectively, these findings suggest that blunted valuation of expected rewards and reward learning might represent MDD-related vulnerabilities.

4.2 Neurobiology of Reward Processing in BD

Theoretical models of BD posit that mania and depression are underpinned by excessive activation and deactivation of brain reward responsiveness, respectively (Bart et al. 2021). Such models have considerable face validity in terms of explaining the hyper-hedonic symptoms of mania (e.g., spending sprees, excessive sociability) and anhedonic symptoms of BD depression. However, findings from neuroimaging studies are far from conclusive, and few have examined neural correlates of anhedonia in the context of BD.

4.2.1 Heightened Reward-Related Activation in the Lateral OFC Characterizes BD

One of the most consistent findings in fMRI studies in BD is increased left lateral OFC (particularly left ventrolateral PFC) activation during reward anticipation. This has been observed across all mood states, including depression (Chase et al. 2013), mania (Bermpohl et al. 2010) as well as during inter-episode periods of euthymia (Nusslock et al. 2012), and in both BD type I (Bermpohl et al. 2010; Chase et al.

2013; Nusslock et al. 2012) and BD type II (Caseras et al. 2013). Similar patterns of activation have also been observed in unaffected first-degree relatives (Cattarinussi et al. 2019), suggesting that abnormal reward-related left lateral OFC activation may be a trait-like vulnerability marker for BD. Some studies have found that this aberrant activation extends to consummatory processes, with heightened consumption-related lateral OFC activation being found in individuals with subthreshold hypomanic symptoms (O'Sullivan et al. 2011), euthymic BD (Linke et al. 2012; Mason et al. 2014), and in unaffected first-degree relatives (Linke et al. 2012). The left ventrolateral PFC has been implicated in evaluating cues denoting the probability of immediate future reward (Coffman et al. 2021), hence, aberrant left ventrolateral PFC function might underpin sensation seeking and impulsivity in BD.

4.2.2 Mixed Pattern of Striatal Activation in Response to Reward in BD

Unlike studies in unipolar MDD, studies in individuals with BD depression do not consistently demonstrate blunted striatal responses to rewards. For example, some studies have shown decreased striatal responses during reward consumption in individuals with BD depression relative to both healthy controls and individuals with MDD (Redlich et al. 2015). Other studies have found no differences in striatal activation (Chase et al. 2013; Satterthwaite et al. 2015) or even increased striatal activation to reward when under stress (Berghorst et al. 2016) in depressed individuals with BD relative to controls. Studies of reward learning in BD have also yielded mixed findings. Studies using behavioral probabilistic reward learning tasks have reported evidence of poorer reward learning in euthymic or mildly depressed individuals with BD relative to controls (Pizzagalli et al. 2008). However, studies using this same task have produced mixed findings depending on whether the BD sample was treatment-seeking (e.g., Whitton et al. 2021) or had psychotic features (Lewandowski et al. 2016). One of the few studies to examine striatal RPE signals during a reinforcement learning task also found no differences between healthy controls or individuals with BD (Whitton et al. 2021). The variability in these findings compared to those in MDD may be attributable to greater use of medicated samples in BD research and different patterns of comorbidity. For example, studies examining striatal responses to reward in BD have used samples where nearly all individuals were taking psychotropic medication, whereas meta-analyses of neural reward responsiveness in individuals with MDD indicate that more than 80% of participants were unmedicated (Keren et al. 2018). However, an alternate possibility is that the hedonic deficits observed in BD depression may be fundamentally different from those in unipolar MDD. If true, this would prompt a revision of theoretical models of BD depression and the role reward hyposensitivity may play in this aspect of the illness. For example, rather than showing blunted responses to reward, individuals with BD depression may show increased sensitivity to reward loss, or a greater sensitivity to differences between expected and actual outcomes regardless of the valence of the outcome. Given that these processes are thought to be underpinned by partially distinct neural pathways, further clarity on these issues could highlight novel treatment targets for BD depression.

4.3 Differences in Reward-Related Brain Activation Between MDD and BD

Given the overlap in clinical presentation between MDD and BD during the depressive phase of the illness and the fact that recollection of prior (hypo)manic episodes in individuals with BD is not always clear, neural markers capable of distinguishing between these two conditions may aid in improving diagnostic precision. Toward this end, Chase et al. (2013) found that depressed individuals with BD showed increased anticipation-related activation in the left ventrolateral PFC compared to those with MDD, despite comparable disease severity. A recent study that included BD individuals in a variety of mood states also found evidence for decreased reward anticipation-related ventral striatal activation in individuals with BD relative to those with MDD (Schwarz et al. 2020). Similar findings were observed by Redlich et al. (2015) in terms of consumption-related activation, where those with BD depression showed decreased reward consumption-related activation in the striatum, thalamus, insula, and PFC relative to individuals with MDD. These studies highlight quantitative differences in neural reward processing in MDD and BD depression, suggesting that hedonic disturbances in these conditions may partly diverge in terms of their underlying causes.

5 Summary

Findings from epidemiological, phenomenological, and neuroimaging studies summarized in this chapter emphasize the clinical significance of anhedonia in mood disorders, and the critical role that anhedonia treatments will play in reducing the global burden of these disorders. Although vulnerability markers and treatment targets for anhedonia are emerging in the context of unipolar MDD, our understanding of anhedonia's causes in BD remain limited, contributing to the clinical challenges inherent in treating BD depression. Finally, despite overlapping in their clinical features, studies highlight potential divergence in anhedonia pathophysiology in MDD and BD. Future research is needed to better understand these points of divergence, as they hold significant clinical utility for improving the early diagnosis and treatment of mood disorders.

Acknowledgements and Disclosures Dr. Pizzagalli was partially supported by R37 MH068376 and P50 MH119467. Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Neumora Therapeutics (former BlackThorn Therapeutics), Boehringer Ingelheim, Compass Pathways, Concert Pharmaceuticals, Engrail Therapeutics, Neurocrine Biosciences, Neuroscience Software, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; honoraria from Springer (for editorial work) and Alkermes, and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, and

Millennium Pharmaceuticals. In addition, he has received stock options from Neumora Therapeutics (former BlackThorn Therapeutics), Compass Pathways, and Neuroscience Software. Dr. Whitton has no financial disclosures, and there are no conflicts of interest with the work conducted in this study. All views expressed are solely those of the authors.

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Anhedonia in Schizophrenia

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Contents

Abstract Anhedonia has long been considered a cardinal symptom of schizophrenia. This symptom is strongly associated with poor functional outcome, and limited

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Curr Topics Behav Neurosci (2022) 58: 129–146
https://doi.org/10.1007/7854_2022_321
Published Online: 3 May 2022

treatment options are available. While originally conceptualized as an inability to experience pleasure, recent work has consistently shown that individuals with schizophrenia have an intact capacity to experience pleasure in-the-moment. Adjacent work in basic affective neuroscience has broadened the conceptualization of anhedonia to include not only the capacity to experience pleasure but highlights important temporal affective dynamics and decision-making processes that go awry in schizophrenia. Here we detail these mechanisms for emotional and motivational impairment in people with schizophrenia including: (1) initial response to reward; (2) reward anticipation; (3) reward learning; (4) effort-cost decision-making; (5) working memory and cognitive control. We will review studies that utilized various types of rewards (e.g., monetary, social), in order to draw conclusions regarding whether findings vary by reward type. We will then discuss how modern assessment methods may best incorporate each of the mechanisms, to provide a more fine-grained understanding of anhedonia in individuals with schizophrenia. We will close by providing a discussion of relevant future directions.

Keywords Anhedonia · Motivation · Reward · Schizophrenia

1 Anhedonia as a Cardinal Symptom of Schizophrenia

Anhedonia, traditionally defined as the diminished capacity to experience pleasure, has long been considered a core clinical feature of schizophrenia (SZ) and is associated with poor functional outcomes (e.g., Mueser et al. 1991). There are limited treatment options for targeting this critical symptom, partially because the mechanisms driving anhedonia in SZ are not yet fully understood. As such, both the field of SZ research broadly and the Research Domain Criteria (RDoC) initiative have recognized the centrality of examining emotional experience, motivation and incentive processing to better understand mechanisms at play. More specifically, the RDoC Matrix includes a "positive valence" systems (PVS) domain (Insel et al. 2010) outlining several constructs that may be critical to understanding mechanisms of anhedonia and motivational impairments in SZ. We describe various components of the RDoC PVS below.

2 A Heuristic Model of the Motivation-Action-Outcome Pathway

The RDoC PVS contains three superordinate constructs: Reward responsiveness, reward learning, and reward valuation. Reward responsiveness includes sub-constructs of initial response to reward, reward anticipation, and reward satiation. Reward learning includes sub-constructs of habit, probabilistic and

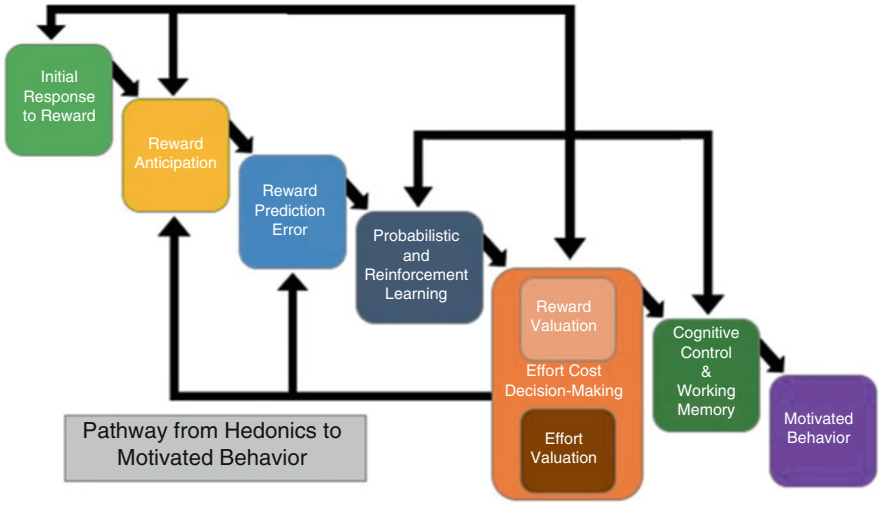

Fig. 1 Pathway from hedonics to motivated behavior

reinforcement learning, and reward prediction error. Reward valuation includes sub-constructs of probability, delay, and effort. Our group has used a complementary model to link experienced or anticipated rewards with the action plans that need to be generated and maintained to obtain these rewards (Kring and Barch 2014). Below, we describe the components within this model, which are thought to be of critical importance when conceptualizing anhedonia in SZ.

In our model (see Fig. 1), the first component is initial response to reward (a subconstruct of reward responsiveness in the RDoC PVS), but has also been referred to as hedonics or liking. Initial response to reward captures the ability to "enjoy" a stimulus or event in the moment, and is what is most closely linked to historical definitions of anhedonia. The second component is reward anticipation (a subconstruct of reward responsiveness in the RDoC PVS) and has also been described as wanting. The third component, probabilistic and reinforcement learning (a subconstruct of reward learning in the RDoC PVS), involves how individuals associate rewarding or punishing outcomes with particular actions (i.e., reward learning). Importantly, such learning can be either implicit (i.e., outside of conscious awareness) or explicit (i.e., including the use of explicit representations about potential reward associations). The fourth component is reward valuation in the RDoC PVS. There are a number of components to reward valuation, including integrating information about the intrinsic hedonic properties of a stimulus, the current state of the organism (Rolls et al. 1989), delay until a reward can occur (Rudebeck et al. 2006), the probability that a reward will occur (Cools et al. 2002), and other potential rewards that are available in the environment. The fifth component in our model is the ability to compute effort relative to reward value (a subconstruct of reward valuation in the RDoC PVS), or what we refer to as effort-cost decision-making (ECDM). ECDM refers to determining the cost of

engaging in actions necessary to obtain a desired outcome and determining how much of that cost you are willing to undertake, or how much effort you are willing to allocate. Finally, the sixth component in our model, cognitive control and working memory (constructs in the cognitive systems RDoC), involves the ability to generate and execute goal-directed action plans necessary to achieve the valued outcome. While not in the RDoC PVS, we consider this component to be an important mechanism for understanding anhedonia as it is necessary to integrate reward information (e.g., anticipatory response, value of reward) while utilizing cognitive systems to generate and maintain internal representations of potential reward to guide behavior. Below we summarize previous research that has examined components of our model in people with SZ.

3 Mechanisms

3.1 Initial Response to Reward

A majority of studies show that people with SZ report similar levels of positive emotion in the presence of evocative stimuli (e.g., pictures, film clips, food) relative to controls (see Cohen and Minor 2010 for review). This intact experience of pleasure in response to evocative stimuli has been shown via self-report and psychophysiologic measures (see Kring and Moran 2008 for review). Similarly, neuroimaging studies examining striatal responses to the receipt of monetary rewards in SZ have shown a consistent pattern of intact responses, with robust ventral striatal responses to the receipt of money in patients (see Radua et al. 2015 for review). However, some of these studies did report abnormal cortical responses to reward receipt. For example, prior work has noted reduced reward-related responses in medial prefrontal cortex (PFC) (Schlagenhauf et al. 2009), abnormal responses in both medial and lateral PFC (Waltz et al. 2010), and reduced salience coding in ventrolateral PFC in SZ (Waltz et al. 2010). Additionally, while some have not found evidence of reduced response to positive stimuli in the ventral striatum, this reduced activation was associated with higher anhedonia ratings in SZ (Dowd and Barch 2010).

While asociality, a limited desire to spend time with others, may suggest a reduction in pleasure in social situations, the research is mixed on pleasure in response to social rewards in SZ. Ecological momentary assessment (EMA) literature suggests that while people with SZ report a preference for being alone, they report greater positive emotion when around others than when alone and similar levels of positive emotion when around others relative to controls (see Mote and Fulford 2020 for review). Similarly, individuals with SZ have similar levels of positive emotion during social role play tasks relative to controls (Aghevli et al. 2003; Blanchard et al. 2015). However, while there were no group differences in positive affect following social interactions, higher negative symptoms in SZ were related to less positive affect in response to interactions (Blanchard et al. 2015).

Further, other work suggests that individuals with SZ find smiles less rewarding than controls (Catalano et al. 2018) and show reduced activation for social rewards in the ventral striatum, anterior cingulate, and ventromedial PFC relative to controls (Lee et al. 2019). Thus, across studies there is consistent evidence that people with SZ report experiencing pleasure in response to rewards such as pictures/film clips, monetary rewards, and while spending time with others. This extends to neuroimaging studies showing intact striatal responses to positive pictures (Ursu et al. 2011) or monetary reward (e.g., Dowd and Barch 2012). However, there is also evidence of reduced sensitivity to social reward cues such as a smiling face or cooperative social behavior and this reduced sensitivity may be related to negative symptoms and anhedonia in particular.

3.2 Reward Anticipation and Reinforcement Learning

3.2.1 Reward Anticipation

There is a mixed literature on anticipated pleasure in SZ. For example, some studies assessing anticipatory pleasure via retrospective self-report measures (Gard et al. 2007) and anticipation to evocative stimuli (e.g., pictures) show reduced anticipated pleasure relative to controls (e.g., Moran and Kring 2018). Further, some studies have found that decreased anticipatory responses have been shown to be related to negative symptoms including anhedonia (e.g., Gard et al. 2007). However, other studies do not find a difference in self-reported anticipatory pleasure (Frost and Strauss 2016). While there are relatively few behavioral studies directly measuring reward anticipation/prediction in SZ, these studies show evidence for reduced anticipation (Heerey and Gold 2007; Moran and Kring 2018). Much of the focus instead has been on neuroimaging studies, which have reported reduced ventral striatum activity to cues predicting food (Grimm et al. 2012) or monetary reward in SZ relative to controls (for review, see Radua et al. 2015). These results have been found in unmedicated individuals with SZ (Nielsen et al. 2018) and medicated individuals with SZ (Moran et al. 2019). However, these deficits may not be present in individuals taking atypical medication (Juckel et al. 2006). Other work has noted reduced ventral striatal responses to anticipation cues in antipsychotic-naïve SZ patients, which improved following atypical antipsychotic treatment (Nielsen et al. 2012). In addition, disruptions in ventral striatal activity during anticipation of reward has been associated with anhedonia in SZ (e.g., Dowd and Barch 2012).

Only a handful of studies assessed anticipation of social interactions, with findings suggesting reduced anticipatory pleasure for social interactions/rewards. Laboratory social interaction studies have found that people with SZ anticipated more negative emotion during a social inclusion task (Engel et al. 2016) and anticipate less pleasure for social interactions with smiling partners (Campellone and Kring 2018). Similar to studies examining anticipation of monetary reward, when anticipating a social reward, individuals with SZ showed blunting of striatal

regions relative to controls (Schwarz et al. 2020). And further, an EMA study found a trend in people with SZ anticipating social activities as being less enjoyable than controls (Gard et al. 2014). Thus, consistent with literature showing disrupted anticipatory responses in SZ in response to evocative stimuli and monetary rewards, research suggests disrupted anticipatory responses to social rewards; however, more research is needed to further clarify how and when anticipation for social interactions is disrupted and its relationship to anhedonia.

3.2.2 Reinforcement Learning and Prediction Error

Intriguingly, several behavioral studies have suggested that reinforcement learning in response to monetary gain is intact in SZ when learning is fairly implicit (e.g., Barch et al. 2017). Similarly, several studies using the Weather Prediction task have shown a relatively intact learning rate, but impaired asymptotic performance, which provides mixed evidence for striatal learning impairments (Kéri et al. 2005). When the paradigms become more difficult and require the explicit use of representations about stimulus-reward contingencies, individuals with SZ show more consistent evidence of impaired reinforcement learning (e.g., Culbreth et al. 2016a). Interestingly, these impairments may be greater when individuals with SZ must learn from reward versus from punishment and have consistently been related to anhedonia and motivational impairments in SZ (e.g., Gold et al. 2012). A number of studies have also shown altered prediction error responses (e.g., differences between expected and observed outcomes) in SZ (Radua et al. 2015), both in terms of reductions in responses to unpredicted rewards and larger than expected responses to predicted rewards (Reinen et al. 2016). However, this finding does not appear to be consistent across all patients as other studies have found intact prediction error responses in the striatum among medicated individuals (Culbreth et al. 2017), and even evidence for increased prediction error responses in medicated patients (White et al. 2015). Thus, further work is needed to understand under what conditions prediction error responses are intact in SZ in order to further understand the specific computational mechanisms that may underlie aberrant reinforcement learning.

While the majority of reinforcement learning literature has focused on learning via monetary reward, a growing literature has shown that learning from social rewards (e.g., a smiling face, trusting behavior) follows a similar pattern of learning and activates similar neural circuitry including the ventral striatal and orbital frontal cortex (e.g., Jones et al. 2011). Only a handful of studies have assessed social reinforcement learning in SZ, usually via social trust laboratory tasks. In a series of behavioral trust experiments, people with SZ failed to use social feedback to adapt their trusting behavior, thus suggesting a reduced ability to learn from social rewards relative to controls (Fett et al. 2012; Hanssen et al. 2020). Similarly, another study found that people with SZ showed less trust in smiling partners relative to controls, but were sensitive to negative social outcomes (e.g., scowling face) (Campellone et al. 2016). Thus similar to learning from monetary reward, SZ may be sensitive to

learning from negative but not positive (gaining money, or smiling faces) outcomes but more work is needed on social learning and its symptom correlates in SZ.

3.3 Effort Valuation

The last decade has seen a burgeoning of research on effort allocation and its relationship to anhedonia and motivation processing. Physical effort to receive monetary reward studies has found relatively consistent evidence for impairment in SZ (e.g., Reddy et al. 2015). The majority of studies found that the degree of reduction in effort allocation was associated with either negative symptoms (e.g., Gold et al. 2013) or functional status (Barch et al. 2014). Several recent studies have also examined cognitive effort allocation for monetary reward in SZ. One study using a progressive ratio task found evidence for reduced effort allocation in SZ (Wolf et al. 2014). Further, recent work utilizing a cognitive effort paradigm that assesses discounting of rewards as a function of effort found impaired cognitive effort allocation in SZ (Culbreth et al. 2016b). In contrast, others have found little evidence of reduced cognitive effort in SZ, though these studies did suggest that individuals with SZ had difficulty detecting variations in cognitive effect among conditions (Gold et al. 2015).

Only a few studies have examined the neural correlates of aberrant effort-based decision-making in SZ. Our group showed that BOLD activation while making decisions about cognitive effort was similar in controls and SZ participants. However, reduced BOLD activation in the ventral striatum was associated with negative symptoms (Culbreth et al. 2020). Similarly, an additional study showed greater BOLD activation in the ventral striatum during effort-based choice was associated with greater willingness to exert physical effort across both individuals with SZ and control (Huang et al. 2016). Another study showed somewhat surprisingly greater activation of the caudate for individuals with SZ compared to controls as a function of effort. However, this task did not include a choice, but rather required individuals to perform either a hard or easy option, thus it is not clear if these findings relate to the larger effort-based decision-making literature. Based on this small number of studies, the literature suggests potential contributions to effort-based decision-making deficits in SZ from the ventral striatum and that these deficits are related to negative symptoms, though clearly more work is needed in this domain.

To the best of our knowledge, there has only been one study that has examined effort-based decision-making for social rewards in SZ. Participants with SZ and controls completed a button pressing effort task under a social encouragement (e.g., a confederate cheered the participant on) and a neutral condition (e.g., a confederate sat quietly). Both groups showed increased vigor (i.e., more rapid button pressing) during the social encouragement condition, suggesting that people with SZ show normative levels of effort exertion in the context of social encouragement (Fulford et al. 2018). Further, clinician rated social withdrawal was associated with reduced effort across both social and non-social conditions. Thus, while one study suggests

social encouragement has a similar effect on people with and without SZ, further work is needed to understand effort-based decision-making in social contexts and its relationship to anhedonia.

3.4 Cognitive Control and Goal-Directed Action

Numerous reviews have outlined the evidence for impairments in goal representation and cognitive control in SZ (e.g., Barch and Ceaser 2012), as well as the evidence for altered activation, connectivity, and structure of brain regions such as the dorsolateral prefrontal cortex (DLPFC) (e.g., Minzenberg et al. 2009). Several studies suggest that individuals with SZ are not able to improve their performance on cognitive tasks when offered monetary incentives (e.g., Rassovsky et al. 2005). A study examining whether or not individuals with SZ could improve cognitive control on a response inhibition task found that patients were able to speed their responses when presented with specific cues about winning money, and to a certain extent could speed their responses on trials in the reward "context" even when they could not earn money, an effect thought to reflect the maintenance of reward information through proactive control mechanisms. However, individuals with SZ showed a significantly smaller incentive context effect than controls (Mann et al. 2013). In an fMRI study examining whether monetary incentives modulate DLPFC activity during a cognitive control task in SZ, results found no behavioral differences between patients and controls and found a somewhat intact pattern of increased sustained DLPFC activity during rewarded blocks in individuals with SZ as a group. However, individual differences in anhedonia symptom severity were associated with reduced sustained DLPFC activation in the same region that showed overall increased activity as a function of reward (Chung and Barch 2016).

The bulk of research examining the use of rewards to improve cognitive task performance has focused on monetary rewards. However, there is a growing literature examining other forms of rewards such as liquids and social stimuli in healthy populations. In controls, research has found that performance on a cognitive control task was greater on positively valenced liquid feedback trials relative to neutral valenced liquid feedback (e.g., Yee et al. 2016). Work examining social reward's influence on cognitive control found that social stimuli (i.e., short dynamic facial responses) did not significantly improve cognitive control performance in controls; however, it did relate to greater positive affect suggesting that social feedback was interpreted but may not be as powerful as rewards such as juice or money (Crawford et al. 2020). To the best of our knowledge, no studies have examined social rewards impact on cognitive task performance in SZ but it will be important for future work to examine whether the benefits seen in utilizing monetary rewards to boost cognitive performance extend to other reward types such as liquid or social reward types.

There has also been a myriad of work describing interactions between cognitive control/working memory and reinforcement learning processes in SZ. For example, Collins and colleagues published a series of studies suggesting that working memory

impairments may make a significant contribution to reinforcement learning deficits in SZ (Collins et al. 2017). In addition, there is a literature reporting altered activity in cortical regions involved in cognitive control during anticipation/prediction error (Gilleen et al. 2015) and during reinforcement learning (e.g., Culbreth et al. 2016a). These results are consistent with the literature documenting altered cognitive control function in SZ, and point to a need to examine interactions between these control systems and dopamine-mediated reinforcement learning systems.

4 Using Technology to Assess Anhedonia in Daily Life

Research examining anhedonia in SZ has typically involved relating experimental measures, thought to probe the aforementioned mechanisms of anhedonia, to interview-based assessments of anhedonia. Newer interview-based measures have been developed that better reflect our current understanding of anhedonia in SZ (e.g., Brief Negative Symptom Scale (BNSS) Kirkpatrick et al. 2010; Clinical Assessment Interview for Negative Symptoms (CAINS) Kring et al. 2013), allowing for a more accurate way to examine relationships between experimental tasks and clinical interviews. An adjacent literature has taken advantage of technological advances to assess anhedonia in daily life using mobile-based applications (see Fig. 2). Mobile assessments can capture emotional experience and motivated behavior in a variety of contexts as they unfold (i.e., public settings, with other vs. alone), and these contexts may be integral to understanding anhedonia. Below, we discuss current work in this area and areas for future investigation.

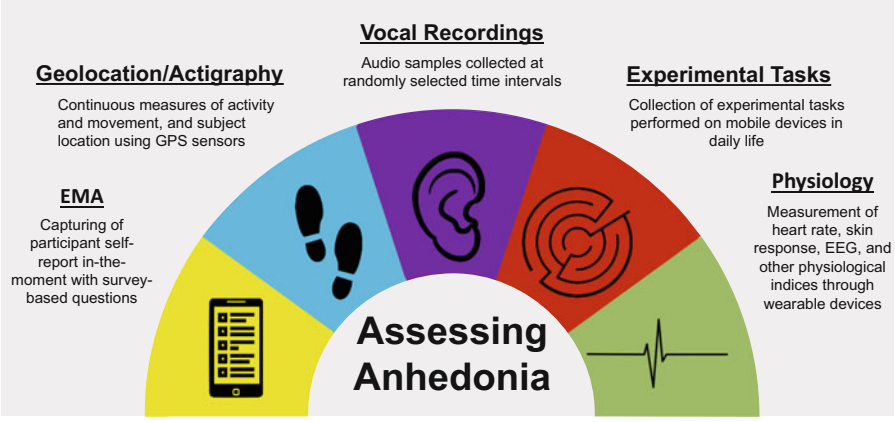

Fig. 2 Methods of assessing anhedonia utilizing mobile technology

4.1 Ecological Momentary Assessment

Ecological Momentary Assessment (EMA) utilizes smartphone technology to capture experiences as they occur in daily life (Stone and Shiffman 1994). A number of studies have used EMA to help better understand the emotion and motivation in the daily lives of people with SZ. Studies assessing emotion in daily life typically find that individuals with SZ report less positive and more negative affect when compared to controls (see Cho et al. 2017 for review). While this result may seem to contrast with previously described experimental work suggesting intact hedonic capacity in SZ, it is important to consider that ratings of positive and negative affect via EMA are not necessarily linked to a particular experience or behavior, let alone an experience or behavior that is standardized across participants (e.g., tasting a cookie, receiving money). Thus, EMA helps to extend our understanding of anhedonia in SZ to suggest that while the capacity to experience pleasure in the moment may be intact, the actual experience of pleasure throughout their daily lives may be reduced relative to controls.

EMA studies have also yielded important contextual information by clarifying emotional experience in specific contexts. As reviewed above, in social situations people with SZ report greater levels of positive affect with others compared to being alone, suggesting that social context is important for emotional experience (Mote and Fulford 2020). Further, EMA has aided mechanistic understanding of anhedonia. For example, regarding experience of effort in daily life, one study showed that people with SZ reported engaging in less effortful behaviors and setting less effortful goals than controls (Gard et al. 2014). Taken together, recent EMA studies have begun to delineate how anhedonia may manifest in the daily lives of people with SZ and point to important contexts for future study.

Several recent studies have attempted to integrate EMA methods with experimental tasks to link mechanisms relevant to anhedonia in SZ with measures of daily emotional experience. Our group found that poorer performance on a reward learning task and reduced willingness to expend effort on a physical effort task were related to decreased enjoyment and motivation in daily life (Moran et al. 2017). Similarly, another study linked better performance on a reward learning task to greater dopamine activity in striatal, caudate, and putamen during reward learning and to more reward-related behavior in daily life (Kasanova et al. 2017). Further, another study showed that people with SZ who reported greater anticipatory pleasure in daily life showed greater BOLD activation of putamen, caudate insula, and cingulate when anticipating future reward (Moran et al. 2019). These studies highlight that tasks and clinical assessments thought to tap into mechanisms relevant to EMA are relating to emotional experiences in daily life, thus giving us evidence supporting models developed based on laboratory tests and providing future directions for improved understanding.

4.2 Mobile Sensing Applications

A more recent literature is looking to get a snapshot of people outside the laboratory utilizing passive sensing data. Passive sensing allows collection of data outside of self-report to get a sense of a person's functioning across a variety of measures, without burdening the participant with frequent questions. Passive sensing can involve a number of different measures assessed via mobile technology including such things as social behavior (e.g., calls received, text messages sent), physical activity (number of steps taken, GPS location, accelerometer), environmental surroundings (e.g., ambient light, ambient noise), phone usage (e.g., apps used, number of phone pickups), physiologic recordings (e.g., heart rate variability), and sleep (e.g., Ben-Zeev et al. 2016).

Perhaps the most frequently studied metric for passive data in SZ thus far are measures of movement. In terms of actigraphy, lower levels of motor activity have been associated with higher levels of negative symptoms (including anhedonia) in people with SZ (see Wee et al. 2019 for review). Further, multiple GPS studies have found that people with SZ exhibit lower average distance traveled, distance traveled from home, and a higher rate of samples at home when compared to controls (e.g., Depp et al. 2019; Raugh et al. 2020). Importantly, these GPS measures are related to symptoms, such that patients experiencing the greatest severity of anhedonia have the greatest reduction in GPS measures. Thus, participants with SZ demonstrate reduced measures of mobility compared to controls. To date, studies in SZ have not attempted to integrate experimental task with measures of participant mobility, nor have many studies contextualized EMA self-report of daily experience through simultaneous collection of GPS or actigraphy measures. Such analyses represent a critical next step as researchers attempt to understand how anhedonia manifests in the daily lives of SZ patients and attempt to link objective measures of movement to particular experimental task variables. Finally, to the best of our knowledge, only a handful of studies have examined physiologic measures such as electrodermal activity or heart rate variability in psychosis outside of the lab, however, there are a number of exciting avenues for future work (Reinertsen and Clifford 2018). One study did find that combining physiologic measures with EMA outside the lab was feasible in a psychosis population and that variables such as electrodermal activity were significantly related to symptoms reported via EMA (Cella et al. 2019).

In regard to social experience, a few studies have sought to better understand social experience in people with SZ utilizing passive data. For example, one study found that stability in social activity measured via sensing data (e.g., frequency of calls and text messages) was associated with reduced symptoms in a SZ population (He-Yueya et al. 2020). Recent research has also used a collection of short audio or video recordings collected at randomly selected time intervals. These recordings can then be coded for a variety of different social metrics (e.g., number of voices, participant engagement in conversation, vocal intonation, facial expression). For example, one study using this method found that people with SZ interacted with others at similar rates as controls but the quality of the interaction was reduced

relative to controls (Abel et al. 2021). Another study coded these random audio recordings for social interactions and found that they were moderately correlated with measures of clinician rated social functioning measures in SZ, however showed little relationship with EMA ratings of social interaction in daily life (Abel and Minor 2021). A study of vocal and facial features found that both vocal and facial features were significantly related to social engagement and clinician rated negative symptoms (Cohen et al. 2020). Thus, findings suggest that passive sensing data such as audio, video, and phone usage metrics collected in daily life may be a useful way of gaining additional insight into the social functioning and negative symptoms in people with SZ. Future work is needed to continue to clarify what these various data streams relate to and how to code them for questions of interest.

4.3 Deploying Experimental Tasks on Mobile Devices

A small number of studies have begun deploying experimental tasks, similar to those described in the aforementioned sections, onto mobile phones as a means to understand the temporal dynamics of task performance as well as how specific contexts may affect task performance (e.g., Moore et al. 2017; Weizenbaum et al. 2020). For example, one study in elderly participants found that performance on a memory and semantic reasoning task improved following intellectually stimulating activity (Allard et al. 2014). In the domain of reinforcement learning, one study collected repeated tasks assessments on a mobile phone in non-psychiatric healthy controls and found evidence of both slow and fast learning processes over the course of a week (Eldar et al. 2018). However, studies using such methods to probe temporal dynamics and contextual effects of processes relevant to anhedonia in SZ have not been conducted to date, representing an important avenue for future research.

5 Summary

Anhedonia has long been considered a cardinal symptom of SZ, which is strongly associated with poor functional outcome. Throughout this chapter, we have provided evidence for a heuristic model of anhedonia in SZ, wherein disruption of various component processes (e.g., reward anticipation, effort valuation) results in alterations in emotional experience and reductions in motivated behavior. We argue that future research is needed to better clarify the temporal dynamics of such component processes, the contexts in which they extend (e.g., social and monetary rewards) as well as how these processes unfold and manifest in daily life.

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Anhedonia, Hyperkatifeia, and Negative Reinforcement in Substance Use Disorders

George F. Koob

Contents

Abstract Drug addiction has been defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take a drug or stimulus, the loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug or stimulus is prevented, a component of which is anhedonia. The present review explores a heuristic framework for understanding the role of anhedonia in addiction, in which anhedonia is a key component of hyperkatifeia (conceptualized as the potentiated intensity of negative emotional/motivational symptoms during drug withdrawal) and negative reinforcement in addiction. The neural substrates that mediate such anhedonia and crosstalk between elements of hyperkatifeia that contribute to anhedonia are then explored, including crosstalk between physical pain and emotional pain systems. The present review explores current knowledge of neurochemical neurocircuitry changes that are associated with conditioned hyperkatifeia/anhedonia. The overall hypothesis is that the shift in motivation toward negative reinforcement in addiction reflects the allostatic misregulation of hedonic tone, such that drug taking makes anhedonia worse during the process of

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Curr Topics Behav Neurosci (2022) 58: 147–166
https://doi.org/10.1007/7854_2021_288
Published Online: 3 February 2022

seeking temporary relief by compulsive drug taking, thereby perpetuating the addiction cycle and hedonic comorbidities that are associated with addiction.

Keywords Addiction · Anhedonia · Hyperkatifeia · Negative reinforcement · Substance use disorders

1 Addiction, Hyperkatifeia, and Anhedonia: Definitions and Heuristic Framework

1.1 Addiction, Hyperkatifeia, Anhedonia, Negative Reinforcement, and Opponent Process

Drug addiction, or substance use disorder (American Psychiatric Association 2013), has been defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take a drug or stimulus, the loss of control in limiting intake, and the emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) when access to the drug or stimulus is prevented (Koob and Le Moal 2008). This latter negative emotional state that is associated with withdrawal from chronic drug misuse has been termed hyperkatifeia (Shurman et al. 2010), providing a focal point for the role of anhedonia in addiction and recognition of the intersection of anhedonia, addiction, and mental illness that afflict society.

Hyperkatifeia (derived from the Greek *katifeia* for dejection or negative emotional state) is defined as an increase in intensity of the constellation of negative emotional or motivational signs and symptoms of withdrawal from drugs of abuse. Hyperkatifeia can be considered an emotional parallel to hyperalgesia (i.e., greater sensitivity to physical pain) that is observed with the repeated administration of chronic opioids and alcohol (Shurman et al. 2010; Koob 2020). Such an overactive negative emotional state is also hypothesized to sensitize with repeated drug exposure and withdrawal and drive negative reinforcement (Ahmed and Koob 2005). The construct of hyperkatifeia embraces all motivational signs of withdrawal that characterize the withdrawal/negative affect stage of the addiction cycle in humans, including chronic irritability, sleep disturbances, malaise, dysphoria, pain, emotional pain, and anhedonia.

Anhedonia is generally defined as a psychological condition that is characterized by an inability to experience pleasure in normally pleasurable acts, specifically defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), as "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day" (American Psychiatric Association 2013). Thus, anhedonia is the inability to derive pleasure from situations and stimuli that normally induce pleasure or hedonia. This simple definition of less pleasure from situations and stimuli that normally induce pleasure or hedonia is a common element of withdrawal from all drugs of abuse (Koob 2017) and considered, for the purposes

of this chapter, to be a subset of the hypersensitivity to negative emotional states that is defined as hyperkatifeia.

In humans, anhedonia includes both social anhedonia, such as a disinterest in social contact and a lack of pleasure in social situations, and physical anhedonia, such as the inability to feel tactile pleasures, such as eating, touching, or sex (Chapman et al. 1976). As such, symptoms of anhedonia include social withdrawal, a lack of relationships or withdrawal from previous relationships, negative feelings toward yourself and others, reduced emotional abilities (e.g., fewer verbal or non-verbal expressions), difficulty adjusting to social situations, a loss of libido or a lack of interest in physical intimacy, and persistent physical problems (e.g., often being ill; Whitton et al. 2015). Some have also argued that anhedonia also extends to impairments in learning about pleasure, which may not always be accessible to conscious awareness (Thomsen 2015), a position that is relevant to the conditioning of negative emotional states in addiction.

After increasing for decades, life expectancy in the United States began to decline in 2014, with drugs and alcohol playing a prominent role in this decline. Case and Deaton (2015) postulated that the decline in life expectancy was driven by deaths from drug and alcohol overdoses, alcohol-related liver disease, and suicide. They referred to such deaths as "deaths of despair" because they are linked to declining quality of life, including reductions of physical and mental health, increases in chronic pain, financial difficulties, and serious mental illness. Initial studies of the epidemiology of "deaths of despair" showed that they were particularly prominent among non-Hispanic whites aged 45–54 with less than a high school education (Case and Deaton 2015; Shanahan et al. 2019). However, recent reports suggest that measures of despair (e.g., depressive symptoms and suicidal ideation) and deaths from drug and alcohol overdoses, suicides, and alcohol-related cirrhosis are increasing among people in mid-life across gender, racial, and ethnic groups (Woolf and Schoomaker 2019). The focus of the present review is the way in which addiction is driven by hyperkatifeia, a key component of which is anhedonia, providing insights into an allostatic framework that perpetuates deaths of despair (Koob et al. 2020).

A heuristic framework for studying addiction, characterized by a three-stage cycle (binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation), provides a starting point for exploring the theme that anhedonia is a salient motivational component of addiction (Koob and Le Moal 1997; Koob 2020). In the three-stage cycle framework, dysfunction occurs in three domains that reflect three stages of the addiction cycle: incentive salience/pathological habits in the binge/intoxication stage, negative emotional states in the withdrawal/negative affect stage, and executive function in the preoccupation/anticipation stage. The three stages feed into each other and become more intense, ultimately leading to the pathological state known as addiction (Koob and Le Moal 1997).

These three domains and stages are hypothesized to be mediated by three major neurocircuits: basal ganglia, extended amygdala, and prefrontal cortex, respectively (Koob and Le Moal 1997). For thorough reviews and more detailed explorations of the neurobiology of addiction using this heuristic framework, see Koob and Le Moal (2008), Koob and Volkow (2010), Koob and Volkow (2016), Kwako et al. (2019),

Voon et al. (2020), Koob (2020), and Koob (2021). From a theoretical perspective, excessive drug taking in the binge/intoxication stage has been hypothesized to drive drug seeking, incentive salience, and pathological habits but simultaneously allostatic-like alterations of hedonic processing, in which the over-engagement of reward (hedonic) activity triggers compensatory responses in the brain reward and stress systems to generate negative emotional states that are associated with the withdrawal/negative affect stage and preoccupation/anticipation stage (Koob and Le Moal 1997), thereby generating a second motivational drive from negative reinforcement. Protracted abstinence incorporates residual elements of negative emotional states and cue and contextual craving to form the preoccupation/anticipation stage.

Positive reinforcement and drug reward have historically dominated as driving motivational constructs in addiction. Much is known about the neurocircuits that are engaged in drug reinforcement and, by extrapolation, the positive hedonic effects of drugs. However, a growing focus of addiction research is on another major motivational source that drives and perpetuates addiction, namely negative reinforcement. Negative reinforcement can be defined as an increase in the probability of a response that is produced by the removal of an aversive event. In the context of addiction, negative reinforcement is manifest by an individual who works to reduce, terminate, or prevent the negative emotional state of drug withdrawal or hyperkatifeia. As noted above, the argument herein is that anhedonia is a critical component of hyperkatifeia.

The argument that hyperkatifeia is a driving force in negative reinforcement in addiction has its roots in opponent process theory. In pharmacology, counteradaptations have long been shown to result from initial drug action and be opposite in valence (Martin 1968; Himmelsbach 1943). In opponent process theory, hedonic counteradaptations, in particular, were hypothesized to explain how the initial acute hedonic effects of a drug are opposed or counteracted by homeostatic changes in systems that mediate primary effects of the drug (Solomon 1980; Solomon and Corbit 1973, 1974; Koob and Bloom 1988). Indeed, opponent process theory was argued to be a general phenomenon that is associated with hedonic breaks from homeostasis, including fear conditioning, tonic immobility, ulcer formation, eating disorders, jogging, peer separation, glucose preference, and even skydiving (Solomon 1980; Solomon and Corbit 1973, 1974).

In opponent process theory, affective control mechanisms in the brain were hypothesized to serve as an emotional stabilization system that counteracts or opposes departures from emotional neutrality or equilibrium (Solomon and Corbit 1974). A negative feed-forward control construct was theorized that maintains mood in homeostatic balance, even with strong perturbations. Under this framework, the first, initial use of a drug triggers a primary affective process (a positive hedonic process), termed the *a-process*, that has a short time constant. The signal from the *a-process* triggers an opposing *b-process*, which responds with a slow rise and slow decay. For drugs that produce positive hedonic effects, the *b-process* presents as an aversive negative emotional state and is described as intensely aversive, consequently reducing hedonic intensity of the *a-process* (Solomon and Corbit 1974). These two opposing responses are temporally linked (*a* triggers *b*), with the

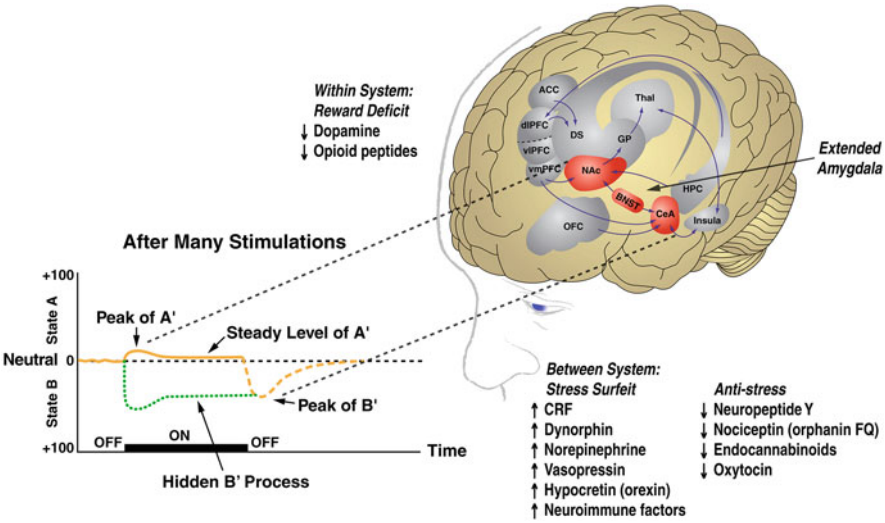

Fig. 1 Neurocircuitry relevant to allostatic changes in the extended amygdala associated with the withdrawal/negative affect stage of the addiction cycle. Neurotransmitters/neuromodulators that are associated with within-system neuroadaptations and between-system neuroadaptations are listed. Neurotransmitter systems that are activated in neurocircuitry of the extended amygdala to convey hyperkatifeia/anhedonia are indicated by upward arrows. Neurotransmitter systems with lower activity to convey hyperkatifeia/anhedonia are indicated by downward arrows. The bottom left plot illustrates the hypothetical opponent process basis of hyperkatifeia/anhedonia and the hypothesized exaggerated *b-process* that reflects hyperkatifeia/anhedonia and contributes to apparent tolerance. *NAc* nucleus accumbens, *ACC* anterior cingulate cortex, *BLA* basolateral amygdala, *BNST* bed nucleus of the stria terminalis, *CeA* central nucleus of the amygdala, *CRF* corticotropin-releasing factor, *DGP* dorsal globus pallidus, *dlPFC* dorsolateral prefrontal cortex, *NE* norepinephrine, *OFC* orbitofrontal cortex, *vlPFC* and *vmPFC* ventral prefrontal cortex. (Modified with permission from Koob and Schulkin 2019)

b-process subtracting the impact of the already existing *a-process* (Fig. 1). With repeated stimulation (e.g., with repeated drug taking to the point of dependence), the *b-process* is strengthened so that it has a faster onset and greater intensity and takes longer to decay (Solomon and Corbit 1974). Opponent process presents an interaction with tolerance, in which masking of the *a-process* by the ever-growing *b-process* is hypothesized to contribute to tolerance in what has been termed "apparent tolerance" (Laulin et al. 1999; Colpaert 1996). As a result, a greater amount and more frequent use of the previously rewarding drug is needed to maintain or approach euthymia.

1.2 *Learned Hyperkatifeia/Anhedonia and Conditioned Negative Reinforcement*

Previously neutral cues that are conditioned to drug taking can acquire conditioned positive reinforcing properties, and these cues can also stimulate drug seeking, termed incentive salience. However, cues can also be paired with unpleasant somatic and emotional states during acute withdrawal and acquire aversive properties that signal stress and promote relapse, termed conditioned withdrawal. In humans, most studies of conditioned withdrawal have involved opioids. Here, patients with opioid use disorder who are given an opioid receptor antagonist exhibit precipitated opioid withdrawal, and previously neutral stimuli that are paired with this withdrawal also elicit withdrawal (O'Brien et al. 1977; Wikler 1973). In animal studies, using place conditioning, contextual cues were paired with injections of naloxone in opioid-dependent rodents. The rodents then developed aversion to the chamber that was previously paired with naloxone (Schulteis et al. 1994). Cues that are paired with withdrawal can also have motivational (incentive salience) properties in opioid-dependent laboratory animals, in which conditioned-withdrawal cues increase their responding for an opioid (Goldberg et al. 1969; Carmack et al. 2019; Kenny et al. 2006).

Many human studies have focused on cues that are associated with drug taking that come to elicit conditioned positive reinforcing effects, reflecting craving, particularly in psychostimulant addiction. However, for opioid and alcohol addiction, craving has historically been associated with conditioned hyperkatifeia. For example, when the individual with addiction feels that heroin is available, they experience a dysphoric response that may be marked by classically conditioned abstinence but also by anxiety and tension (Meyer and Mirin 1979). For alcohol, some have argued that craving is engaged in situations that evoke feeling states that are likely to produce physiological effects that resemble characteristics of withdrawal from alcohol: "under these situations, the alcoholic is more likely to believe he needs a drink to alleviate his perceived distress" (Ludwig 1975, p. 7).

Indeed, in alcohol use disorder, negative emotional states have been strongly linked to relapse (Marlatt 1969, 1985; Marlatt and Gordon 1980). In a large-scale replication of Marlatt's taxonomy analysis, the leading precipitant of relapse was negative affect (Lowman et al. 1996). Others found that negative emotion, including elements of anger, frustration, sadness, anxiety, and guilt, was a key factor in relapse (Zywiak et al. 1996).

Such studies suggest yet another potential source of motivation for drug seeking in addiction, namely escape from impending symptoms of emotional discomfort (i.e., hyperkatifeia and anhedonia) that are associated with withdrawal. In human subjects with opioid use disorder, avoiding the onset of conditioned-withdrawal symptoms may be a major motivation for continuing opioid use and is associated with successful escape or the avoidance of negative emotional states (i.e., relief; Baker et al. 2004). This motivation can be considered conditioned negative reinforcement (Pergolizzi Jr et al. 2020; Weiss et al. 2014; Bentzley et al. 2015).

In alcohol use disorder, conditioned responses to alcohol cues can be both agonistic and antagonistic, and an individual will drink if positive outcome expectancy is attached to drinking (Drummond et al. 1990). Given that most relapse occurs under conditions of negative emotional states as noted above, it follows that this may set the stage for conditioned negative reinforcement, in which drug-related cues also gain motivational power from the ability of such cues to produce temporary relief from withdrawal. Indeed, Pavlovian cues that were associated with opioids and alcohol were hypothesized to temporarily block opioid and alcohol withdrawal in humans (Lynch et al. 1973). Indeed, saline injections can substitute, temporarily sustaining a "high" (and blocking withdrawal) for the opioid in dependent individuals (O'Brien 1974). One preclinical study showed that the cue-associated delivery of low doses of morphine actually caused a reduction of somatic and behavioral signs of opioid withdrawal (Lal et al. 1976). Changes in neuroendocrine responses that were observed in subjects with alcohol use disorder following the consumption of a placebo beer were associated with psychophysiological and subjective responses that generally occurred before or shortly after beverage consumption (Dolinsky et al. 1987).

2 Neurochemical Neurocircuitry Mediating Hyperkatifeia/Anhedonia

The neurocircuitry that is involved in mediating hyperkatifeia/anhedonia derives from both preclinical animal studies and clinical, largely imaging, studies. Many clinical studies documented hyperkatifeia during withdrawal from all drugs, of which a significant component is anhedonia. For example, for psychostimulants, a cardinal symptom of the "crash" phase is anhedonia (Gawin and Kleber 1986). Dysphoria is characteristic of both spontaneous and precipitated opioid withdrawal in humans (Handelsman et al. 1992; Kanof et al. 1992).

In animal studies, one salient measure of anhedonia-like responses is the elevation of brain stimulation reward thresholds during acute spontaneous or precipitated withdrawal from all drugs of addiction (Koob 2017), including cocaine, amphetamine, opioids, cannabinoids, nicotine, and alcohol, and some of these elevations of reward thresholds can persist for up to 1 week (Koob 2017). Perhaps even more compelling is that rodents that are allowed extended access to all drugs of addiction with extended access exhibit elevations of brain reward thresholds that parallel the increase in drug taking (Koob 2015). In the domain of reward function, rapid acute tolerance and opponent process-like effects in response to the hedonic effects of cocaine have been reported in human studies, and individuals actually report "dysphoria," even despite having high blood levels of cocaine (Breiter et al. 1997). Similar observations have been quantified in animal models of intravenous cocaine self-administration, in which elevations of reward thresholds begin rapidly and can be observed within a single session of self-administration (Kenny et al. 2003).

Analogous effects have been observed with acute precipitated withdrawal from morphine and alcohol (Liu and Schulteis 2004; Schulteis and Liu 2006). Altogether, these results demonstrate that the elevation of brain reward thresholds following drugs occurs during initial administration, and they fail to return to baseline levels between repeated, prolonged exposure and show residual hysteresis, thus creating a progressively greater elevation of brain reward thresholds and supporting the hedonic allostasis model of drug addiction.

From a theoretic perspective, counteradaptive processes that are related to addiction were hypothesized to be mediated by two processes: within-system neuroadaptations and between-system neuroadaptations (Koob and Bloom 1988). Within-system neuroadaptations were defined as the process by which the primary cellular response element to the drug adapts to neutralize the drug's effects. Persistence of the opposing effects after the drug disappears produces adaptation. A between-system neuroadaptation was hypothesized to be a circuitry change, in which another, opposing circuit was activated by the reward circuit, and activity in this circuit counteracted the reward effects. Both within- and between-system neuroadaptations contribute to the development of hyperkatifeia and also anhedonia.

The neuroanatomical substrates of hyperkatifeia/anhedonia are hypothesized to encompass a neuroanatomical construct known as the "extended amygdala." The extended amygdala is composed of the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and a transition zone in the medial subregion of the nucleus accumbens (shell of the nucleus accumbens), regions that have cytoarchitectural similarities and similar neuroanatomical connections (Heimer and Alheid 1991; Alheid et al. 1995). The extended amygdala receives numerous afferents from limbic structures, such as the basolateral amygdala and hippocampus, and sends efferents to the medial part of the ventral pallidum and lateral hypothalamus, thus further defining specific brain areas that interface classic emotion structures with the extrapyramidal motor system (Alheid et al. 1995). Note that the shell of the nucleus accumbens is also a key part of the ventral striatum and as such part of another motivational circuit that consists of cortico-striatal, pallidal, and thalamo-cortical loops that are implicated in the incentive salience-habit component of compulsive-like behavior (Haber et al. 2000; Everitt and Robbins 2005). Specific within-system neurochemical systems that are hypothesized to mediate hyperkatifeia, particularly anhedonia, include acute losses of function of dopamine, serotonin, and endogenous opioid systems and neuroadaptations in the γ-aminobutyric acid (GABA)/glutamate systems (Koob 2020, 2021; Fig. 1).

For example, withdrawal from the chronic or excessive administration of most major drugs of addiction decreases the firing of dopaminergic neurons in the ventral tegmental area and decreases dopaminergic transmission in the ventral striatum (nucleus accumbens) during drug withdrawal (Koob and Volkow 2016). Human imaging studies of individuals with addiction during withdrawal or protracted abstinence have shown results that are consistent with animal studies with decreases in dopamine D_2 receptors (hypothesized to reflect hypodopaminergic functioning) and hyporesponsiveness to dopamine challenge (Koob and Volkow 2016; Ashok et al. 2017).

Perhaps even more compelling for the development and maintenance of hyperkatifeia in general, but perhaps less obvious for anhedonia in particular, are between-system neuroadaptations, in which different neurochemical neurocircuits are recruited (Koob and Bloom 1988; Koob and Le Moal 1997). Brain stress systems, such as corticotropin-releasing factor (CRF), glucocorticoids, norepinephrine, dynorphin, vasopressin, hypocretin, and substance P, and neuroimmune systems, are recruited by excessive alcohol consumption, producing aversive or stress-like states, also contributing to hyperkatifeia (Koob 2008; for extensive reviews of the role of brain stress systems in hyperkatifeia, see Koob 2015, 2020, 2021; Fig. 1).

Additionally, anti-stress systems act as buffers of between-system neuroadaptations that can return the brain emotional systems to a homeostatic state (Koob 2015). A loss of function of, or deficits in, the stress-buffering systems, such as neuropeptide Y, nociceptin, endocannabinoids, and oxytocin, may also contribute to hyperkatifeia (Koob 2015, 2021; Koob and Volkow 2016; Fig. 1).

More specifically with regard to anhedonia, neuropharmacological studies in animal models of anhedonia that are associated with drug withdrawal also support the within/between-system hypothesis. Here, drug withdrawal-induced elevations of brain reward thresholds were reversed by various neuropharmacological agonists and antagonists (Koob 2017). For example, agents that acted as both direct and indirect dopamine receptor agonists, serotonin modulators, and glutamate receptor antagonists reversed the elevation of brain stimulation reward thresholds that was associated with drug withdrawal (Koob 2017). In the between-system framework, antidepressants, CRF receptor antagonists, a vasopressin-1b receptor antagonist, and an α-adrenergic receptor antagonist reversed the elevation of brain stimulation reward thresholds that was associated with drug withdrawal (Koob 2017).

The argument here is that between-system neuroadaptations can produce hyperkatifeia/anhedonia via actions on anti-reward circuits and directly contribute to hyperkatifeia/anhedonia by acting on reward circuits by facilitating the loss of mesolimbic dopamine function and loss of opioid peptide function. For example, at least two of the prominent brain stress systems, CRF and dynorphin/κ-opioid systems, that when activated are hypothesized to contribute to various measures that reflect symptoms associated with hyperkatifeia also interact to suppress dopamine function and, by extrapolation, anhedonia.

An increase in CRF system activity is associated with hyperkatifeia and anhedonia. The activation of CRF in both the ventral tegmental area and nucleus accumbens is associated with the motivational effects of nicotine withdrawal (Grieder et al. 2014) and a shift toward low-effort/low-reward choices and a shift away from high-effort/high-reward choices, similar to observations with dopamine receptor antagonists (Bryce and Floresco 2016). Similarly, in the nucleus accumbens, CRF plays a role in driving stress-induced decreases in social interaction (Walsh et al. 2014).

In humans, several molecular genetic studies have provided a potential translational perspective. Polymorphisms of the *CRHR1* gene in humans have been linked to stress-induced blunted responses to rewards (Bogdan et al. 2011) and alcohol use disorder phenotypes, many that involve interactions with a history of stress

(Treutlein et al. 2006; Chen et al. 2010). Thus, both animal and human studies suggest that stress-induced CRF activation can contribute to elements of behavior that are associated with hyperkatifeia/anhedonia (Stanton et al. 2019).

However, CRF acts in complex and often opposing directions in the mesolimbic dopamine system and as such can increase or decrease excitatory and/or inhibitory transmission in the ventral tegmental area–nucleus accumbens through multiple mechanisms, determined by the CRF receptor involved, terminal area involved, acute vs. chronic administration, and a history of stress (Bryce and Floresco 2016). For example, in the ventral tegmental area, CRF administration in the ventral tegmental area increased the baseline firing rate of dopamine neurons (Wanat et al. 2008) but decreased the phasic dopamine response to food (Wanat et al. 2013). Chronic nicotine administration upregulated CRF mRNA in ventral tegmental area dopamine neurons and dysregulated GABA-dopamine synapses (Grieder et al. 2014). Similarly, increases in CRF activity in the nucleus accumbens can facilitate reward, measured by cue-induced sucrose seeking and conditioned place preference (Pecina et al. 2006; Lemos et al. 2012). However, chronic and severe forced swim stress eliminated the increase in dopamine release by CRF; consequently, CRF comes to produce conditioned place aversion (Lemos et al. 2012). Thus, CRF activation in the mesolimbic dopamine system can decrease reward motivation following stress and during withdrawal and can decrease dopaminergic activity, consistent with decreases in dopaminergic activity that are observed during withdrawal from drugs of abuse.

The dynorphin/κ-opioid system has also been hypothesized to bridge between-system and within-system neuroadaptations. The excessive release of dopamine and opioid peptides was hypothesized to produce subsequent dynorphin system activation in the nucleus accumbens and then feedback to decrease dopamine release and contribute to dysphoric syndrome that is associated with cocaine dependence (Carlezon et al. 2000; Nestler 2004). The systemic administration of κ-opioid receptor agonists and the intracerebral administration of dynorphins produce aversive-like effects in both animals and humans (Shippenberg et al. 2007) and elevate brain stimulation reward thresholds (Todtenkopf et al. 2004). A κ-opioid receptor agonist suppressed dopamine release in the nucleus accumbens in heroin self-administering rats, resulting in an increase in immediate heroin intake (Xi et al. 1998). κ-Opioid receptor antagonists also block the escalation of drug consumption in extended-access models (Koob 2015). Human studies have been intriguing in this regard. A multicenter, 8-week, double-blind, placebo-controlled, randomized trial in patients with anhedonia and mood or anxiety disorders showed that a κ-opioid receptor antagonist increased reward-related functional magnetic resonance imaging activation during reward anticipation and decreased self-reported anhedonia, again providing some translation of hypotheses that were generated in animal models to human studies of anhedonia (Krystal et al. 2020).

3 Crosstalk with Physical and Emotional Pain

In humans, chronic pain is associated with anhedonia, and acute withdrawal from opioids and alcohol can lower pain thresholds and exacerbate pain (Ho and Dole 1979). Such heightened responsivity to pain can persist into protracted abstinence. Patients who are on methadone maintenance have low pain tolerance (Doverty et al. 2001). Heighted pain perception has also been observed during alcohol withdrawal. Patients who were undergoing acute withdrawal from alcohol exhibited greater heat pain sensitivity to a noxious thermal stimulus (Jochum et al. 2010), and their pain tolerance correlated with their scores on the Beck Depression Inventory (Jochum et al. 2010).

In animal models, withdrawal from the chronic self-administration of opioids and alcohol produced hyperalgesia, and animals with extended access to opioid or alcohol self-administration during dependence developed compulsive-like responding and exhibited hyperalgesia during withdrawal (Koob 2021; Koob and Schulkin 2019). Critically, repeated, every-other-day administration of a CRF receptor antagonist blocked the escalation of heroin intake and development of hyperalgesia (Park et al. 2015). CRF_1 receptors mediate the pronociceptive effects of this peptide, and this relationship is mediated at least partially by the central nucleus of the amygdala (Ji et al. 2007; Fu and Neugebauer 2008). Along similar lines, CRF_1 receptor antagonists blunt nociceptive hypersensitivity behaviors in animal models (Hummel et al. 2010). CRF_1 receptors, particularly those in the central nucleus of the amygdala, also block pain-related anxiety (Ji et al. 2007; Fu and Neugebauer 2008). Chronic alcohol administration also produces hyperalgesia during withdrawal (Dina et al. 2000; Dina et al. 2006; Edwards et al. 2012), and these effects are also blocked by a CRF_1 receptor antagonist (Edwards et al. 2012). Microinjections of a nonselective peptide CRF receptor antagonist in the amygdala reversed opioid withdrawal-induced hyperalgesia in the tail-flick test (McNally and Akil 2002). Thus, CRF receptor antagonism reverses elements of both physical pain (hyperalgesia) and emotional-like pain (pain-related anxiety), suggesting overlap among pain and hyperkatifeia with a focal point on nociceptive neurons in the amygdala.

The systemic administration of a long-acting κ-opioid receptor antagonist also reversed opioid-induced hyperalgesia in rats (Marchette et al. 2021). Several studies have shown that κ-opioid receptor signaling contributes to aversive affective states that are evoked by pain and pain-conditioned cues. The systemic or intra-nucleus accumbens shell blockade of κ-opioid receptors with nor-binaltorphimine reduced inflammatory pain-induced decreases in morphine-induced conditioned place preference (Kelsey et al. 2015). Local infusions of the κ-opioid receptor antagonist nor-binaltorphimine in the ventral nucleus accumbens shell blocked inflammation-induced conditioned place aversion and lowered the motivation to self-administer sucrose (Massaly et al. 2019). Altogether, these results suggest a role for extrahypothalamic brain stress systems in pain modulation and the affective component of pain.

Indeed, evidence suggests that the neural substrates of stress system neuroadaptations that are associated with addiction may overlap with substrates of emotional aspects of pain processing in such areas as the amygdala (Neugebauer 2007). Indeed, the laterocapsular division of the central nucleus of the amygdala also receives nociceptive-specific information directly (i.e., not processed by the thalamus or cortex) from the parabrachial area through the spino-parabrachio-amygdaloid pain pathway (Gauriau and Bernard 2004; Neugebauer and Li 2002), a pathway implicated in processing emotional components of pain perception (Price 2000; Bester et al. 1995). The central nucleus of the amygdala is a brain site that is also involved in negative emotional responses that are associated with drug withdrawal (Heinrichs et al. 1995; Koob 2021).

4 Neurobiology of Conditioned Hyperkatifeia, Including Anhedonia

Much of the work on conditioned anhedonia in addiction involves studies of conditioned withdrawal from opioids in preclinical models and two behavioral tasks, cues that are paired with precipitated opioid withdrawal in place conditioning and cues that are paired with precipitated withdrawal in the context of operant opioid self-administration or the self-administration of other rewards. For example, neuronal activation as measured by Fos immunoreactivity increases in the extended amygdala during opioid withdrawal, paralleling the development of opioid-induced conditioned place aversion (Gracy et al. 2001; Lucas et al. 2008).

Additionally, odor cues that were conditioned to naloxone-precipitated withdrawal provoked an increase in heroin consumption and elevations of intracranial self-stimulation thresholds in dependent rats (Kenny et al. 2006) and activated the extended amygdala and other brain stress systems in dependent rats, measured by Fos and functional magnetic resonance imaging (Carmack et al. 2019). Here, the naloxone-paired cue increased extended amygdala activity in heroin-dependent rats, whereas it decreased activity in nondependent rats. Withdrawal severity was associated with the activity of a hypothalamic cluster and extended amygdala cluster. Moreover, withdrawal-associated cue exposure upregulated the activity of a rat neuronal salience network (Tsai et al. 2020), including the anterior insula and anterior cingulate cortex. Analogous to a human neuronal salience network, it was hypothesized to facilitate behavioral adaptations to environmental stimuli.

Cues that were conditioned to aversive stimuli also inhibited activity in all dopamine terminals of the mesolimbic dopamine system except the ventromedial nucleus accumbens shell, which showed activation (de Jong et al. 2019). As noted above, antagonists of the norepinephrine, CRF, and dynorphin/κ-opioid receptor systems block the development of conditioned place aversions to precipitated opioid withdrawal, with such effects of CRF and norepinephrine localized to the extended amygdala (Kelsey et al. 2015; Delfs et al. 2000; Simpson et al. 2020; Heinrichs et al.

1995). Such conditioning also requires inputs from the basolateral amygdala. Cell body-specific lesions of the basolateral amygdala also blocked development of the conditioned aversive effect of precipitated opioid withdrawal (Schulteis et al. 2000). Altogether, conditioning that is associated with opioid withdrawal induces long-lasting neuroadaptations that may involve the engagement of emotional learning neurocircuitry (Pantazis et al. 2021).

5 Hedonic Set Point: An Allostatic View

Given the above premise that hyperkatifeia/anhedonia via negative reinforcement contributes to compulsive drug seeking in addiction (Koob 2021), any attempts to restore hedonic homeostasis take the form of misregulation and instead lead to hedonic allostasis. When the counteradaptive opponent process becomes excessive and overcompensates for the drug's rewarding effects, allostasis develops, reflected by a concomitant shift in reward balance toward hyperkatifeia, more specially anhedonia. In other words, taking the drug to relieve anhedonia only serves to exacerbate anhedonia. With further compulsive drug seeking, one ends up defending a hedonic set point that gradually gains allostatic load and shifts from a homeostatic hedonic state to an allostatic negative hedonic state (Koob and Le Moal 2001).

A major fear of human patients with opioid use disorder is the anticipated hyperkatifeia/anhedonia symptoms of opioid withdrawal and the desire to escape impending somatic and emotional discomfort. As noted above, hyperkatifeia brain circuit networks have been hypothesized to be activated not only during withdrawal but also by conditioned appetitive and nonappetitive predictors of withdrawal (e.g., conditioned drug cues or conditioned-withdrawal cues; Baker et al. 1987; Carmack et al. 2019). Relevant to such a conceptualization is the argument that signaled avoidance learning may act as a primary motivational process to account for addictive behavior (Baker et al. 2004). Here, the animal performs an avoidance response, and this avoidance response delays the aversive unconditioned stimulus and but also terminates the conditioned stimulus, which acts as a "warning" stimulus (Baker et al. 2004). In this context, drug use in individuals with substance use disorder would in effect eliminate negative affect (or anhedonia), and sensations of the drug or even stimuli that are conditioned to the drug could serve as safety signals that the drug withdrawal avoidance response was effective. Notably, stressful events during protracted abstinence may generalize to such an anhedonic state and produce memories that opioid drugs can relieve such a negative state (Koob 2008; Evans and Cahill 2016), possibly contributing to the high comorbidity of affective disorders with addiction.

Thus, authors of opponent process and allostasis theories have argued that the escape from and avoidance of hyperkatifeia in general, and anhedonia in particular, are powerful motives for compulsive drug use (Koob and Le Moal 2001; Solomon 1980; Baker et al. 2004; Evans and Cahill 2016). Some have also argued that addiction is sustained by a learned association between drugs and relief from an

existing dysphoric state, and this learned association is formed through negative reinforcement (Baker et al. 2004; Evans and Cahill 2016) such that individuals with substance use disorders learn, through iterative trials, to immediately extract the affective meaning of partially developed interoceptive cues and then reduce them through drug use (Baker et al. 2004).

Given that (1) hyperkatifeia is hypothesized to be a prominent component of protracted abstinence, (2) studies have reported hypersensitivity to pain and discomfort with opioids that can last longer than 1 year post-detoxification, and (3) hypersensitivity to pain is linked to the misregulation of alcohol consumption as a coping response (Koob et al. 2020), the link between pain, particularly the emotional component of pain, with anhedonia is a ripe area for future study, certainly in addiction. Based on preclinical studies, multiple brain systems that have been identified in mediating hyperkatifeia in addiction could be targets for the treatment of anhedonia that is associated with other mental illnesses and comorbidities with addiction. Allostatic loads that are associated with childhood trauma, adverse childhood events, environmental stress (e.g., social isolation that is produced by the COVID-19 pandemic), genetic and epigenetic factors, and excessive drug taking itself can all contribute to anhedonia that appears to be part of the higher mortality that is associated with deaths of despair (Koob et al. 2020; Koob 2021).

Acknowledgements The author thanks Michael Arends for assistance with manuscript preparation.

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Anhedonia in Nicotine Dependence

David G. Gilbert and Bryant M. Stone

Contents

Abstract Prior findings indicate that trait anhedonia enhances the likelihood of becoming a tobacco smoker, and preliminary evidence suggests that smoking abstinence leads to anhedonic states in some individuals and situations, and nicotine administration reduces anhedonic states. Nevertheless, many vital questions exist concerning relationships between anhedonia and nicotine dependence, including situational and individual difference factors that may moderate the strength of these associations. This chapter provides a critical review of the literature assessing relationships of anhedonia to nicotine dependence and the effects of acute nicotine through the lenses of the Research Domain Criteria's (RDoC) Positive Valence Systems (NIMH, RDoC changes to the matrix (CMAT) workgroup update: proposed positive valence domain revisions. A report by the national advisory mental health council workgroup on changes to the research domain criteria matrix, 2018) and the Situation x Trait Affective Response (STAR) model of nicotine's effects and nicotine dependence (Gilbert, Smoking individual differences, psychopathology, and emotion. Taylor and Francis, Washington, DC, 1995; Gilbert, Hum

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Curr Topics Behav Neurosci (2022) 58: 167–184
https://doi.org/10.1007/7854_2022_320
Published Online: 30 April 2022

Psychopharmacol Clin Exp 12:S89–S102, 1997). The effects of nicotine and nicotine withdrawal on subjective, behavioral, and brain indices vary across the three RDoC Positive Valences Systems (Reward Responsiveness, Reward Learning, and Reward Valuation) in a manner that supports the research and potential clinical utility of using RDoC criteria and the STAR model to guide research and clinical innovation. We provide a revision of the STAR model that incorporates the three RDoC Positive Valence Systems with evidence that nicotine's effects on hedonic and affective processes vary as a function of the dominance/salience of (1) situational hedonic and affective cues and task/active coping cues, and (2) state executive functioning level/capacity and state reward sensitivity such that these effects of nicotine are maximal during states of suboptimal cognitive functioning and reward sensitivity, combined with low situational stimulus salience and low task-related cues/demands.

Keywords Anhedonia · Nicotine dependence · RDOC · Smoking · STAR model · State-dependent

1 Introduction

Cook et al. (2015) assessed self-reported anhedonia across 10 days of abstinence in 1,175 smokers (20% of whom quit on placebo treatment) and found that during the first day of abstinence, the participants reported less pleasure from the most pleasurable event of the day than during the pre-quit baseline assessment. However, because pleasurable events were not randomized or kept constant, the causal mechanisms for this change are confounded. Possibly, individuals chose to engage in fewer or different pleasurable activities to cope with their effort to maintain abstinence. Also, the conclusion that anhedonia returned to baseline levels after a day or two may not reflect the actual duration of abstinence on anhedonic processes, given that there was no randomized no-quit control group to demonstrate withdrawal symptom duration (Gilbert et al. 2019). Despite these limitations, the Cook et al. (2015) study replicated earlier findings that pre-quit, post-quit, and change from pre- to post-quit anhedonia predicted outcomes (Leventhal et al. 2009). Another longitudinal study of daily smokers trying to quit (Hughes et al. 2020) revealed that abstinence decreased self-reported pleasure from rewards to a small extent (i.e., 6%–14%) that lasted for less than a week, but did not decrease operant task-assessed willingness to work relative to former smokers. Experimental and quasi-experimental research suggests that trait and state anhedonia may be important maintenance factors in nicotine dependence and other substance use disorders (Garfield et al. 2014). However, information concerning the modulation of the effects of nicotine by situations and anhedonic states and traits is minimal.

2 Neurobiological Overlaps of Nicotine Dependence and Anhedonia

Acute nicotine enhances cognitive performance in both nonusers and nicotine-dependent humans (Heishman et al. 2010; McClernon et al. 2006), especially in low-baseline performing individuals (Perkins 1999; Newhouse et al. 2004). Moreover, as reviewed by Volkow et al. (2019), substantial evidence suggests that after chronic large-dose nicotine administration, neuroadaptations to its effects lead to a lower basal hedonic set point and dopaminergic (DA) functioning in such a manner that negative reinforcement becomes a stronger use motivation. In addition, chronic heavy use of nicotine alters nicotinic cholinergic receptor numbers and functions in many brain areas, including those associated with cognition, approach behavior, positive affect, and attentional biases to stimuli associated with reward/reinforcement (Regner et al. 2019; Sutherland and Stein 2018). However, nicotine withdrawal symptoms take longer to resolve than might be expected based solely on neuroadaptation models (Gilbert et al. 2019), suggesting that nicotine use for some may reflect an attempt to self-medicate state or trait anhedonia or other forms of suboptimal affective or cognitive functioning. Furthermore, the effects of nicotine and abstinence on anhedonia may, in part, reflect their modulation of the hypothalamic-pituitary-adrenal axis (HPA) activity given that nicotine increases (Gilbert et al. 2000a, b) and abstinence is associated with substantial and sustained (31+ day) decreases in serum cortisol (Gilbert et al. 1999). Further, abnormal HPA and immune reactivity are associated with anhedonia and MDD (Nandam et al. 2020), and antidepressants increase serum cortisol (Nandam et al. 2020), while inflammatory markers are associated with increased anhedonia (Jha et al. 2018). Finally, HPA activity modulates immune system functioning (Wang et al. 2019), and smoking abstinence is associated with increased natural killer cell activity (Meliska et al. 1995). These HPA and inflammatory processes modulate DA and other brain neurocircuitry (George and Koob 2017), but the importance of this modulation in nicotine dependence and anhedonia is not well characterized.

Both acute and chronic nicotine, directly and indirectly, influence activity in many brain regions, including those associated with reward sensitivity and positive affect (e.g., the nucleus accumbens; George and Koob 2017), executive functioning (e.g., the frontal cortex stimulated by both DA and nicotinic cholinergic projections; Regner et al. 2019), and the gating of information flow between regions associated with emotion and motivation-related processes and executive control (e.g., the subgenual anterior cingulate gyrus, Pizzagalli 2011; and the insula, Regner et al. 2019). These gating functions are consistent with the Situation x Trait Affective Response (STAR) model (1995) view that the effects of nicotine on hedonic and affective states are a function of the situational context and individual differences in pre-nicotine brain states and traits. The insular cortex and thalamus have among the highest densities of brain nicotinic cholinergic receptors and appear to be critically involved in smoking motivation and the gating of information flow between affective subcortical and executive control regions (Regner et al. 2019). These complex

effects may explain how nicotine can produce strong dependence, while animal models of nicotine's direct reinforcing effects are weaker than cocaine (Risner and Goldberg 1983). In humans, there is strong support for the view that the affect-enhancing and reinforcing effects of nicotine use reflect cognitive enhancement (which is reported by smokers to be rewarding and to increase positive affect; Gilbert et al. 2000a, b), increased motivational drive, cognitive control, and reduced distraction by negatively valent internal and external stimuli (Ashare et al. 2014; Gilbert 1995), possibly reflecting enhanced frontal-parietal and frontal-dorsal anterior cingulate activation and suppression of DMN and amygdala activity and connectivity with the insula (Fedota and Stein 2015; Sutherland et al. 2017; Regner et al. 2019).

3 Anhedonia and Nicotine Dependence Within the Frameworks of the NIMH Research Domain Criteria (RDoC) and the Situation by Trait Affective Response (STAR) Model

The RDOC and STAR models complement each other and identify critically important affect-related dimensions that moderate relationships of nicotine dependence to anhedonic processes. The recently revised proposed reorganization of Positive Valence Systems of the Research Domain Criteria (RDoC) of the National Institute of Mental Health (NIMH 2018) includes three major constructs (i.e., Reward Responsiveness, Reward Learning, and Reward Valuation), all of which are important potential contributors to the associations of nicotine dependence with anhedonic and affective processes. As depicted below in Fig. 1, the STAR model of moderators of nicotine's effects on hedonic and affective processes is based on evidence that these effects vary as a function of the dominance/salience of (1) situational hedonic and affective cues and task/active coping cues, and (2) state executive functioning level/capacity and state reward sensitivity that in part reflect temperamental traits. Importantly for the current review, the STAR model suggests that the effects of nicotine are greatest (**++**) in states of suboptimal cognitive functioning and reward sensitivity, combined with low situational stimulus salience and low task-related cues/demands (bottom row four cells of the figure). At the same time, the model and its supporting evidence suggest that nicotine has minimal or no effects (o) during optimal states of cognitive and affective functioning. As noted in the figure and Sect. 2, nicotine exerts its neurophysiological effects both directly via nicotinic receptor (nAch) activation and indirectly via nicotinic dopaminergic (DA), serotoninergic (5-HT), noradrenergic (NE), and glutaminergic (Glut.) neurotransmission systems. The immediately subsequent sections of our review focus on experimental findings of the effects of nicotine and smoking abstinence (in dependent users) on the RDoC Positive Valence Systems and subsystems and, when available, note the effects of STAR-model hypothesized situational moderators.

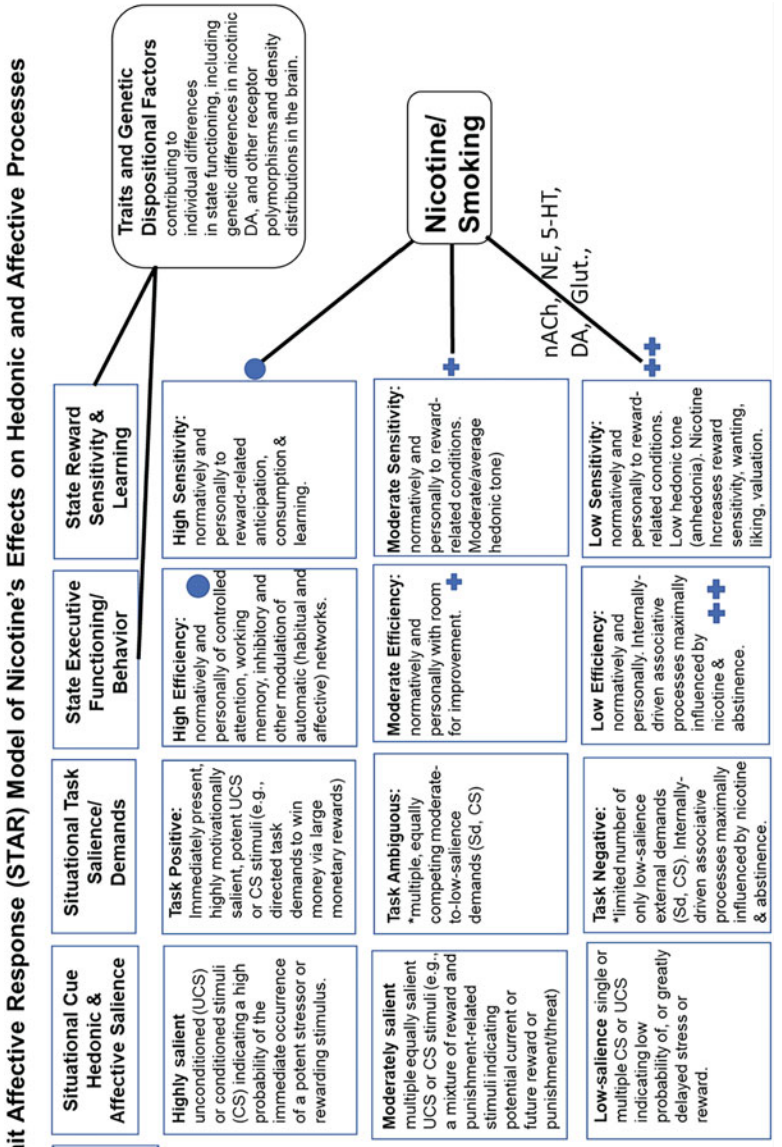

Fig. 1 A three-level characterization (high, moderate, and low) of the STAR-model hypothesized critical moderators of the effects of nicotine on hedonic, affective, and cognitive states, the dominance/salience of: (1) situational hedonic and affect cues, (2) situational task salience/demands, (3) state executive functioning level, and (4) state reward sensitivity. Genetically influenced- and learning-related traits interact with these state moderators to determine pre-drug executive functioning and hedonic sensitivity

The STAR model incorporates the concept of "alliesthesia," as described by Cabanac (1971), meaning that hedonic sensations are not constant, but the same stimulus may elicit differing, even the opposite hedonic responses in the same individual at different points in time because of changes in the internal state caused by any of a variety of factors ranging from food or sleep satiety versus deprivation to task demands determining whether a drug versus placebo is rewarding (Silverman et al. 1994a, b). Baseline state-dependency of the effects of acute nicotine on executive functioning has been replicated in numerous studies showing those with low pre-nicotine baseline functioning to exhibit greater task performance benefits from nicotine than those with high pre-drug performance (Eysenck 1980; Perkins 1999; Newhouse et al. 2004; Wachter and Gilbert 2013). Many investigators have assessed baseline and trait-dependency effects of nicotine and nicotine withdrawal in those with high baseline depressive states (Gilbert et al. 1998, 2002; Nikčević et al. 2017; Spring et al. 2008) and traits (Liverant et al. 2014; Janes et al. 2015; Gilbert and Pergadia 2017). These studies show greater increases in depressive withdrawal symptoms as long as assessed (65 days; Gilbert et al. 2019) in those with depressive state or traits, relative to those without them. Consistent with the STAR-model lateralized neural network hypothesis of nicotine's effects on cognitive and affective information processing (Gilbert 1995), Loughead et al. (2015) found that relapse to smoking was predicted by decreased executive functioning-related left dorsolateral prefrontal cortex and increased default-mode network (posterior cingulate cortex) BOLD percent signal change from smoking satiety to abstinence. Additionally, there is moderately strong evidence that supports the STAR-model hypothesis that nicotine tends to reduce negative affect and anxiety when threat-related cues signal potential mild-to-moderate distal/potential threat (e.g., anxiety or recovery from negative affect induction), but not when stimuli cue highly salient, immediately present specific threat (e.g., fear); reviewed by Gilbert 1995 and by Gilbert and Gilbert 1995; see also Hogle et al. 2010).

Evidence of the importance of the salience of task demands comes from studies showing that nicotine has larger effects on EEG during resting and low-demand states than during acute stress (Gilbert et al. 1997), and that during smoking abstinence, individuals high in depressive traits, relative to those low in such traits, exhibit greater EEG slowing during a stressful math and noise-stress task (Gilbert et al. 2004) – findings consistent with studies indicating that major depressive disorder (MDD) is associated with a failure of tasks to entirely suppress the default-mode network (DMN; Marchetti et al. 2012) and with evidence that nicotine suppresses DMN activation and enhances task network activation (Fedota and Stein 2015). The DMN is associated with inward preoccupation and rumination, two factors that appear to be critical for the maintenance of positive hedonic tone via enhancing effort-related reward and reward-related information processing (Marchetti et al. 2012). However, we are not aware of any study that has assessed the difference in the effects of acute nicotine hedonic tone or affect as a function of positive stimulus salience, and only a few studies have assessed the degree to which the effects of nicotine or nicotine withdrawal are moderated by the situational factors

(hedonic and affective cue salience, task salience/demands) proposed by the STAR model to be critical in moderating the effects of nicotine.

3.1 Reward Responsiveness

3.1.1 Reward Anticipation

The effects of nicotine and withdrawal on the anticipation of reward have been assessed in a few studies. Nicotine abstinence decreased self-reported reward anticipation by 5% and increased self-reported reward anticipation by 4% using the Rewarding Events Inventory (REI; Hughes et al. 2017) and the Temporal Experience of Pleasure Scale (TEPS; Gard et al. 2006), respectively. The REI assesses the degree of enjoying, wanting, and the frequency of occurrence for 54 potentially rewarding events (e.g., social gatherings, hobbies). Acute nicotine administration has reliably been found to increase dorsal, but not ventral, striatal activation during monetary reward anticipation, as assessed by functional magnetic resonance imaging (fMRI)-based changes in blood oxygenation-level dependent (BOLD) activity during the monetary incentive delay (MID) task (Rose et al. 2013; Fedota et al. 2015). Similarly, a study (Addicott et al. 2012) using the wheel of fortune task found greater BOLD activation of the dorsal striatum (putamen). Overall, it appears that during reward anticipation, nicotine, relative to deprivation/placebo, is associated with increased activation of the dorsal striatum, a structure related to habitual responding, while only one small study using nonsmokers (Wang et al. 2020) suggests that nicotine may increase ventral striatal, reward-related, activation. The increase in dorsal striatal activation by nicotine could reflect an increased tendency toward habituation of responding to the onset of rewarding stimuli, as noted below in Sect. 3.1.2. None of the studies of reward anticipation has been large enough to assess individual differences in these effects as a function of situational or trait modulators, or dose or abstinence duration.

3.1.2 Initial Response to Reward

Hughes et al. (2017) observed significant decreases in enjoyment (5%) and frequency of rewarding events (8%) during abstinence, relative to baseline smoking, and others have observed reduced responsiveness to financial incentives, increased self-reported anhedonia, and diminished happiness in response to positive film clips during acute (usually overnight) nicotine abstinence (Al-Adawi and Powell 1997; Dawkins et al. 2007; Powell et al. 2002). Of the three studies assessing BOLD responses to the receipt of reward stimuli (e.g., a stimulus indicating monetary reward) using the MID task, one (Addicott et al. 2019) found that smokers exhibited a trend toward greater nucleus accumbens (NAcc) activation during satiety compared with withdrawal ($p = 0.054$), while nonsmokers showed greater NAcc

activation on rewarded trials after acute nicotine inhalation compared with placebo ($p = 0.032$). The second MID study (Wang et al. 2020) found that nicotine decreased functional connectivity between the nucleus accumbens and the anterior cingulate in response to reward receipt; while the third (Fedota et al. 2015) reported that nicotine enhanced reward receipt activation of the putamen – a dorsal striatal structure associated with habitual responding. Thus, the effects of nicotine and abstinence involved the nucleus accumbens in all cases, but the specific brain patterns varied across studies. None of the fMRI or behavioral studies of reward anticipation was large enough to assess individual differences in these effects as a function of situational or trait modulators, or dose or abstinence duration.

3.1.3 Reward Satiation and Habituation

In one of the few studies in the area, using a within-subjects design, Karelitz and Perkins (2018) found that the rate of responding on a simple operant fixed ratio computer task declined significantly more slowly on the smoking-sated day relative to the smoking-abstinent day; these findings are consistent with delayed habituation of reinforcer effectiveness during smoking satiety, suggesting that nicotine slows the habituation of reinforcer efficacy. However, nicotine's effects on reward-satiation are limited and may vary across reward types. For example, evidence indicates that nicotine decreases appetite and food intake (Mineur et al. 2011) and thus may facilitate habituation to food reward. Recent preclinical research also suggests that nicotine may prolong the duration of a reinforcer's efficacy. In rodent models, some stimulant drugs have been shown to delay habituation of reinforcer effectiveness (i.e., to maintain responding for that reinforcer longer; Gancarz et al. 2012; Lloyd et al. 2014). It seems reasonable to hypothesize that the effects of nicotine vary across phylogenetically differently stimuli, and relative to higher-order conditioning. Individual differences in body weight and different forms of alliesthesia (deviation from hedonically and physiologically ideal states; Cabanac 1971) will likely be found to moderate the effects of nicotine and abstinence on satiation and habituation to reward.

3.2 Reward Learning

3.2.1 Probabilistic and Reinforcement Learning

The Probabilistic Reward Task (PRT; Pizzagalli et al. 2005) is a widely used measure of implicit reward learning. This PRT presents schematic faces with two eyes and a nose. A horizontal straight-line mouth is presented quickly (100 ms), and participants indicate whether the mouth was long (11 mm) or short (10 mm), and on 40% of correct trials, participants receive a monetary reward. Unknown to the subject, correct identification of one mouth is rewarded three times more frequently

than the other, which induces a response bias toward the more-frequently reinforced stimulus (Pizzagalli et al. 2005), reflective of an individual's sensitivity to reward. Nicotine has significantly enhanced response bias in never-smokers (Barr et al. 2008), light smokers (Whitton et al. 2021), abstinent smokers, and rats (Pergadia et al. 2014). However, a study failed to replicate these findings in smokers (Audrain-McGovern et al. 2014). Supporting the findings of Pergadia et al. (2014), the Whitton et al. (2021) study of light smokers found that the effects of nicotine were greater in those high in depressive traits and those with the nicotine dependence "risk" allele rs16969968 experienced greater nicotine benefits. Similarly, smoker status, relative to nonsmoker status, in both currently (Liverant et al. 2014) and formerly (Janes et al. 2015) depressed individuals has been linked to greater-reward bias on the PRT, and nicotine has been found to normalize cortico-striatal connectivity in nonsmokers (Janes et al. 2018).

3.2.2 Reward Prediction Error (RPE)

Behavior is shaped (changed/learned) when outcomes deviate from expectations. Consistent with the hypothesis that nicotine enhances responses to salient stimuli and their motivational salience (Gilbert 1995; Caggiula et al. 2009), nicotine amplifies the salience of other stimuli with some incentive value (Caggiula et al. 2009). In animal models, the phasic firing of DA neurons occurs in the ventral tegmental area (VTA) in response to an RPE, and these signals then project to the striatum and cortex for the updating of stimulus-action outcome expectations that guide future behavior (Schultz 1997). Kumar et al. (2018) found that, relative to controls, individuals with MDD exhibited less efficient reward learning, blunted RPE activation in the striatum, and reduced VTA-striatal connectivity to feedback, but learned from monetary punishments as effectively as controls. Similarly, Baker et al. (2020) found that learning from positive prediction error signals was reduced during smoking abstinence and enhanced during satiety while learning from negative prediction errors was enhanced during abstinence and reduced during satiety. Finally, using the outcome expectation task, Addicott et al. (2017) observed that in nonsmokers, nicotine increased BOLD activation in the anterior insula/inferior frontal gyrus and decreased activation in the caudate across both outcome types (both rewards and non-rewards), highlighting the importance of comparing rewards with non-rewards. The fact that the effects of nicotine and abstinence differentially impact prediction errors as a function of their nature (positive vs. negative) and of the need for comparison with non-rewarding stimuli is consistent with the STAR model's emphasis on the critical role of the hedonic quality and salience of situational and task-related cues. The STAR model suggests that further variations along this line (e.g., the degree of reward or threat) should also be assessed in parametric studies.

3.2.3 Habit

Models of drug dependence generally propose that initial intentional drug use leads to a more automatic stimulus-elicited use (Robinson and Berridge 1993; Drobes and Tiffany 1997). For example, manipulations of nicotine satiety versus deprivation have robust effects on tonic craving without smoking cues while not affecting habit-based cue-elicited craving (Drobes and Tiffany 1997). Similarly, in animal models, responding is initially sensitive to current nicotine value and is thus goal-directed; however, after extensive training, responding becomes habitual (e.g., Clemens et al. 2014). Attenuated hedonic capacity may promote loss of control over reward-related behavior, leading to a shift toward predominantly habit-based nicotine-seeking. While some habitual influence of nicotine seeking is supported by substantial literature (Drobes and Tiffany 1997), nicotine-seeking in humans is also strongly influenced by the expected value, and pharmacotherapy may be somewhat effective because it selectively affects expected drug value (Hogarth et al. 2014). Thus, to the degree that individuals with anhedonia experience reward-enhancing effects from acute nicotine use, they would be expected to choose to smoke more often and be more likely to develop strong habitual use of nicotine. Smoking cue stimulus salience and dominance (e.g., distal vs. proximal smoking cues) have been initially explored (Conklin et al. 2008), but virtually nothing is known about how the effects of nicotine and abstinence are moderated by the distal-proximal dimension or other situation and trait modulators. Such trait modulators may include the type of initial primary nicotine reinforcement (e.g., negative affect reduction, positive-affect enhancement, cognitive enhancement, appetite suppression; Gilbert et al. 2000b) that could prove to be important contributors to strength and longevity of the smoking habit and the severity of anhedonia experience during abstinence.

3.3 Reward Valuation

3.3.1 Probability/Reward (Ambiguity/Risk) of Reward

The behavioral economics model of addiction suggests that the accessibility of a reward increases the chances of using the reward (Voss et al. 2021). Animal studies demonstrate decreased drug self-administration when using alternative environmental rewards, such as social rewards, alternative activities, and food (Venniro et al. 2019). In a study by Russell and Robinson (2019), rats were assigned to one of four conditions, saline with high probability reward, saline with low probability reward, nicotine with high probability reward, and nicotine with low probability reward using a progressive ratio paradigm. Acute nicotine increased attraction to high probability rewards (i.e., sucrose food pellet), but not when the probability of the reward was uncertain or low. This effect has been reproduced in human studies, where individuals in environments with low non-substance-related rewards are more likely to engage in substance use (Higgins et al. 2004; Leventhal et al. 2015). Thus,

efforts to abstain from nicotine may be more challenging for individuals who live in an environment with few non-nicotine rewards or otherwise are in an environmentally induced anhedonic state. Similarly, individuals with suboptimal cognitive functioning may experience even normal environments as suboptimally rewarding because of the challenges of experiencing task performance-related rewards. To the degree that nicotine enhances performance rewards, feeling of self-efficacy, etc., individuals would be expected to find nicotine rewarding and challenging tasks outcomes less ambiguous (Gilbert 1995).

3.3.2 Delayed Reward Value

Delay discounting in nicotine use is conceptualized as individuals assessing the immediate positive effects of nicotine consumption as more rewarding than the delayed consequences of use (DeHart et al. 2020). Across studies, delay discounting has been greater in heavier, relative to lighter smokers (e.g., Sweitzer et al. 2008) and in smokers relative to nonsmokers (reviewed by Mitchell 2004). However, the effects of acute nicotine on delay discounting have varied across studies. For example, Hughes et al. (2017) used a behavioral task in which participants were given a choice between receiving money now or later and found that nicotine abstinence increased delay discounting by 6%. However, using a pre-post design without a no-quit control group limits causal inference. Although the effects of Sweitzer and colleagues were replicated in one study (Field et al. 2006), Grosskopf et al. (2021) failed to observe changes in either performance on a delay discounting task from before to 21 days of sustained smoking abstinence or in fMRI-assessed brain activity in valuation and decision networks in 27 smokers, or differences relative to nonsmoker controls. In animal studies, nicotine decreased impulsivity and delayed discounting (Anderson et al. 2010). Eight rats were trained to respond to one of two reinforcers, either one food pellet after no delay or three food pellets after an increased delay across trials. The researchers administered 0.1–1.0 mg/kg of nicotine subcutaneously, examined percent choice and indifference points during an acute-testing phase and a re-administration phase, and found that acute nicotine administration decreased delay discounting; however, upon repeated nicotine exposure, delay discounting returned to baseline levels. Additional studies of the effects of acute and chronic nicotine on delay discounted are needed.

3.3.3 Effort to Obtain Reward

The Effort Expenditure for Rewards Task (EEfRT; Treadway et al. 2009) was designed to provide an objective measure of anhedonia defined as decreased willingness to exert effort to obtain a reward (e.g., choose greater-effort/greater-reward options) (Treadway et al. 2009). The task examines responding as a function of explicitly indicated response cost, reward magnitude, and probability of reward. The EEfRT presents participants with repeated choices, each linked to a choice between a

more difficult task in which success is rewarded with more money and a less difficult task in which success is rewarded with less money. Individuals with self-reported anhedonia made fewer hard-task choices in a validation study (Treadway et al. 2009), but smoking abstinence was associated with increases, rather than decreases, in high-effort choices in a less than optimally-controlled study by Hughes et al. (2017). In contrast, using a somewhat different experimental paradigm, well-designed crossover studies have reliably found that nicotine, relative to placebo, enhances willingness to work for rewards (videos or music, but not money) in humans (reviewed by Perkins et al. 2017, 2019) and in rodents (reviewed by Donny et al. 2003). The Perkins tasks started with a fixed ratio (FR10) and after that progressively more work was required to obtain each subsequent reward (Perkins and Karelitz 2013). In contrast, Lawn et al. (2015) found no effects of nicotine on willingness to work for music (or chocolate), possibly because of the use of an essential experimental difference in procedures from those used by Perkins and colleagues. Specifically, Lawn did not present the reinforcers until the end of the experimental session and included smoking reinforcers as one of the alternative reinforcers. Thus, the Perkins paradigm allows frequent sampling of the reinforcers through the study, while the Lawn study did not. Consistent with Perkins et al. and Lawn et al., Bühler et al. (2010) failed to detect an effect of nicotine on enhancing willingness to work for money, but, like Lawn, did not assess work for videos or music. Thus, the experimental paradigm used by Perkins et al. appears to identify conditions (videos and sometimes music but not money) in which nicotine and abstinence reliably exhibit significant effects on willingness to work for rewards. The Perkins paradigm provides individuals with frequent samples of the reward (music or videos) throughout the task. In contrast, the secondary and delayed effects of monetary rewards used by Lawn and associates were not impacted by nicotine in any of these studies, supporting the view that the reward-enhancing effects of nicotine are situation and/or reward dependent.

4 Summary: Toward a Situation × Trait Anhedonic Response (STAR) RDoC Framework for Understanding Nicotine Dependence

The present review supports the view that nicotine dependence, the acute effects of nicotine, and abstinence are substantially related to non-obvious situational factors and to anhedonia/hedonic states and traits. The degree of situational hedonic and task salience as well as executive and hedonic functioning appear to be highly impactful moderators of these relationships. For example, the reviewed evidence suggests that the effects of nicotine and abstinence on different RDoC positive-affect constructs vary due to subtle variations in the situation (experimental paradigms, e.g., anticipation vs. outcomes, monetary vs. immediately consumable rewards, proximal vs. distal reward/threat). The observed moderation of the effects of nicotine

on reward learning by depressive traits suggests the likely importance of other potential moderators, including state and trait anhedonia. Surprisingly, there were generally no effects of acute nicotine during the anticipation of rewards (or during other reward-related tasks) on the ventral tegmental areas hypothesized to drive nicotine dependence. In summary, our knowledge of the relationships of anhedonic states and traits to smoking and chronic and acute nicotine effects and their biological bases is limited. Little is known about situational and trait factors that moderate nicotine's effects on anhedonic states or the stability of nicotine-anhedonia relationships across different subtypes (e.g., anticipatory vs. consummatory vs. learning) of anhedonia. In addition, research is also needed to assess: (1) individual differences in anhedonia recovery trajectories during nicotine abstinence; (2) changes in hedonic tone across stages of nicotine use and levels of nicotine intake; (3) influences of learning and stress; and (4) nicotine and abstinence effects across different types of anhedonia. Unfortunately, few of the studies in our review were large enough to assess individual differences in these effects as a function of situational or trait modulators, or dose or abstinence duration.

Despite the limitations of the extant literature, findings to date suggest several potential treatment implications. First, as noted by Liverant et al. (2014), studies finding nicotine and smoking to be associated with greater-reward learning support a focus on behavioral activation methods as aids to enhance smoking cessation in individuals with MDD. Such activation studies could compare the efficacy of activation therapy when on placebo relative to nicotine-replacement therapy and also assess the relative efficacy of activations to different types of rewarding stimuli, training in the performance of cognitively challenging tasks, and active coping during different types of situations, including the various degrees of situational hedonic salience, task salience, and executive and hedonic states suggested by the STAR model to moderate the reinforcing effects of nicotine. Second, the STAR model suggests that cessation interventions and research should compare the efficacy of exposure to smoking cues and coping situations that vary in affective and coping cues, as well as during states of varying executive functioning (e.g., when fatigued or while drinking) and reward sensitivity/mood (e.g., phone prompts when phone responses indicate an anhedonic state).

Given the broad body of evidence demonstrating that state and trait anhedonia and smoking are associated with both situational factors (contexts) and genetically influenced personality and other temperamental traits, it is reasonable to adopt a conceptual model of nicotine dependence and anhedonia treatment that includes both situations and traits as causal determinants of critical processes. The Situation by Trait Adaptive Response (STAR) model (Gilbert 1995, 1997) and the above-reviewed literature suggests that the rewarding effects of nicotine use are primarily accomplished by three overall mechanisms: (1) enhanced goal achievement via cognitive and automatic reward learning and performance enhancement; (2) alteration of cognitive capacity and attentional processes; and (3) cognitive-affective information priming/biasing toward positive associations and reward-related stimuli and away from negative schemas. Novel smoking cessation and relapse prevention

interventions could be based on these processes and the situational moderators reviewed above.

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Anhedonia in Posttraumatic Stress Disorder: Prevalence, Phenotypes, and Neural Circuitry

Meghan Vinograd, Daniel M. Stout, and Victoria B. Risbrough

Contents

Abstract Anhedonia, the reduction of pleasure and reward-seeking behavior, is a transdiagnostic construct associated with a range of important health outcomes. As with other psychiatric disorders, anhedonia is a relatively common, though understudied, feature of posttraumatic stress disorder (PTSD) that is not adequately targeted by existing treatments. The purpose of this review is to describe the current state of the literature on anhedonia in PTSD and highlight areas for future research based on gaps in the existing evidence base. First, we review evidence for anhedonia symptoms as a distinct PTSD symptom factor and its associations with psychiatric comorbidity, disease trajectory, and quality of life outcomes, as well as describe theories that seek to explain the occurrence of anhedonia among individuals with PTSD. Second, we review evidence for behavioral and neural alterations in reward processing and circuitry, a marker of anhedonia, among individuals with PTSD and in animal models relevant to this disorder. Finally, we discuss key gaps in our understanding of anhedonia in PTSD and suggest areas for future research. Specifically, the timing of anhedonia symptom development and underlying circuit dysfunction in the trauma response trajectory, as well as potential differential associations of facets of anhedonia on clinical outcomes, remain unclear. Additionally, further research is needed to determine potential moderators of anhedonia, as well as the efficacy and effectiveness of psychotherapeutic, psychopharmacological,

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Curr Topics Behav Neurosci (2022) 58: 185–200
https://doi.org/10.1007/7854_2021_292
Published Online: 15 December 2021

and device-based interventions targeting anhedonia among individuals with PTSD. A more thorough understanding of these topics will ultimately improve prevention and intervention efforts for PTSD.

Keywords Anhedonia · Circuitry · Posttraumatic stress disorder · Reward

1 Anhedonia: A Consequential Transdiagnostic Construct

Anhedonia is characterized by an inability to experience pleasure, as well as reduced responsivity to and pursuit of pleasurable or rewarding stimuli (Rizvi et al. 2016; Fonzo 2018). Anhedonia is elevated among individuals with a range of psychiatric and neurological disorders, including major depressive disorder, schizophrenia, substance use disorder, obsessive compulsive disorder, Parkinson's disease, and chronic pain (Abramovitch et al. 2014; Garfield et al. 2014; Trøstheim et al. 2020). It is also associated with current suicidal ideation independent of psychiatric disorders, including depression (Ducasse et al. 2018). Further, anhedonia among adults (Spijker et al. 2001) and adolescents (Gabbay et al. 2015) with depression is a risk factor for poor prognosis. Anhedonia is associated with poorer psychosocial functioning among adults with depression (Fried and Nesse 2014; Vinckier et al. 2017) and poorer health-related quality of life among adults with schizophrenia and schizoaffective disorder (Ritsner et al. 2011). Finally, anhedonia predicts poorer response to psychotherapeutic, psychopharmacological, and neuromodulatory treatments among individuals with depression (McMakin et al. 2012; Uher et al. 2012; Downar et al. 2014; Khazanov 2020), and evidence suggests that existing psychotherapeutic treatments do not adequately treat anhedonia (Boumparis et al. 2016; Dunn et al. 2020).

Given anhedonia's transdiagnostic importance, it has increasingly received attention in investigations of the etiology and treatment of psychiatric disorders, including posttraumatic stress disorder (PTSD). This review describes the current state of the literature on anhedonia in PTSD and suggests areas of future research. First, we review evidence for anhedonia symptoms as a distinct PTSD symptom cluster and for associations of anhedonia with key clinical outcomes among individuals with PTSD, as well as describe theories that explain the phenomenon of anhedonia among these individuals. Second, we review evidence for alterations in reward processing and circuitry, a marker of anhedonia, among individuals with PTSD and in animal models relevant to the disorder. Finally, we discuss gaps in our understanding of anhedonia in PTSD and suggest areas for future research in order to improve prevention and intervention efforts.

2 Anhedonia in Posttraumatic Stress Disorder: Prevalence, Outcomes, and Theories

Some individuals who experience, witness, or learn about a traumatic event develop PTSD, a disorder characterized by persistent symptoms of intrusions, avoidance of trauma-related stimuli, alterations in cognition and mood, and alterations in arousal and reactivity that result in subjective distress or functional impairment. Though often conceptualized as a disorder of negative affect, accumulating evidence suggests that anhedonia is a prevalent and consequential feature of PTSD. Factor analytic studies of Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 PTSD symptoms provide evidence for superior fit of models that include a distinct anhedonia symptom cluster over other models, including the DSM-5 criteria model, across diverse samples (Liu et al. 2014; Armour et al. 2015, 2016; Wang et al. 2015; Zelazny and Simms 2015; Bovin et al. 2016; Soberón et al. 2016; Specker et al. 2018; though see Rasmussen et al. 2019 for critique of PTSD symptom factor analyses). This anhedonia factor is comprised of the DSM-5 symptoms "markedly diminished interest or participation in significant activities" (D5), "feelings of detachment or estrangement from others" (D6), and "persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings)" (D7; American Psychiatric Association 2013). Importantly, these three symptoms are sometimes referred to as "emotional numbing," though this term is used inconsistently in the literature (Wisco et al. 2020). Prevalence rates of these three symptoms as assessed via self-report measures range from 24 to 75% depending upon the population and trauma type (see Table 1; Carmassi et al. 2014; Hoge et al. 2014; Zelazny and Simms 2015; Carragher et al. 2016). Further, network analyses of PTSD symptoms among Veterans demonstrate high centrality of anhedonia symptoms, signifying their interconnectedness with and likelihood of

Table 1 Prevalence of self-reported anhedonia symptoms in trauma-exposed and PTSD populations

Trauma type/population	D5: markedly diminished interest or participation in significant activities	D6: feelings of detachment or estrangement from others	D7: persistent inability to experience positive emotions
Deployed infantry soldiers Hoge et al. (2014)	25%	27%	24%
Trauma-exposed adults Carragher et al. (2016)	32.5% (females) 34.5% (males)	51.7% (females) 56% (males)	35.9% (females) 33.9% (males)
Trauma-exposed community treatment sample Zelazny and Simms (2015)	40%	52%	37%
Adolescent earthquake survivors with PTSD Carmassi et al. (2014)	75%	37.3%	55.9%

contributing to other symptoms once present (Armour et al. 2017; Mitchell et al. 2017; Ross et al. 2018; von Stockert et al. 2018), though a systematic review of PTSD network analyses finds significant heterogeneity of symptom centrality across studies, possibly due to methodological or sample differences (Birkeland et al. 2020). Finally, endorsement rates of anhedonia symptoms among individuals with lifetime PTSD with and without lifetime major depressive disorder (MDD) do not differ (Franklin and Zimmerman 2001), suggesting that anhedonia in PTSD is not solely due to comorbid depression, of which anhedonia is also a diagnostic feature.

Discrepancies between PTSD diagnostic criteria and the underlying factor structure of PTSD symptoms impede a clear understanding of the prevalence of anhedonia and its associated outcomes. Recent and current iterations of the DSM group anhedonia symptoms with internal/external avoidance symptoms (DSM-IV-TR; American Psychiatric Association 2000) or other symptoms related to negative cognitions and affect (DSM-5; American Psychiatric Association 2013). Previous literature relates these DSM-defined PTSD symptom clusters to clinical and functional outcomes (e.g., Breslau et al. 2005; Guerra and Calhoun 2011; Hassija et al. 2012; Birkley et al. 2016), but it is difficult to establish the prevalence and impact of anhedonia symptoms specifically when they are grouped with other symptoms. The more precise anhedonia factor derived from factor analyses significantly associates with depression (Pietrzak et al. 2015; Wang et al. 2015; Zelazny and Simms 2015), suicidal ideation (Pietrzak et al. 2015; Blais and Geiser 2019; Chou et al. 2020), anger and impulsivity (Armour et al. 2016), and reduced mental functioning and quality of life (Pietrzak et al. 2015). Anhedonia is associated with increased substance use in individuals recently exposed to trauma (Fani et al. 2020), as well as increased risk for anxiety and psychotic disorders among combat Veterans with PTSD (Kashdan et al. 2006). Importantly, these associations are specific to anhedonia symptoms and not to other PTSD or depression symptoms. Post-trauma anhedonia symptoms can also predict greater PTSD severity and symptom chronicity at follow-up (Feeny et al. 2000). Taken together, these findings suggest that anhedonia is not only prevalent among individuals with PTSD and trauma exposure, but that it also relates to important psychiatric comorbidity, disease trajectory, and functional outcomes.

Multiple theories seek to explain the occurrence of anhedonia among individuals with PTSD. Litz and Gray suggest anhedonia arises from both inhibited emotional expression and the need for more intense stimulation to respond to positively-valenced stimuli due to competing hyperresponsivity to negatively-valenced stimuli (2002). Frewen and colleagues find evidence that individuals with PTSD not only experience reduced positive affect but also interfering negative affect in response to positive stimuli (2012), suggesting that positive stimuli may be aversive for this population and thus avoided. Relatedly, Weiss and colleagues suggest that the physiological arousal associated with positive affect may serve as a cue for other trauma-related symptoms, contributing to negative evaluations of positive emotion, and thus the positive emotion dysregulation (e.g., non-acceptance of positive emotions) evident among individuals with trauma exposure and PTSD (2018; 2020). These theories underscore the importance of interactions between positive and

negative affect to our understanding of anhedonia among individuals with PTSD. Relatedly, anhedonia among individuals with PTSD or trauma exposure may arise due to overlap and interaction among neural systems underlying positive and negative valence processes (Admon et al. 2013; Fonzo 2018; Ben-Zion et al. 2021). A final theory posits that anhedonia may not only be a consequence of PTSD, but also a pre-trauma risk factor for the subsequent development of the disorder as a result of early-life adversity and resulting alterations in reward circuitry (Risbrough et al. 2018). Consistent with this latter account, animal models suggest that disruption in reward circuits, in particular cortico-striatal and striatal-amygdala circuits, may increase susceptibility to stress as well as disrupt learned fear processes that are critical for trauma recovery such as fear extinction (Muschamp et al. 2011; Han and Nestler 2017).

3 Altered Reward Processing and Circuitry in Posttraumatic Stress Disorder

Experimental tasks that probe reward processing are used to objectively measure the multiple components of reward processing across species. Current models of reward processing posit that it is not a unitary construct, but rather made up of several constituent processes (Treadway and Zald 2011; Kring and Barch 2014; Thomsen et al. 2015), and should also be examined within the context of positive emotion and affect more broadly (for discussion, see Fonzo 2018). As of 2021, the National Institute of Mental Health's Research Domain Criteria Matrix divides the positive valence systems into the constructs of reward responsiveness, reward learning, and reward valuation (though this terminology is not consistently used in the existing literature), which can be measured across various units of analysis. Discussion of findings across each unit of analysis is beyond the scope of this chapter (for multi-unit review, see Nawijn et al. 2015). Here, we focus on findings at the circuit level due to their translational relevance, but point readers to behavioral studies on reward processing among individuals with PTSD (e.g., May and Wisco 2020; Weaver et al. 2020) or posttraumatic stress symptoms (e.g., Myers et al. 2013; Radell et al. 2017), and note that many task-based neuroimaging studies also present task performance findings as an index of behavioral differences in reward processing among individuals with PTSD. Facets of reward processing share both overlapping and unique neural regions, circuits and molecular mechanisms (for detailed review, see Treadway and Zald 2011; Der-Avakian and Markou 2012; Fonzo 2018). The ventral tegmental area (VTA) of the midbrain, the ventral striatum (nucleus accumbens), orbitofrontal cortex and medial prefrontal cortex (PFC) make up the canonical reward circuit and are central to each facet of reward processing (Fonzo 2018).

Multiple reviews (Nawijn et al. 2015; Fonzo 2018; Lokshina et al. 2021; Seidemann et al. 2021) describe the growing body of literature examining reward processing among individuals with PTSD, though to date, the number of

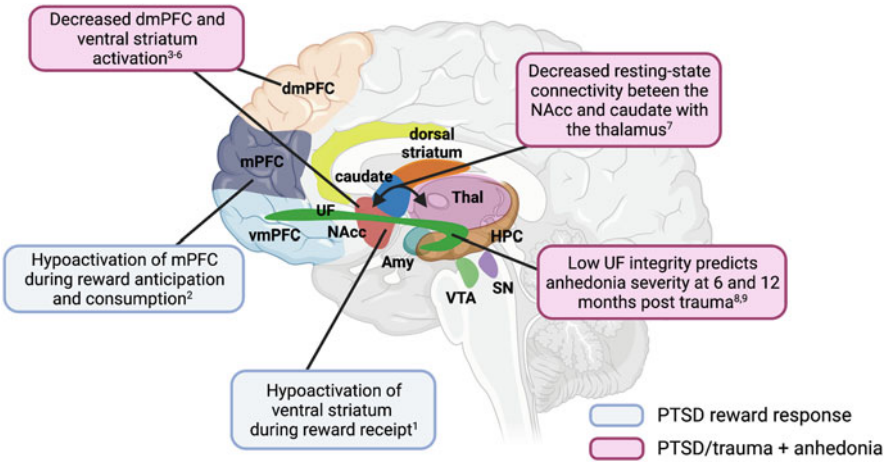

Fig. 1 Mid-sagittal slice depicting key reward circuit findings during reward processing and associations with anhedonia among samples with PTSD or trauma exposure. *dmPFC* dorsomedial prefrontal cortex, *mPFC* medial prefrontal cortex, *vmPFC* ventromedial prefrontal cortex, *NAcc* nucleus accumbens, *Amy* amygdala, *Thal* thalamus, *HPC* hippocampus, *VTA* ventral tegmental area, *SN* substantia nigra, *UF* uncinate fasciculus. Citation guide: 1 = Fonzo (2018) Review; 2 = Lokshina et al. (2021) Review; 3 = Elman et al. (2009); 4 = Frewen et al. (2012); 5 = Felmingham et al. (2014); 6 = Nawijn et al. (2016); 7 = Pessin et al. (2021); 8 = Fani et al. (2019); 9 = Harnett et al. (2020). Created with BioRender.com

neuroimaging studies remains limited. Here, we highlight circuit alterations during reward processing tasks and circuit alterations associated with anhedonia symptoms (Fig. 1). A systematic review of studies using questionnaire, behavioral, physiological, and functional neuroimaging methods concludes that individuals with PTSD demonstrate decreased reward anticipation, approach, and hedonic responses compared to control subjects (Nawijn et al. 2015). Importantly, however, evidence for these reward processing deficits is mixed (including among the neuroimaging studies) and varies by participant sex and stimuli type, such that decreased reward processing is evident more often in female participants and in response to social positive stimuli (Nawijn et al. 2015). Further, this review excludes 13 neuroimaging studies in which positive stimuli were compared to negative stimuli, thus somewhat limiting its conclusions regarding neural alterations in reward processing (Nawijn et al. 2015). An additional cross-methodology review similarly suggests that there is evidence for alterations in reward processing among individuals with PTSD, including decreased activation in cortico-striatal circuits during reward anticipation and consumption (Seidemann et al. 2021).

A third review focused on neuroimaging studies concludes that there is some consistency of evidence for hyporesponsivity of the ventral striatum during the receipt of reward among individuals with PTSD, though notes mixed findings and methodological limitations in the existing literature (Fonzo 2018). Animal models of PTSD also support disruption in ventral striatum signaling after severe stress through

alterations in striatal dopamine receptor and transporter expression, and other transcription regulators (Muschamp et al. 2011; Enman et al. 2015). Finally, an additional review highlights consistency of decreased medial PFC (mPFC) activation during reward consumption, but mixed evidence for reduced ventral striatum/nucleus accumbens (NAcc) activation during reward consumption and anticipation, among individuals with PTSD (Lokshina et al. 2021). Importantly, some of the existing functional neuroimaging studies included in these reviews demonstrate associations between reduced striatal and dorsal mPFC activation and increased severity of anhedonia or emotional numbing symptoms within the PTSD group (Elman et al. 2009; Frewen et al. 2012; Felmingham et al. 2014; Nawijn et al. 2016). Disorganized mPFC-NAcc coordination is also reported in animal models of PTSD with co-occurring anhedonic-like behavior (Ritov et al. 2016).

Meta-analyses of volumetric (Karl et al. 2006; O'Doherty et al. 2015), resting state (Koch et al. 2016; Wang et al. 2016), and structural white matter (Siehl et al. 2018) alterations among individuals with PTSD generally suggest differences in reward-related (e.g., anterior cingulate cortex, amygdala, insula, cingulum), but not canonical (e.g., striatum, orbitofrontal cortex, medial forebrain bundle, though see Wang et al. 2016 for dorsal mPFC resting-state hypoactivity findings) regions and tracts. The increased recognition that anhedonia and reward processing alterations are important features of PTSD is reflected in a growing number of resting-state functional connectivity (rs-FC) and structural neuroimaging studies investigating these constructs. Among women with PTSD, greater anhedonia severity is associated with reduced rs-FC between the left NAcc and a cluster in the left caudate to thalamus after controlling for severity of PTSD and depression symptoms (Pessin et al. 2021). Exploratory analyses reveal that greater anhedonia is associated with lower left ventral striatum-ventromedial PFC rs-FC in women with trauma exposure, some of whom had PTSD, and high levels of peripheral inflammation (Mehta et al. 2020). Somewhat in contrast, higher levels of anhedonia are associated with increased NAcc and dorsomedial PFC rs-FC among adults with community trauma exposure (Olson et al. 2018). Adults with comorbid PTSD and MDD demonstrate reduced rs-FC between the NAcc and thalamus, and between the NAcc and hippocampus, compared to individuals with PTSD only and trauma-exposed controls, though this study lacked an MDD-only group (Zhu et al. 2017). Lower structural integrity of the uncinate fasciculus, a white matter tract connecting prefrontal regions with limbic regions associated with reward processing, predicts both the presence of anhedonia at 6 months (Fani et al. 2019) and greater anhedonia severity at 12 months (Harnett et al. 2020) among individuals with recent trauma exposure. These findings highlight potential neural differences among individuals with trauma exposure versus those that have diagnoses of PTSD, as well as the importance of considering the influence of psychiatric comorbidities and immune function on reward-related circuitry among individuals with PTSD and trauma exposure.

In summary, there is growing evidence that individuals with PTSD demonstrate alterations in reward processing and circuitry across multiple units of analysis. Importantly, however, the number of existing studies is limited and often relied on small sample sizes, and there are heterogenous task designs across studies

(particularly those using neuroimaging methodologies). Further, the heterogeneity in trauma type and symptom presentation among individuals with diagnoses of PTSD likely contributes to the lack of clarity regarding reward processing and circuit alterations, as participants can meet DSM-IV-TR or DSM-5 diagnostic criteria for PTSD without endorsing any anhedonia symptoms. Accordingly, future studies would benefit from considering the symptom profiles of participants, as well as careful assessment of comorbid psychiatric disorders that are commonly associated with anhedonia and reward processing deficits (e.g., major depressive disorder). Doing so would clarify if only those individuals with PTSD who endorse anhedonia symptoms demonstrate alterations in reward processing and circuitry.

4 Areas of Future Research

The existing evidence suggests that anhedonia is an important feature of PTSD, yet a number of outstanding questions remain. First, the timing of the development of anhedonia in the trauma response trajectory remains unclear. Though anhedonia is an established consequence of trauma exposure and diagnostic feature of PTSD, there is growing evidence for the role of anhedonia as a pre-trauma risk factor for the development of PTSD (Risbrough et al. 2018). Additional evidence suggests that individuals with remitted PTSD and resilient responses to significant trauma exposure demonstrate alterations in reward processing at the behavioral and neural levels (Vythilingam et al. 2009; Kalebasi et al. 2015), but these studies employed cross-sectional designs and small sample sizes. Relatedly, anhedonia may increase risk of exposure to potentially traumatic events by contributing to increased stimulation-seeking or risk-taking behaviors (Testa and Steinberg 2010, though see Garfield et al. 2014 for discussion of limited evidence for anhedonia as a pre-morbid risk factor for substance use disorders). Longitudinal, prospective studies prior to and following trauma exposure are needed to elucidate the timing of anhedonia and reward processing alterations, which would inform prevention and intervention efforts.

Second, further investigation of facets of anhedonia in the context of PTSD is warranted. Factor models as described above group the PTSD symptoms of loss of interest, feelings of detachment from others and inability to feel positive emotions into a single anhedonia factor, yet these individual symptoms may relate to differential outcomes (e.g., Davis et al. 2014) and may require targeted interventions. For example, individuals with PTSD endorse more social anhedonia (the reduced ability to experience pleasure or reward from social interactions) than individuals with and without trauma exposure, and social anhedonia is associated with less social network diversity among individuals with PTSD and trauma exposure (Olson et al. 2020). Relatedly, service members with high levels of deployment trauma demonstrate pre- to post-deployment increases in their lack of taking others' perspectives (Moore et al. 2017), possibly indicative of detachment or estrangement from others. Future studies that focus on examinations of anhedonia among individuals with PTSD

should examine potential differential outcomes associated with various facets of anhedonia, similar to the approach often used in the reward processing literature.

Third, the examination of potential factors that moderate the development, maintenance, and endorsement of anhedonia among individuals with PTSD is an additional area of future research. One potential moderator is the type of trauma that the individual experienced, witnessed, or learned about. It is possible that exposure to specific types of trauma increases risk for anhedonic symptoms, such as interpersonal violence, and large-scale studies that sample across a range of trauma types are needed to explore this question. Additionally, demographic and cultural factors, such as racial or ethnic background, acculturation level, age and sex, may also moderate anhedonia, particularly given evidence that associations between self-reported anhedonia, momentary emotional experience, and life satisfaction varies across ethnic groups (Chentsova-Dutton et al. 2015) and that sex moderates reward processing among individuals with PTSD (Nawijn et al. 2015).

Finally, current frontline evidence-based psychotherapies for PTSD do not explicitly target symptoms of anhedonia and to the best of our knowledge, the effects of these treatments on anhedonia have not yet been studied. Indeed, a review of empirically-supported PTSD interventions found that positive emotions and cognitions are rarely the focus of therapeutic intervention (Contractor et al. 2020). Established psychotherapies for depression and anxiety have limited effects on increasing positive affect, including those that purportedly target this construct (Moore et al. 2013; Boumparis et al. 2016; Chaves et al. 2017; Sewart et al. 2019; Dunn et al. 2020; see also Sandman and Craske 2021). As a result, investigators have begun to develop and test novel psychotherapies that focus on positive affect. These targeted positive affect interventions are efficacious in increasing positive affect, as well as reducing negative affect and depression and anxiety symptoms, compared to active (Craske et al. 2019) and waitlist (Taylor et al. 2017) conditions in randomized trials (though see McMakin et al. 2011 for mixed results of a positive affect regulation intervention). It is also possible that anhedonia may moderate the effects of evidence-based trauma psychotherapies. In addition to psychotherapeutic treatments for anhedonia, investigators have begun to demonstrate beneficial effects of novel interventions on increasing positive affect or reducing anhedonia, including positive memory recall (Contractor et al. 2018), positive scene viewing in a virtual reality environment (Chen et al. 2021), a selective κ-opioid receptor antagonist (Krystal et al. 2020), and intravenous ketamine (Rodrigues et al. 2020). It is imperative that these promising psychotherapeutic, pharmacological, and device-based interventions, to date primarily tested in individuals with depression and anxiety symptomatology, are also tested and potentially adapted for use with individuals with PTSD in order to make progress in the treatment of anhedonia within this population.

Acknowledgements Support for this work includes NIMH P50MH096889 (Dr. Risbrough), VA Merit Award and NIH R01AA026560 (Dr. Risbrough), project No. SDR 09-0128 (Dr. Risbrough) from the Veterans Administration Health Service Research and Development, the US Marine Corps and Navy Bureau of Medicine and Surgery (Dr. Risbrough), the Office of Academic Affiliations,

Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs (Dr. Vinograd), VA Clinical Science Research and Development Career Development Award IK2 CX001861 (Dr. Stout), and the Center of Excellence for Stress and Mental Health (all authors). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Disclosures/Conflicts of Interest The authors report no conflicts.

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Anhedonia in Anxiety Disorders

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Contents

Abstract Humans, like other animals, are fundamentally motivated to pursue rewarding outcomes and avoid aversive ones. Anxiety disorders are conceptualized, defined, and treated based on heightened sensitivity to perceived aversive outcomes,

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Curr Topics Behav Neurosci (2022) 58: 201–218
https://doi.org/10.1007/7854_2022_319
Published Online: 25 March 2022

including imminent threats as well as those that are uncertain yet could occur in the future. Avoidance is the central strategy used to mitigate anticipated aversive outcomes – often at the cost of sacrificing potential rewards and hindering people from obtaining desired outcomes. It is for these reasons that people are often motivated to seek treatment. In this chapter, we consider whether and how anhedonia – the loss of interest in pursuing and/or reduced responsiveness to rewarding outcomes – may serve as a barrier to recovering from clinically impairing anxiety. Increasingly recognized as a prominent symptom in many individuals with elevated anxiety, anhedonia is not explicitly considered within prevailing theoretical models or treatment approaches of anxiety. Our goal, therefore, is to review what is known about anhedonia within the anxiety disorders and then integrate this knowledge into a functional perspective to consider how anhedonia could maintain anxiety and limit treatment response. Our overarching thesis is that anhedonia disrupts the key processes that are central to supporting anxiety recovery. We end this chapter by considering how explicitly targeting anhedonia in treatment can optimize outcomes for anxiety disorders.

Keywords Anhedonia · Anxiety · Positive affect · Reward · Threat · Treatment

1 Introduction

Anxiety disorders are defined based on excessive and persistent fear, anxiety, and/or avoidance of perceived threats – whether imminent (e.g., being criticized after sharing one's opinion) or in the future (e.g., losing one's job). They are classified into discrete categories based on the core source of threat and include social anxiety disorder (SAD; fear of embarrassment or negative evaluation in social/performance situations), panic disorder (PD; fear of having a panic attack and its consequences), and generalized anxiety disorder (GAD; worry about uncertain future threats). Responses to perceived threat originate from a defensive motivational system that operates to protect the organism from danger. The perception of threat activates heightened expectancies about the likelihood and cost of aversive outcomes. Inflated threat expectancies induce subjective distress (e.g., anxiety, fear), defensive physiological states (e.g., increased heart rate), and avoidance behaviors intended to mitigate perceived danger. Avoidance behaviors provide temporary relief from anxiety; however, they can maintain exaggerated threat responses over the long-term because the individual fails to learn the situation poses less danger than predicted. Cognitive behavioral models posit that recovery from anxiety disorders is predicated on individuals repeatedly confronting avoided threat-relevant cues or contexts and learning that the threat stimulus is no longer associated with aversive outcomes (Craske et al. 2008). This is the central premise underlying empirically supported exposure-based therapies for anxiety; however, only half of patients achieve a clinically significant response from these first-line treatments (Loerinc et al. 2015). We consider whether and how anhedonia may account in part for incomplete recovery that afflicts a sizeable proportion of the anxiety disorder population.

2 Anhedonia in Anxiety: Early Observations to Current Empirical Status

Initial signs pointing to the presence of anhedonia in anxiety disorders originated from the tripartite model of emotional disorders (Clark and Watson 1991). Anhedonia, a clinical symptom defined by diminished interest in pursuing and/or response to pleasurable or meaningful activities, was initially hypothesized to distinguish depression from anxiety disorders. Early tests of this framework suggested SAD was the exception to the rule – demonstrating associations with anhedonia comparable to those observed for depression (Brown et al. 1998). Accumulating evidence has since established a link between anxiety and anhedonia across various samples (e.g., clinical and non-clinical) and methods of assessment. Much of this evidence comes from surveys measuring temperament or personality (e.g., behavioral activation system; positive emotionality), positive affect (PA; i.e., the frequency and intensity of experiencing positive valence emotions), or clinical symptoms of anhedonia (i.e., pleasure related to specific activities). Among the anxiety disorders, SAD shows the most reliable associations with anhedonia – in studies ranging from surveys of trait-like positive emotionality (Naragon-Gainey et al. 2009) to daily PA (Kashdan and Steger 2006), and confirmed through meta-analysis (Kashdan 2007). Although depression symptoms frequently co-occur with anxiety, this does not fully explain the link between social anxiety and low PA (Kashdan 2007). Depression comorbidity, however, is more common in the subgroup of individuals with SAD characterized by low positive emotionality (Tung and Brown 2020). The link between self-reported anhedonia/low PA and GAD is less well-established – some studies observe an association (e.g., Prenoveau et al. 2010), whereas others do not (Brown et al. 1998; see review by Seager et al. 2019). Anhedonia is not associated with PD in the absence of co-occurring depression (Brown et al. 1998; Prenoveau et al. 2010).

Beyond subjective experiences of diminished interest or pleasure, anhedonia can be understood and studied as a set of dynamic and interactive components unfolding along the temporal stream of reward processing. Neuroscience-informed models of anhedonia (Der-Avakian and Markou 2012) generally agree that reward processing includes: (1) *reward valuation* – the process of predicting the magnitude, likelihood, time horizon, and effort required to obtain a reward; (2) *reward responsiveness* – hedonic experiences during anticipation and receipt of rewards; and (3) *reward learning* – i.e., the process of integrating information about expected vs. actual reward outcomes, which informs future expectancies of reward acquisition and behavior. Evidence supporting the link between anhedonia and deficits in each of these component processes comes primarily from research in depression (see chapter "Anhedonia in Depression and Bipolar Disorder NB" of this Book). Here, we summarize the empirical literature within anxiety disorder and high symptom (analogue) samples specifically.

2.1 Reward Valuation

Reward valuation begins with the individual determining (1) *reward probability*, namely the value of a reinforcer according to its magnitude, valence, and likelihood, (2) the *delay* until the reinforcer will be delivered (immediate vs. future), and (3) the *effort* required to obtain the reward (i.e., perceived costs of physical or cognitive effort required). This information is integrated into a net value signal that informs decisions to pursue the reinforcer and motivation to perform actions required to obtain the reinforcer. A limited body of research links the presence of anxiety with reduced reward probability estimates. Blair et al. (2017) reported a significantly reduced likelihood of predicting future positive events in those with GAD relative to those with SAD and healthy controls. SAD and control participants did not differ, suggesting intact reward probability for those with SAD; however, future probability estimates were made in relation to both social and non-social events, which may have diluted effects in SAD. In support of this hypothesis, another study found individuals with SAD underestimated the likelihood and overestimated the aversiveness of positive social outcomes (Gilboa-Schechtman et al. 2000), suggesting reward probability may be diminished and negatively biased in response to future *social* events specifically (cf. generalized reward expectancy deficits in GAD). Beyond disorder-specific anxiety, evidence suggests that general anticipatory anxiety may also impact hedonic expectancy. In a non-clinical sample, different patterns of neural activation were observed under experimentally induced high vs. low anticipatory anxiety states (threat of shock) in mesolimbic regions that code for the subjective value of expected positive vs. negative valence outcomes (Engelmann et al. 2015). Specifically, when participants selected among outcomes that involved varying magnitudes of possible (but not certain) monetary gains vs. losses, heightened threat expectancies appeared to shift neural valuation from potential positive to aversive outcomes during decisions that could lead to either.

Research findings on the preference of reward timing (delay) in anxiety are mixed. Some studies found that higher self-reported social anxiety (Rounds et al. 2007) or intolerance of uncertainty (Luhmann et al. 2011) was associated with more preference for immediate versus delayed rewards, whereas others failed to find a relationship (Jenks and Lawyer 2015; Steinglass et al. 2017), and still others found trait anxiety was linked to more preference for delayed rewards (Steinglass et al. 2017). To the best of our knowledge, no studies have examined effort for rewards in the context of anxiety. Evidence from depression samples suggests, however, that anhedonia is related to less effort in pursuit of rewards (Treadway et al. 2012). In summary, although studies on reward valuation in anxiety are few and results are mixed across samples, findings generally point to alterations in reward valuation processes in the presence of anxiety.

2.2 Reward Responsiveness

After an incentive value has been assigned, anticipatory processes orient the individual and mobilize resources toward obtaining desired outcomes. Responsiveness to reward can be characterized as the processes evoked from (1) cues signaling a future positive reinforcer (*anticipation*); (2) initial presentation of a positive reinforcer (*initial responsiveness*); (3) changes in the incentive value of a reinforcer over time as that reinforcer is experienced (*satiation*). Neuroimaging work consistently demonstrates alterations in mesolimbic networks involved in reward processing in anxiety disorders (e.g., Richey et al. 2017). Specifically, there is a body of evidence showing hypoactivation in the ventral striatum in anticipation of reward. The majority of the research involved SAD samples using social reward (e.g., Cremers et al. 2015; Richey et al. 2017), but similar patterns of findings have been reported using monetary rewards in the consumption phase in GAD (e.g., Kessel et al. 2015) and the anticipation phase in PD (e.g., Held-Poschardt et al. 2018). Of note, hypoactivation in SAD may be specific to social versus monetary rewards (Richey et al. 2017) and is not observed in adolescents with SAD who instead show *heightened* neural response to reward incentives (Guyer et al. 2012; see Sect. 3.1). Data from daily diary studies (e.g., Kashdan and Steger 2006) show that people with elevated social anxiety report less pleasure from social and non-social positive everyday experiences; however, following positive events perceived as particularly intense, individuals with elevated (cf. low) social anxiety appear to experience *greater* psychological benefits (e.g., reduced anxiety; Doorley et al. 2021). Collectively, research suggests that aberrant neural patterns involved in reward motivation and generally blunted responsivity are present in those with anxiety. It remains unclear, however, whether anxious arousal/threat sensitivity or anhedonia is the mechanism underlying altered reward responsiveness.

2.3 Reward Learning

Actual reward outcomes are compared against anticipated rewards (reward prediction error), which guides learning about the likelihood of obtaining future rewards and the actions required to do so (probabilistic and reinforcement learning). Individuals with anxiety disorders make more errors than healthy controls on reinforcement-based decision-making tasks (e.g., choosing between two objects associated with different levels of reward or punishment; DeVido et al. 2009), which might suggest difficulty incorporating recent learning. For example, people with GAD made significantly more errors in the later (but not early) blocks of a reinforcement-based decision task compared to healthy controls (White et al. 2017). However, several studies failed to find an association between alterations in reward learning and anxiety disorders. For example, performance on a signal-detection task that rewarded one response option more frequently than the other (probabilistic

reward task; Pizzagalli et al. 2005) revealed that individuals diagnosed with GAD showed intact reward learning compared to healthy controls (Morris and Rottenberg 2015). Using a similar task, people with major depressive disorder, SAD, and healthy controls did not differ on probabilistic reward learning performance (Reilly et al. 2020). However, self-reported anhedonia symptoms across diagnoses were associated with impaired reward learning, whereas anxious arousal and general distress symptoms were not. Therefore, poor reward learning may be a consequence of anhedonia rather than anxiety-related symptoms per se. Because some studies used tasks that involved the potential for either punishment or reward on a given trial (cf. reward only), discrepancies observed across studies may also reflect the interactive effect of stress in the presence of reward on learning.

3 Vulnerability and Amplifying Factors

3.1 Etiological Origins

Anxiety disorders appear to be characterized by deficits within each reward processing phase, at least in part driven by anhedonia rather than anxious arousal/threat sensitivity. Each of these processes is dynamically influenced by genes, temperament, culture, and social learning histories that shape currently held beliefs (e.g., perceived success of obtaining positive outcomes), values (e.g., outcome importance), and goals (e.g., balance of rewards to punishments; see review by Kujawa et al. 2020). To briefly expand, genetic susceptibility to heightened reactivity to both the positive and negative effects of environment possibly elevates the risk for anhedonic processes (Belsky 2013). Likewise, prior learning histories involving failed reward acquisition also contribute to the onset and maintenance of altered reward processing (e.g., Richey et al. 2019). Additionally, certain temperaments such as behavioral inhibition and activation (see review by Katz et al. 2020) and personality factors like neuroticism are associated with blunted reward processing (e.g., Bondy et al. 2021). That traits assumed to be parts of punishment/aversion systems are associated with blunted reward processing (in addition to those arising from the appetitive/approach system) could suggest a possible bimodal or interactive pathway to anhedonia. Beyond general approach-avoidance tendencies, individual and situation-specific reward-cost goals play a role in each phase of reward processing (e.g., Gable and Impett 2012).

There are some differences in reward processing along development worth noting. Specifically, SAD in adolescents is associated with greater reward sensitivity (e.g., Guyer et al. 2012), whereas SAD in adults is associated with blunted reward reactivity (e.g., Richey et al. 2017). This may reflect the consequences of repeated failed attempts to obtain rewards throughout adolescence into adulthood (Richey et al. 2019) or may be suggestive of an initial pattern of hypersensitivity that diminishes over time from over-activation. Relatedly, anxiety disorders are characterized by heightened chronic stress and stress reactivity, which may consequently

increase anhedonia (Pizzagalli 2014), consistent with the robust body of evidence showing anxiety disorders precede depression (e.g., Batterham et al. 2013). Finally, avoidance of situations due to anxiety limits exposure to positive experiences and reinforcers, possibly increasing both anxiety and hedonic atrophy (e.g., Winer et al. 2017).

3.2 Cognitive and Regulatory Anhedonia Amplifiers

Reward processing is also influenced by (1) *cognitive processes* that prioritize salient cues (attentional bias), alter the meaning of attended to information (interpretation bias), determine which information is encoded in memory and later retrieved (memory bias), and impact ability to envision personal future events (episodic future thinking), as well as (2) *regulatory processes* serving to up- or downregulate a given experience (e.g., emotion suppression vs. expression, dampening vs. amplifying). Together, these processes can shape how individuals experience positive emotions and events. Individuals with both clinical and non-clinical levels of anxiety have been shown to allocate attention away from rewards relative to threats (Winer and Salem 2016), interpret positive events negatively (Alden et al. 2008), recall positive memories as less positive (Glazier and Alden 2019), and rely on emotion regulation strategies to suppress the experience or expression of positive emotions (Eisner et al. 2009) – all of which may interfere with reward processing. For example, (a) diminished attentional allocation for reward cues may reduce their salience and influence reward valuation processes (Winer and Salem 2016); (b) negative interpretations of positive outcomes (e.g., Alden et al. 2008) could influence the predicted magnitude and valence of potential rewards and responsiveness to rewards by decreasing hedonic experiences and heightening aversive experiences; (c) diminished memory for positive valence events could reduce reward learning (e.g., outcomes were remembered as less positive than they were; Glazier and Alden 2019) which could in turn bias reinforcement learning and future reward valuation processes; and (d) reduced ability to imagine future positive outcomes and their hedonic impact (for a review see Miloyan et al. 2014) could decrease expected reward prediction. Emotion regulation strategies can change the intensity of affective experience (Sheppes et al. 2014). Therefore, positive emotion suppression (i.e., inhibiting outward expression; e.g., Kashdan and Breen 2008) and/or dampening of positive experiences (i.e., minimizing; Eisner et al. 2009) may lead to diminished responsiveness to reward cues and could interfere with reward learning and future valuation. Whether directly modifying cognitive and regulatory processes could augment reward processing in anxiety disorder samples is an open question for future research.

4 A Functional Account of How Anhedonia Could Impede Recovery from Anxiety

Overcoming excessive, chronic, and impairing anxiety is hard work. Current evidence-based therapy approaches require one to repeatedly confront and remain in the presence of (rather than avoid) perceived threat while tolerating associated aversive internal experiences in the service of facilitating new learning. Anhedonia is proposed to be a key disruptor of these processes and therefore a barrier to recovery. See Fig. 1.

4.1 Sacrificing Rewards Due to Costly Avoidance

The decision to engage with typically avoided threat-relevant contexts to achieve desired outcomes is determined by the valuation of potential rewards alongside threat-relevant costs. If anticipated rewards are perceived to be small, unlikely, temporally distant (delayed), and/or too effortful (costly), the balance will be tipped in favor of continued anxiety-related avoidance. Because anxiety disorders are characterized by blunted reward valuation, under-valued rewards may be sacrificed in favor of avoidance. Consistent with this perspective, individuals with elevated anxiety (and those with anxiety disorders; Pittig et al. 2021) fail to reduce threat-induced avoidance behavior that competes with potential reward acquisition (e.g., money, social approval; see review by Pittig et al. 2020). Reward-induced reduction of avoidance does not appear to attenuate fear responses but does facilitate fear extinction learning once the aversive outcome is no longer present (e.g., Pittig 2019), suggesting that intact reward sensitivity may encourage people to tolerate aversive experiences (Craske et al. 2008). Whether failure to reduce threat-related avoidance behavior reflects a lower sensitivity for competing rewards, a higher sensitivity to

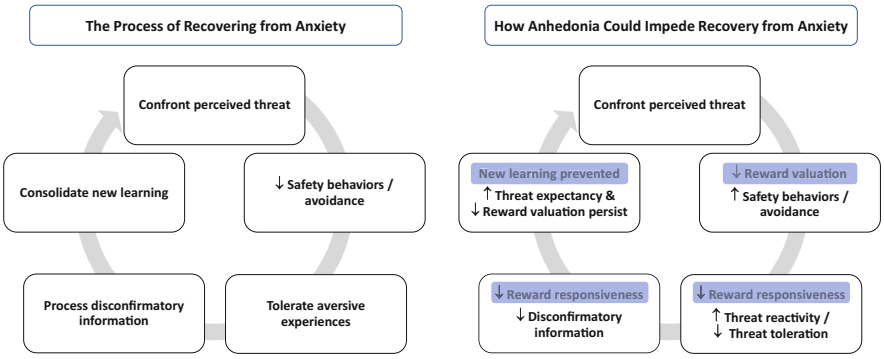

Fig. 1 The process of recovering from anxiety through exposure-based approaches and how anhedonia could interfere

aversive outcomes, or some combination remains unknown. However, to the extent that anhedonia diminishes one's sensitivity to rewards, it would be expected that anxious patients with co-occurring anhedonia would be especially likely to sacrifice potential rewards in service of continued avoidance of perceived threats. Those functional consequences could be reflected in avoidance of naturally occurring reward opportunities when threat is present, failure to seek out or initiate treatment, and/or reduced engagement in treatment activities that involve confronting threat-relevant contexts. Research is needed to test those predictions.

4.2 Consequences of Diminished Responsiveness

Diminished anticipatory and/or consummatory reward responsiveness may disrupt processes occurring before or during therapeutic exposures to threat that require the individual to initiate approach toward and remain engaged with threat-relevant contexts until new learning occurs. Reduced reward anticipation may lead the individual to devote more resources toward averting potential aversive outcomes (e.g., engaging in safety behaviors) rather than garnering positive ones, which may limit their success in achieving desired outcomes (Taylor and Alden 2011). Diminished responsiveness to rewarding outcomes during or after an exposure may bias outcome appraisals (i.e., reduced reward prediction error) and reduce the likelihood (through blunted reinforcement learning and subsequent valuation) that the individual will engage with similar contexts again in the future. Additionally, anhedonia may interrupt positively valenced subjective experiences following the omission of expected negative outcomes. Violation of negative (threat) expectancies is theorized as the core mechanism that facilitates response to exposure-based therapies (Craske et al. 2008). Relief experienced following the omission or reduction of an anticipated aversive outcome can be subjectively pleasurable and relies on the same mesolimbic circuit involved in reward processing (Leknes et al. 2011). Anhedonia may therefore blunt hedonic responses to either the presence of rewards and/or the absence of threats, both of which would be expected to perpetuate future avoidance behavior and prevent new threat-inconsistent learning.

4.3 Lessons from Positive Emotion Science

Positive affect is the subjective emotional experience that occurs in response to anticipating and/or receiving rewards. Although not synonymous with anhedonia, diminished PA represents its primary subjective experience. Research from non-clinical samples demonstrates that positive emotions support many of the processes believed to optimize responses to acute threat and promote new, non-threat learning – the key drivers of successful response to exposure-based treatments for anxiety. Individual differences in positive emotions as well as

experimentally inducing positive emotions relative to neutral or negative emotions (e.g., sadness): (1) downregulates the physiological sequelae of threat reactivity, including speeding cardiovascular recovery following exposure to impending threat (Fredrickson et al. 2000); (2) facilitates tolerance of aversive experiences (de Wied and Verbaten 2001); (3) promotes adaptive coping strategies (e.g., positive reappraisal) in stressful situations (Tugade and Fredrickson 2004; and (4) increases awareness and assimilation of new information including widening attentional scope, increasing cognitive flexibility, and promoting openness to new information and patterns of information processing (see review by Fredrickson 2013). PA has also been shown to facilitate mechanisms that support learning and memory, including enhancing encoding, rehearsal, and retrieval (see review by Zbozinek and Craske 2017a). Finally, positive emotions can facilitate the initiation and maintenance of new behavioral intentions. Experimental studies in non-clinical samples reveal that PA experienced during a given activity induces approach motivation and effort for that activity (see review by Van Cappellen et al. 2018). This effect may even translate to supporting targeted longer-term behavior change (e.g., Cohn and Fredrickson 2010). To the extent that anhedonia robs individuals of positive emotional experiences, it would be expected to perpetuate heightened threat reactivity, reduce tolerability of aversive experiences, inhibit assimilation of new, threat-inconsistent information, and interfere with enduring behavior change directed toward threat-opposing actions.

4.4 Anhedonia and Threat Reactivity in Analogue and Clinical Samples

Studies using laboratory fear conditioning and extinction paradigms in healthy samples – an experimental analogue of exposure therapy – suggest positive emotions may inhibit the return of fear following extinction training (Zbozinek and Craske 2017b; Zbozinek et al. 2015). In a cross-sectional study, higher PA (but not negative affect) before and after extinction was associated with less return of fear during reacquisition as measured by skin conductance arousal and fear expectancy (Zbozinek and Craske 2017b). Experimental evidence shows positive mood induction prior to extinction training can decrease the subsequent negative valence of conditioned aversive stimuli and lessen the return of fear during reinstatement 1 week later (Zbozinek et al. 2015). A cross-sectional study of young adults found anhedonia (but not general distress or fears) was associated with increased activity in threat-related neural circuitry (e.g., amygdala, anterior insula) in response to an extinguished threat stimulus (Young et al. 2021). Those findings suggest a persistence of inflated threat reactivity when danger is no longer present – converging with prior studies linking positive emotions and extinction learning in healthy subjects. In a sample of adults with SAD and those without (Taylor et al. 2020b), higher PA significantly predicted lower anticipatory anxiety and less anxiety-related behavior

(markers of diminished threat reactivity) in response to a social stressor, even beyond level of negative affect. In summary, emerging evidence from fear conditioning paradigms and anxiety disorder samples supports an association between anhedonia (including diminished PA) and both inflated threat reactivity and impaired non-threat learning. Although these studies cannot speak to the mechanism underlying the anhedonia-threat reactivity link (e.g., cognitive flexibility, openness to new information, fear tolerance), they suggest anhedonia may perpetuate anxiety and impede extinction learning.

5 Treatment Implications

5.1 Anhedonia as a Predictor of Treatment Response

To the extent that anhedonia perpetuates avoidance in the face of rewards, exaggerates threat reactivity, inhibits threat-inconsistent behavior change, and/or interferes new learning, it would be expected to predict response to contemporary exposure-based treatments for anxiety. Several studies support this prediction. In a sample of patients with PD or GAD receiving exposure-based cognitive behavioral therapy (CBT), higher pre-treatment levels of trait positive emotionality predicted superior treatment response (i.e., greater reduction in anxiety symptoms and fewer symptoms post-treatment), even when accounting for baseline depression, neuroticism, or disorder-specific symptom severity (Taylor et al. 2017a). Responder status was greater in participants who scored above the normative sample mean on positive emotionality vs. those who scored below (71% vs. 40%). Similarly, higher trait levels of self-reported reward responsiveness in youths (ages 7–17) completing CBT for anxiety predicted lower post-treatment anxiety and depression symptoms, improved functioning, and responder status (Norris et al. 2021). Younger (but not older) youth with higher reward sensitivity completed more exposure exercises, suggesting a greater willingness to confront threat-related contexts as part of treatment. One study, however, did not find evidence that baseline levels of PA predicted response to CBT or acceptance and commitment therapy for SAD (Sewart et al. 2019).

Initial evidence suggests neural markers of reward processing predict exposure therapy success. In a sample of youths (ages 9–14) receiving CBT for an anxiety disorder, treatment responders displayed greater pre-treatment striatal activation (encompassing the bilateral subgenual anterior cingulate cortex extending into the nucleus accumbens) to monetary rewards vs. losses relative to non-responders (Sequeira et al. 2021). In a sample of adults diagnosed with spider phobia, superior response to exposure therapy was predicted by higher neural activation in the ventrolateral prefrontal cortex during reward anticipation – a region involved in attentional allocation toward reward cues and goal-directed behavior that is positively associated with reward sensitivity (Papalini et al. 2019). Yet, hypothesized activation differences in mesolimbic brain regions involved in reward anticipation

and outcome processing were not predictive of outcome. In contrast to the hypothesis that anhedonia predicts worse treatment outcomes, one study in adults receiving CBT for anxiety revealed that better treatment response was predicted by blunted reward responsiveness as measured using the reward positivity (RewP) event-related potential component (Burkhouse et al. 2016). Some evidence therefore suggests that anhedonia may interfere with treatment response, yet other studies did not find it to be predictive of response or to predict better response. Given the heterogeneity of samples, assessments, and treatment approaches, more work is needed to reconcile those outcomes. It also suggests that personalized approaches to treatment are likely needed based on an idiographic understanding of anhedonia across its different component processes.

Studies examining anhedonia as a predictor of pharmacotherapy response for anxiety are sparse and were conducted in combined anxiety and depressive disorder samples – often collapsing outcomes across psychosocial and pharmacological interventions. Results are mixed and generally consistent with findings observed for prediction of exposure-based psychotherapy outcomes; for example, higher pre-treatment positive affect predicted superior response in adolescents receiving CBT, selective serotonin reuptake inhibitors (SSRIs), or their combination (Forbes et al. 2012), whereas reduced reward responsiveness (RewP) in adults predicted a greater reduction in depressive (but not anxiety) symptoms following SSRIs (Burkhouse et al. 2018). It remains to be established, however, whether anhedonia predicts recovery to pharmacotherapy for anxiety disorders specifically.

5.2 Anhedonia as a Treatment Target to Improve Outcomes for Anxiety

Extant literature suggests directly targeting anhedonia may improve response to traditional exposure-based therapies for anxiety. Emerging behavioral treatments focused on transdiagnostic deficits in PA and reward processing across the anxiety and mood disorders have shown promise in improving positive emotions to levels beyond that which is typically achieved with established negative valence treatments (Craske et al. 2019; Taylor et al. 2017b) as well as strengthening functional connectivity in reward processing brain regions (Kryza-Lacombe et al. 2021; see chapter "Psychological Treatments for Anhedonia" of this Book for a review of anhedonia-targeted interventions). These interventions use cognitive and behavioral strategies to increase exposure and responsiveness to rewarding experiences, for example, attending to positive aspects of events (including events perceived to be neutral or negative), savoring, gratitude, and engaging in kind or generous acts. Pharmacotherapies that engage neural systems believed to underlie anhedonia (e.g., enhancing dopamine signaling) have also shown promise in improving neural responsiveness to reward (in depression; Admon et al. 2017) and enhancing fear extinction learning (Esser et al. 2021). It remains to be established, however, whether and how these

psychosocial or pharmacological treatments improve response to exposure-based therapies for anxiety disorders specifically. It is also unknown which reward processing components are most critical to target in facilitating treatment response, and which specific treatment activities are most efficacious in targeting those deficits. For example, some strategies may enhance reward outcome expectancies (e.g., visualizing one's best possible future; Taylor et al. 2017b, or episodic future thinking; Hallford et al. 2020), whereas others may potentiate reward responsiveness and valuation (e.g., reminiscing about positive memories; Speer et al. 2014). Determining the optimal timing and dose of anhedonia-targeted interventions in the context of anxiety recovery will also be important (e.g., directly within the context of exposure exercises vs. sequencing treatments). Aside from facilitating anxiety reduction in therapy, targeting anhedonia may improve other outcomes governed by the positive valence system (e.g., social functioning; Taylor et al. 2020a; psychological well-being; Das et al. 2020) that show modest response to first-line approaches (Hofmann et al. 2014).

6 Concluding Remarks

Once considered to be a symptom that distinguished the anxiety disorders from depression, anhedonia is now recognized as a prominent feature of many individuals meeting diagnostic criteria for a principal anxiety disorder. Evidence across neural, behavioral, and self-report units of analysis points to deficits in multiple domains of reward processing, including valuation, responsiveness, and learning. This literature, however, is relatively nascent. Some reward processing domains (e.g., effort) have not been examined in anxiety disorder samples, and few attempts have been made to untangle the relative influence of anhedonia vs. anxious arousal/threat sensitivity to observed reward processing deficits. It remains an open question, therefore, to what extent such deficits are the result of low reward sensitivity, heightened threat sensitivity, or both. This issue is especially relevant for anxiety disorders wherein reward processing in real life often occurs against the backdrop of heightened sensitivity to aversive outcomes. Given heterogeneity within and across the anxiety disorders, it is likely that anhedonia varies considerably across individuals and may characterize a meaningful subtype within the overarching class of anxiety disorders (e.g., Tung and Brown 2020). Although this chapter focused on anhedonia as a maintenance factor in anxiety, it is also possible that anhedonia presages anxiety onset – a question ripe for empirical inquiry. To the extent that it is present, anhedonia may prevent anxious individuals from achieving optimal outcomes through several mechanisms, including perpetuating costly avoidance, elevating threat reactivity, diminishing tolerance of aversive experiences, and impairing new learning. Directly targeting anhedonia in anxiety disorder treatment may therefore boost response to first-line exposure-based treatments. Exactly when and how best to do so remains an important unanswered question. We hope this chapter will encourage researchers to address this and other related questions.

Disclosures Dr. Taylor's effort was partially supported by the National Institute of Mental Health (R33MH113769). Dr. Taylor declares that in the past 3 years he has been a paid consultant for Bionomics, and receives payment for editorial work for *UpToDate* and the journal, *Depression and Anxiety*. All other authors report no potential conflicts of interest.

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Anhedonia in Eating Disorders

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Contents

Abstract Anhedonia is frequently observed among individuals with eating disorders (ED), though its relevance to ED pathology and clinical outcomes remain poorly understood. This chapter will present the latest findings regarding anhedonia in ED, with the majority of data available for anorexia nervosa (AN) and bulimia nervosa (BN). We consider anhedonia from the mechanistic lens of altered reward processing, with attention given to subjective experience, neurotransmitter function, neural correlates, and cognitive performance corresponding to distinct components of reward (i.e., liking, wanting, and learning). Findings from animal models are also highlighted. The chapter concludes with a discussion of implications for treatment and future directions aimed at better understanding anhedonia in ED.

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Curr Topics Behav Neurosci (2022) 58: 219–236
https://doi.org/10.1007/7854_2021_287
Published Online: 30 December 2021

Keywords Anhedonia · Anorexia nervosa · Bulimia nervosa · Eating disorders · Reward

1 Introduction

Eating disorders (ED) are severe, life-threatening, and often chronic psychiatric illnesses. Anorexia nervosa (AN) is marked by caloric restriction, low body weight, a profound fear of weight gain, and a disproportionate influence of shape or weight on one's self-esteem. Individuals with bulimia nervosa (BN) also show overvaluation of shape and weight on self-worth but engage in regular episodes of binge eating and the use of inappropriate weight control behaviors to compensate for caloric intake (e.g., self-induced vomiting, excessive exercise, or misuse of laxatives) and are not low weight. Individuals with ED often report anhedonia defined by the DSM-5 (American Psychiatric Association 2013) as diminished interest in or ability to experience pleasure from activities or stimuli that were previously enjoyed (Boehm et al. 2018; Davis and Woodside 2002). Though the precise etiology of ED remains unknown, increasing evidence points to neurobiological alterations in reward processing underlying extremes of eating behavior (Wierenga et al. 2014) which may also contribute to clinical presentations of anhedonia. While traditional definitions of anhedonia focus largely on a diminished subjective experience of pleasure, contemporary models specify distinct reward processes as contributing to anhedonia, including reduced motivation to pursue rewards ("wanting"), reduced pleasure derived from reward ("liking"), and reduced ability to modify behavior based on reward feedback (i.e., learning; Thomsen et al. 2015). As discussed throughout the chapter, existing data consistently indicate elevated anhedonia in ED samples, whereas data regarding the involvement of distinct components of reward processing in ED remain mixed, warranting further study.

2 Clinical Presentation of Anhedonia in ED

Though somewhat limited, self-report measures show that ED are characterized by elevated anhedonia (see Table 1) with available data suggesting that one third of patients with AN report clinically elevated anhedonia (Boehm et al. 2018). Common self-report measures assess general or physical anhedonia (e.g., enjoyment of television, beautiful scenery, food). Importantly, studies have confirmed higher anhedonia in AN even after removing food-related items from self-report measures, given the disorder-specific nature of such stimuli (Boehm et al. 2018). ED are frequently co-morbid with depression, making it difficult to determine whether higher anhedonia scores are state or trait-related features of ED. To better understand this, Boehm et al. (2018) measured both depression and anhedonia in acutely ill and recovered

Table 1 Means and standard deviations of self-report measures assessing general/physical and social anhedonia in eating disorders

		AN		RAN		BN		ED		HC			Comparison
Citation	Measure	M	SD	M	SD	M	SD	M	SD	M	SD	*d*	
General/physical anhedonia													
Eiber et al. (2002)	a	31.1	2.1			31.1	3.9					0	AN vs. BN
Davis and Woodside (2002)	a	20.9	7.5			13.3[a]	7.2					–	
Deborde et al. (2006)	a							18.7	10.1	10.6	5.6	–	
Boehm et al. (2018)	b	2.43	2.55	1.61	1.78					0.87	1.57	0.7	AN vs. HC
Social anhedonia													
Eiber et al. (2002)	c	14.5	9.4			11.7	6.2					0.4	AN vs. BN
Deborde et al. (2006)	c							11.9	6.5	6.9	4.2	–	
Tchanturia et al. (2012)	d	16.4	8.6	9.5	6.7	17.2	8.3			5.5	4.7	1.6; 1.7; 0.1	AN vs. HC; BN vs. HC; AN vs. BN
Harrison et al. (2014)	d	16.2	8.8	11.2	8.4	15.3	8.4			6.1	5.2	1.4; 1.3; 0.1	AN vs. HC; BN vs. HC; AN vs. BN

a = Chapman's Physical Anhedonia Scale; b = Snaith-Hamilton Pleasure Scale; c = Chapman's Social Anhedonia Scale; d = Revised Social Anhedonia Scale; *AN* Anorexia Nervosa, *RAN* Anorexia Nervosa, Remitted/Recovered, *BN* Bulimia Nervosa, *ED* Patients with Eating Disorders, *HC* Healthy Controls

[a]BN nonexcessive exercisers (BN excessive exercisers report M (SD) = 17.8 (7.2)

patients with AN (RAN). Results showed significantly lower depression scores in RAN compared to patients who were acutely ill; in fact, these scores were not significantly different from healthy controls. In contrast, though anhedonia scores also tended to improve with weight restoration, anhedonia remained higher in RAN compared to healthy controls. Together, these findings provide initial data dissociating depression and anhedonia in AN and suggest that anhedonia may be a residual symptom or trait-based characteristic of AN.

The literature remains mixed regarding whether differences in anhedonia exist between ED diagnostic groups, with one study showing that participants with AN report higher anhedonia compared to those with BN (Davis and Woodside 2002) and another showing no difference (Eiber et al. 2002). When observed, elevated anhedonia in AN relative to BN has been thought to account for symptom divergence; "individual differences in sensitivity to reward contribute to the respective avoidance and approach relationships to food found in these two groups" (p.192; Davis and Woodside 2002). To the best of our knowledge, studies have not yet explored anhedonia among patients with binge eating disorder (BED). However, a recently proposed theoretical maintenance model of BED posits that individuals may engage in binge eating to compensate for low positive affect (Mason et al. 2021). Little is known about anhedonia in avoidant/restrictive food intake disorder (ARFID) as well. Interestingly however, one study found no differences in anhedonia between youth with ARFID, AN, BN, or other specified feeding and eating disorder (OSFED; Nicely et al. (2014)). Given the high rates of anhedonia observed in AN and BN, this suggests that research is needed to better understand anhedonia in individuals with other ED subtypes.

Additional research has sought to explore the relevance of other trait-based factors for understanding anhedonia in ED. For example, alexithymia, a common characteristic of those with ED, marked by difficulty identifying and expressing one's emotional experience, was positively correlated with physical anhedonia in both control and ED groups (Deborde et al. 2006). In fact, two-thirds of participants reporting anhedonia were above the clinical cut-off for alexithymia. Though speculative, it stands to reason that deficits in experiencing emotions more generally may be associated with an inability to experience reward. Moreover, research shows positive correlations between anxiety, a common co-morbidity in ED, and anhedonia in ED and control groups (Deborde et al. 2006). As discussed below, anxiety may relate to anhedonia in ED in that typically rewarding stimuli are experienced as threatening.

Unlike depressed mood which is marked by the presence of negative affect, anhedonia is thought to be distinguished by a dearth of positive affect (De Fruyt et al. 2020). Interestingly, Coniglio et al. (2019) suggest a role for non-adaptive positive affect in the etiology and maintenance of disordered eating, noting that weight loss and social reinforcement for weight loss can result in positive affect that perpetuates unhealthy weight control behaviors. This framework is not necessarily incompatible with data showing higher levels of anhedonia in ED as it is possible that individuals with persistent difficulty experiencing positive affect may be especially sensitive to and motivated to seek out reinforcement through continued engagement in disordered behaviors (Coniglio et al. 2019). This is consistent with

findings showing a positive association between anhedonia and excessive exercise reported among those with ED (Davis and Woodside 2002). Positive affect may also reinforce restrictive behaviors during early stages of the disorder, whereas anhedonia may worsen with illness progression.

2.1 Social Anhedonia

Like general anhedonia, individuals with ED also report significantly higher levels of social anhedonia, which is defined as a diminished interest in or capacity to experience pleasure from social encounters, compared to healthy controls, with rates as high as 67% in patients with AN and 59% in patients with BN (Tchanturia et al. 2012; Harrison et al. 2014). In fact, in one study, individuals with ED reported comparable scores on a measure of social anhedonia to patients with schizophrenia (Harrison et al. 2014). Despite early research showing higher social anhedonia in AN relative to BN (Davis and Woodside 2002), more recent studies find similarly elevated social anhedonia scores across groups (Tchanturia et al. 2012; Harrison et al. 2014), highlighting a possible transdiagnostic vulnerability factor for ED development. On average, RAN report less social anhedonia than those with active AN (Harrison et al. 2014), consistent with reports of increased social withdrawal during acute illness. However, recovered individuals still show higher social anhedonia than controls (Harrison et al. 2014). Like findings of general anhedonia, this suggests that social anhedonia may represent a risk factor for ED development or a "scar" of having had an ED.

Several theories have been put forth to understand social anhedonia in individuals with ED. Given that illness duration and depressive symptoms account for a large percentage of variance in social anhedonia in ED, it is hypothesized that elevated social anhedonia may reflect a manifestation of general anhedonia (Tchanturia et al. 2012). Additionally, altered social reward processing noted in ED samples might contribute to reduced pleasure from social interactions. When viewing images of women, weight-restored women with AN avoided looking at faces or eyes and did not find the images to be rewarding, unlike women without an ED (Watson et al. 2010). A separate study also reported that individuals with lifetime diagnoses of an ED demonstrated attentional bias to rejecting faces (e.g., frowning faces) and difficulty disengaging from such stimuli, while also showing avoidance of accepting faces (Cardi et al. 2013). Future research examining possible associations between social anhedonia in ED and psychiatric co-morbidities characterized by social threat sensitivity or deficits in social processing, such as social anxiety disorder and autism spectrum disorder, may be clarifying.

3 Anhedonia and Reward Processing in ED

Anhedonia is thought to reflect dysfunction within the brain reward system which is increasingly understood as multidimensional, with recent models suggesting that reward is composed of three primary components with distinct, corresponding neural circuitry: "liking," which refers to the hedonic aspects of reward consumption; "wanting," which refers to motivation to pursue a reward; and learning, or the acquisition of reward-outcome contingencies that informs future behavior (Berridge et al. 2009; Baskin-Sommers and Foti 2015). Emerging evidence suggests that psychiatric disorders characterized by anhedonia and maladaptive avoidance motivation (e.g., major depressive disorder) may demonstrate reduced "liking" and/or "wanting," and reduced learning (Halahakoon et al. 2020; Borsini et al. 2020), whereas those characterized by excessive approach motivation (e.g., substance use disorders) show intact "liking," and increased "wanting" and learning (Baskin-Sommers and Foti 2015), raising the question of whether similar patterns are observed in ED.

3.1 Altered Sensitivity and Motivation to Pursue Reward in ED: Evidence from Subjective Measures

Studies using the Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ) report that both self-reported reward and punishment sensitivity are increased in AN compared to control women (Glashouwer et al. 2014; Jappe et al. 2011). The reward sensitivity subscale of the SPSRQ assesses multiple dimensions of reward, with several items that capture "drive" or the motivation to pursue rewards (e.g., "Do you like to compete and do everything you can do to win?" and "Do you spend a lot of your time on obtaining a good image?"). Therefore, elevated reward sensitivity on this measure may reflect the highly achievement-oriented and perfectionistic tendencies frequently observed in ED as opposed to an enhanced capacity to experience or enjoy pleasure. Studies using other types of self-report measures of motivation to approach rewards and avoid punishment indicate that individuals with AN tend to have lower reward sensitivity and individuals with BN have higher reward sensitivity compared to healthy controls, whereas both ED groups have higher punishment sensitivity (Harrison et al. 2010; Harrison et al. 2011; Matton et al. 2015). Thus, it is possible individuals with AN experience high drive to pursue certain rewards (e.g., thinness), lower reward responsiveness in the moment (e.g., to palatable food), and high punishment sensitivity resulting in avoidance of stimuli associated with perceived aversive consequences (e.g., food). Higher reward and punishment sensitivity in BN, on the other hand, may contribute to cycles of binge eating and subsequent purge episodes to avoid aversive weight gain.

Results from studies examining behavioral response to food offer further evidence of altered "liking" and/or "wanting" in ED. Patients with AN tend to report that they like, want, and find high-fat foods less tasty than controls (Cowdrey et al. 2011; Foerde et al. 2021). While palatable foods are often considered less preferable and evaded in this population, these preferences may not necessarily imply changes in hedonic responding or the capacity to "like" rewarding stimuli (Keating 2010; Keating et al. 2012), as recent research shows similar pleasantness ratings between RAN and healthy controls for palatable food (e.g., sucrose water and chocolate milkshake) (Cowdrey et al. 2011; Kaye et al. 2020). This suggests individuals with AN are able to identify tastes that are "likeable" and instead lack the motivation or desire to obtain this reward. It has been argued that pathological ED behavior is reinforced by reward contamination which may result when traditionally rewarding stimuli like palatable food are paired with an aversive consequence like weight gain, and typically punishing stimuli such as starvation are paired with another perceived reward such as weight loss (Keating et al. 2012; Keating 2010). However, it is also possible that measures of taste pleasantness relying on self-report may not adequately reflect alterations in reward processing that may occur on a neural, physiological, or cognitive level.

3.2 Altered Reward Responsiveness (Liking) and Anticipation (Wanting) in ED: Evidence of Altered Neurotransmitter Function

Dysfunction in neural circuits and neurotransmitters associated with reward including dopamine (DA) and opioids is believed to result in disrupted regulation of behavior contributing to ED psychopathology. Both food restriction and extreme exercise have been described as stressors that stimulate the hypothalamic-pituitary-adrenal (HPA) axis, releasing beta-endorphins that activate DA neurons along reward pathways of the brain, a conceptualization that mirrors neurobiological formulations of addiction (Davis and Woodside 2002). Once thought to be a pleasure neurotransmitter linked to sensory processing, more recent work implicates DA primarily in reward learning and incentive salience ("wanting") (Berridge 2007). Early research suggesting altered DA in AN pathophysiology found reduced concentrations of the DA metabolite, homovanillic acid (HVA), in the cerebrospinal fluid of RAN women relative to healthy females (Kaye et al. 1999). This finding is thought to reflect the anhedonic presentation or reduced novelty seeking seen in this population as well as a possible trait-related neural risk factor. More recent studies using positron emission tomography (PET) demonstrate increased binding of D2/D3 DA receptors, also thought to reflect lower DA receptor concentrations, in the anterior ventral striatum of RAN relative to healthy controls (Frank et al. 2005). Moreover, positive correlations between D2/D3 DA binding potential in the dorsal caudate and harm avoidance in both RAN and recovered BN (RBN) implicate

altered DA in increased avoidance motivation (Frank et al. 2005). However, studies of DA receptor binding have been mixed, with one showing no difference between controls and AN regardless of weight status (Broft et al. 2015) and another reporting decreased striatal DA receptor binding in BN (Broft et al. 2012).

In contrast to DA's role in "wanting," the opioid system is associated with the "liking" aspect of food consumption (Nathan and Bullmore 2009). Specifically, μ-opioids are believed to mediate hedonic and motivational processes associated with consumption of highly palatable foods in BED (Nathan and Bullmore 2009). Several studies demonstrate that opioid receptor antagonists reduce incentive motivation for food (Giuliano et al. 2012). While there is less evidence regarding the role of opioids in AN, recent data show decreased opioid receptor binding, perhaps reflecting increased opioid tone, in ill AN and RAN compared to controls (Galusca et al. 2020). BN patients also show decreased mu-opioid receptor binding in the insula and this is inversely correlated with recent fasting (Bencherif et al. 2005). Additional research is needed to determine how altered opioid receptor availability may be linked to anhedonia or reward sensitivity in ED. Finally, disturbance in the serotonergic system has also been implicated in anhedonia (Gorwood 2008). Early evidence demonstrated elevated CSF 5-hydroxyindoleacetic acid, the major serotonin metabolite, indicating increased serotonin activity in RAN subjects who were long-term weight restored (Kaye et al. 1991). PET studies found that RAN show decreased 5-HT2A binding relative to controls in the amygdala, hippocampus, as well as cingulate cortical regions (Frank et al. 2002). Those who recovered from AN binge-purge subtype also show reduced 5-HT2A binding in the left subgenual cingulate, the left parietal cortex, and the right occipital cortex (Bailer et al. 2004). In this group, 5-HT2A binding was positively correlated with harm avoidance and negatively correlated with novelty seeking; however, the relevance of altered serotonin to anhedonia and reward sensitivity remains unknown.

3.3 Altered Reward Responsiveness (Liking) and Anticipation (Wanting) in ED: Evidence from Task-Based Functional Neuroimaging Studies

In several fMRI studies examining neural processing related to receipt of rewarding taste stimuli (e.g., sucrose and water), RAN participants exhibited dampened activation in the insula, anterior cingulate cortex, and dorsal and ventral striatum (Oberndorfer et al. 2013; Wagner et al. 2008), even when hungry (Kaye et al. 2020; Fig. 1). Likewise, both AN and RAN showed reduced activity in the hypothalamus, amygdala, and anterior insula in response to food images before eating a meal in comparison with controls (Holsen et al. 2012). Interestingly, reduced anterior insula activation when viewing food images was still observed post-meal in those with active AN, suggesting maladaptive regulation of appetitive signals. These findings of widespread hypoactivation to food tastes and images in AN

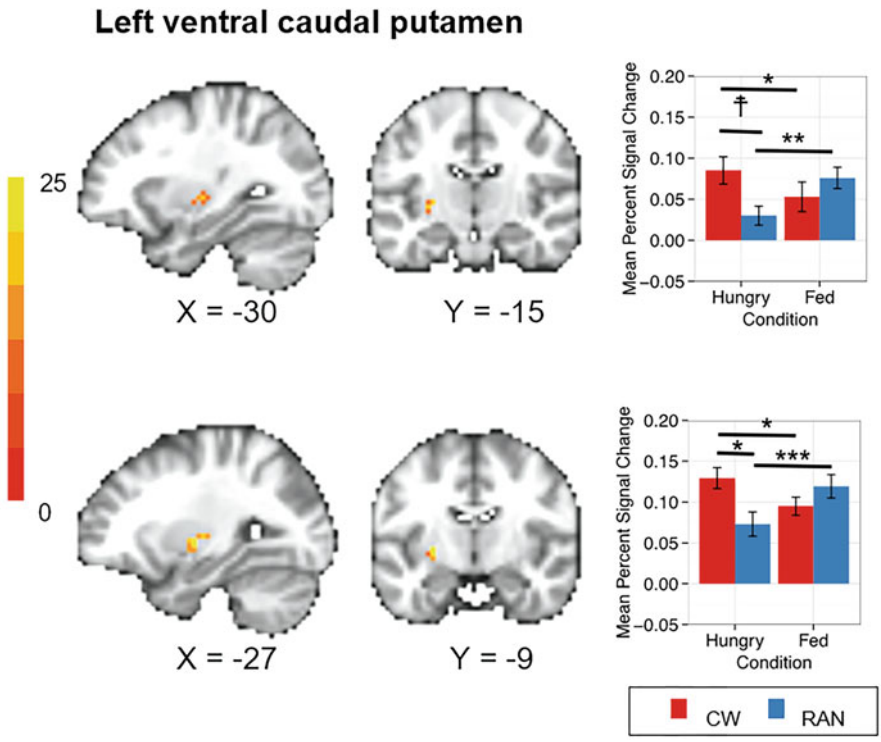

Fig. 1 Neuroimaging results showing that those remitted from anorexia nervosa (RAN) were significantly less responsive to pleasant taste stimuli (i.e., water and sucrose) when hungry versus fed (Kaye et al. 2020)

suggest decreased reward responsivity that may facilitate prolonged periods of food restriction. Meanwhile, other studies examining neural responses to both pleasant and aversive tastes revealed increased activation in the ventral striatum for chocolate in RAN compared to healthy controls (Cowdrey et al. 2011) and for sucrose vs a bitter taste in AN (Monteleone et al. 2017). Together these studies provide evidence of altered neural activation in response to taste stimuli in AN, though results are mixed as to whether food reward is associated with hypo- or hyperactivation of reward circuitry, with differences possibly due to study designs and methods.

While fMRI studies involving primary rewards (e.g., food) are illuminating with regard to mechanisms directly related to eating pathology, interrogating reward responsiveness with secondary non-disorder-specific rewards (e.g., money) may reveal reward processing distortions that could otherwise be confounded with symptom provocation. Neuroimaging studies using guessing game tasks reveal a failure to distinguish between monetary wins and losses in ventral striatal regions within RAN and RBN samples (Bischoff-Grethe et al. 2013; Wagner et al. 2010; Wagner et al. 2007) and increased caudate and prefrontal response for loss in ill AN (Bischoff-Grethe et al. 2013). RAN samples also showed elevated neural responses

in areas commonly associated with cognitive control (e.g., dorsolateral prefrontal cortex (dlPFC) during a delay discounting monetary reward task (Wierenga et al. 2015). These findings may reflect enhanced self-regulatory processes in AN that could indicate behavioral inhibition and hyperactive cognitive control in response to reward and punishment. Similarly, individuals with AN showed greater connectivity between the dorsal striatum and the dlPFC when exposed to low-fat versus high-fat foods, while healthy controls showed the opposite pattern (Foerde et al. 2015). Moreover, the magnitude of difference in connectivity for low-fat and high-fat foods in AN was associated with lower caloric intake the following day, indicating that a circuit between dlPFC and dorsal striatum may be involved in restrictive food intake. These findings introduce the possibility that increased inhibitory control may impact altered reward functioning in AN which may contribute to an anhedonic presentation. Meanwhile, Fladung et al. (2010) found that images of underweight bodies were associated with activity in the ventral striatum of individuals with AN, whereas images of normal weight bodies were associated with striatal activation in healthy controls, suggesting that disorder-specific stimuli may activate reward circuitry in AN, perhaps reinforcing ED thoughts and behaviors.

Neural processing of primary rewards in BN and BED reveals disparate patterns of activity compared to AN. Visual processing of food images is associated with increased insula activation in BN (Brooks et al. 2011; Schienle et al. 2009; Weygandt et al. 2012), and Oberndorfer et al. (2013) report elevated activation in the right anterior insula during receipt of a sucrose solution in women recovered from BN (Oberndorfer et al. 2013). Patients with BN and BED also exhibited elevated activity in the medial orbitofrontal cortex, anterior medial prefrontal cortex, and posterior cingulate cortex during food consumption compared to controls, with no differences in activation observed during a monetary reward task (Simon et al. 2016). Interestingly, Ely et al. (2017) report greater activation in the left amygdala in response to pleasant taste stimuli (i.e., water and sucrose) among women recovered from BN compared to controls when fed, indicating that neural response to rewarding stimuli may not be modulated by metabolic state in BN and raising the possibility that disinhibited eating could result from a failure to devalue food reward when fed.

Much less is known about the neural correlates of reward anticipation (wanting) in ED. Limited studies in AN report mixed findings, with one study reporting increased prefrontal activation, but no difference in striatal activation, during monetary reward anticipation in RAN (Ehrlich et al. 2015). Our pilot data using a modified monetary incentive delay task in adolescents with AN indicate elevated anticipatory response and decreased response to receipt of monetary reward and pleasant taste in the ventral putamen in patients compared to controls, with a similar pattern of response localized to the prefrontal cortex for money and the insula for taste (Wierenga 2021). This suggests a pattern of increased "wanting" and decreased "liking" in AN. Given the heterogeneity of findings, more research is needed to interrogate aberrant "wanting" in this disorder and understand how this may relate to anhedonia. In contrast to AN, patients with BN showed less activation in the right anterior insula when anticipating a chocolate milkshake along with lower activation in the left middle frontal gyrus, right precentral gyrus, and insula when consuming a

milkshake (Bohon and Stice 2011). Interestingly, this same group found that patients with BN who report higher negative affect show greater activity within the putamen, caudate, and pallidum during anticipation of a pleasurable taste (Bohon and Stice 2012), suggesting that negative affect may enhance the reward value of food, perpetuating binge eating. In patients with BED, poorer response to treatment was associated with less activation of the ventral striatum during reward anticipation along with less activation of the medial prefrontal cortex during the outcome phase of a monetary reward task (Balodis et al. 2014), highlighting the relevance of reward dysregulation for treatment outcomes.

3.4 Altered Reward Learning in ED: Evidence from Neurocognitive and Neuroimaging Studies

Increasing evidence implicates deficits in reward or reinforcement-based learning in ED thought to maintain maladaptive behaviors and symptoms (Schaefer and Steinglass 2021). The majority of studies of learning in AN have focused on passive Pavlovian conditioning (Schaefer and Steinglass 2021), with evidence of elevated reward prediction error signals in the ventral striatum and orbitofrontal cortex in ill and remitted AN (Frank et al. 2012, 2016). However, Pavlovian tasks have demonstrated poor behavioral profiles (National Institute of Mental Health 2016). Given the importance of choice behavior and decision-making in ED, instrumental response-outcome reward learning may be more relevant to psychopathology. For instance, Foerde and Steinglass (2017) report decreased overall learning accuracy from reward feedback in both acutely ill and weight-restored AN, indicating that this may represent a trait-related vulnerability factor for this disorder. Consistent with this, a recent computational modeling study showed lower rates of reinforcement learning in AN following both positive and negative prediction errors (Wierenga et al. 2021), consistent with findings of altered punishment learning in AN during reversal learning tasks (Ritschel et al. 2017). Adolescents with BN show altered patterns of neural activation, despite equivocal task performance, during reward learning compared to controls (Cyr et al. 2016). Moreover, Grob and colleagues found impaired reward learning following catecholamine depletion in a sample of participants with remitted BN which was also associated with anhedonia (Grob et al. 2012). However, a recent report showed that patients with BN exhibit greater reward learning than controls (Hagan and Forbush 2021). Discrepancies in findings in BN may be attributed to different tasks, outcome measures, and clinical characteristics across studies and more data are needed to form definitive conclusions.

4 Anhedonia in Animal Models of Disordered Eating

The primary animal model of AN is activity-based anorexia (ABA), a protocol that includes limited access (e.g., 90 min/day) to food and unlimited access to a running wheel. Under these conditions, animals demonstrate increased physical activity and significant weight loss, sometimes resulting in death. In one study, a quarter of animals exposed to the ABA paradigm developed anhedonia measured using a sucrose preference test (Milton et al. 2018). These rates mirror research in humans showing that approximately one third of patients with AN report clinically elevated anhedonia (Boehm et al. 2018). Recent data show enhanced taste reactivity to sucrose in rats that are "resistant" to weight loss in the ABA paradigm compared to those that were "prone" to the ABA model during food restriction in particular, with no group differences at baseline or 10 days after recovery (Hurley et al. 2021). These data suggest that reduced hedonic "liking" of sweet taste during food restriction may represent a vulnerability factor for weight loss in this model. At the neurochemical level, altered DA and serotonin have been detected within reward-related brain regions of ABA animals. Specifically, greater DA release in the nucleus accumbens (NAc) has been observed during feeding in ABA subjects, whereas serotonin is reduced within the NAc of ABA subjects (Verhagen et al. 2009). Direct activation of predominantly dopaminergic cells within the VTA-NAc reward pathway leads to increased food intake and a prevention of the characteristic precipitous weight loss in ABA subjects (Foldi et al. 2017). Therefore, the authors propose that activating the reward system may be useful in disrupting an imbalance in AN between heightened inhibitory control within prefrontal brain regions (e.g., dlPFC) and reduced activity within reward-related regions (e.g., ventral striatum).

5 Future Research Directions and Implications for Treatment

Given the relationship between anhedonia and suicidal ideation (Ducasse et al. 2018) and poorer treatment outcomes (Khazanov et al. 2020) in other psychiatric populations, and the relative paucity of available research on the topic of anhedonia in ED, future studies are needed to better understand the experience and impact of anhedonia in this population. For example, longitudinal studies may lend insight into whether anhedonia precedes ED onset, constituting a trait-related risk factor. Importantly, existing studies examining anhedonia in ED rely on self-report measures which are subjective and conflate reward-related processes (e.g., reward anticipation/motivation, reward valuation, reward learning, and pleasure experienced during reward receipt). Future research adapting measures that dissociate distinct aspects of reward processes, such as the Temporal Experience of Pleasure Scale (TEPS; Gard et al. (2006)), and utilizing behavioral measures of reward valuation, such as the Energy Expenditure for Rewards Task (EEfrt; Treadway et al. 2009)), may help

to characterize reward deficits in ED and clarify their relationship to anhedonia to identify more precise treatment targets. Additional research is also needed to assess whether anhedonia persists after treatment in BN to determine whether this might represent a transdiagnostic vulnerability factor and to inform our understanding of anhedonia in other ED, such as BED and ARFID. Preliminary evidence (data not yet published) from our group suggests that change in anhedonia scores is positively associated with change in ED symptoms during treatment in a mixed diagnostic sample, suggesting the potential relevance of anhedonia for treatment success. Specifically targeting anhedonia using promising approaches such as positive affect treatment (Haynos et al. 2021) and deep brain stimulation (Potes et al. 2021) may lead to better outcomes in patients with ED. Initial findings show improvements in social anhedonia and alexithymia in AN following cognitive remediation and emotion skills training (CREST), a brief skills-based therapy designed to assist patients in understanding and expressing emotions (Tchanturia et al. 2014).

6 Conclusion

ED are consistently associated with both general and social anhedonia. Though anhedonia appears to improve with weight restoration in AN, it remains elevated in remitted individuals, suggesting that anhedonia may represent a trait-related vulnerability factor for ED development. Similar anhedonia scores between those with AN and BN suggest that anhedonia might be a transdiagnostic risk factor for ED development, with recent models also suggesting a role for anhedonia in the etiology of BED. Elevated anhedonia is consistent with conceptualizations of ED pathology implicating altered reward sensitivity; reduced sensitivity to food reward in AN has been thought to facilitate food avoidance, whereas heightened sensitivity in BN and BED is thought to perpetuate overconsumption of palatable foods. However, studies using neuroimaging or self-report measures show conflicting accounts. Moreover, some studies show heightened reward responsivity to disorder-specific stimuli in AN suggesting that hedonic capacity may be intact and that lower response to food reward may be explained by reward contamination. Further research is needed to clarify how altered reward processing in ED is related to symptoms of anhedonia. Though anhedonia is known to increase risk for suicidal ideation and predict poorer treatment outcomes, both significant issues in ED populations, relatively little is known about anhedonia in ED highlighting an important area for future research.

Acknowledgments None of the authors have conflicts of interest to disclose. This work was supported in part by grants from the National Institute of Mental Health (R01MH113588 to CEW, R21MH118409 to CEW). The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official view of the NIH.

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Anhedonia and Hyperhedonia in Autism and Related Neurodevelopmental Disorders

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Contents

Abstract Although autism spectrum disorder (ASD) is defined by impaired social communication and restricted and repetitive behaviors and interests, ASD is also characterized by impaired motivational processes. The "social motivation theory of autism" describes how social motivation disruptions in ASD in early childhood may impede the drive to engage in reciprocal social behaviors and ultimately interfere with the development of neural networks critical for social communication

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Curr Topics Behav Neurosci (2022) 58: 237–254
https://doi.org/10.1007/7854_2022_312
Published Online: 10 April 2022

(Chevallier et al., Trends Cogn Sci 16:231–239, 2012b). Importantly, clinical studies and preclinical research using model organisms for ASD indicate that motivational impairments in ASD are not constrained to social rewards but are evident in response to a range of nonsocial rewards as well. Additionally, translational studies on certain genetically defined neurodevelopmental disorders associated with ASD indicate that these syndromic forms of ASD are also characterized by motivational deficits and mesolimbic dopamine impairments. In this chapter we summarize clinical and preclinical research relevant to reward processing impairments in ASD and related neurodevelopmental disorders. We also propose a nosology to describe reward processing impairments in these disorders that uses a three-axes model. In this triaxial nosology, the first axis defines the direction of the reward response (i.e., anhedonic, hyperhedonic); the second axis defines the construct of the reward process (e.g., reward liking, reward wanting); and the third axis defines the context of the reward response (e.g., social, nonsocial). A more precise nosology for describing reward processing impairments in ASD and related neurodevelopmental disorders will aid in the translation of preclinical research to clinical investigations which will ultimately help to speed up the development of interventions that target motivational systems for ASD and related neurodevelopmental disorders.

Keywords Autism · Dopamine · Preclinical · Reward · Social motivation

1 The Social Motivation Theory of Autism

Social communication impairments are a defining feature of autism spectrum disorder (ASD). This has been demonstrated in the domains of social cognition, social perception, and social attention (Levy et al. 2009). Recently, there has been increased interest in examining the impact of motivational factors on social functioning in ASD (Clements et al. 2018; Tschida and Yerys 2021). The "social motivation theory of autism" posits that disruptions in brain mechanisms that mediate social motivation from infancy decrease the motivation to engage in social behaviors during early development (Chevallier et al. 2012b). This, in turn, results in fewer experiences with social rewards which has deleterious downstream effects on the development of social skills (Dawson et al. 2005). The diagnosis of ASD is based on the presence of social communication impairments and repetitive behaviors and not on impaired motivation (APA 2013), and decreased social motivation is not the only mechanistic account of the full range of social deficits associated with ASD (e.g., some individuals with ASD have social interest and actively seek out social interactions but fail to form friendships due to impaired social cognition and pragmatic language). However, even during the first year of life, infants who will later receive a diagnosis of ASD demonstrate infrequent orienting to their own name and diminished eye contact (Ozonoff et al. 2010), suggesting that decreased social orienting and social interest are evident in infants who will receive a diagnosis

of ASD and may interfere with the development of social cognition in at least a significant proportion of those with ASD.

Consistent with this model, very young children with ASD demonstrate decreased orienting to social stimuli (Klin et al. 2009), atypical social orienting predicts decreased social competence in adolescents with ASD (Klin et al. 2002), and adolescents with ASD are characterized by selective deficits in social anhedonia relative to other hedonic processes (Chevallier et al. 2012a). There is also evidence that social motivation remains impaired in individuals with ASD despite growth in other areas of cognitive development. More generally, ASD across the lifespan is characterized by lower levels of reward responsivity (Soderstrom et al. 2002) and impaired reward-based learning (Johnson et al. 2006).

In support of this model, fMRI studies have consistently found altered activation in and connectivity across brain regions implicated in processing rewards in ASD (Clements et al. 2018). Likewise, eye tracking studies indicate that individuals with ASD show diminished visual attention to social stimuli (Franchini et al. 2019), and behavioral studies have found diminished valuation of social rewards in ASD (Bottini 2018). Of note, impaired reward-based responses in ASD are evident to both social and nonsocial rewards, suggesting that motivational impairments in ASD are not specific to social rewards (for a review, see Carter et al. 2020): children and adults with ASD demonstrate atypical behavioral and neural responses to a variety of social and nonsocial rewards, including monetary rewards, images of faces, images of objects, and images of restricted interests (Clements et al. 2018). Finally, certain interventions that target core social impairments in ASD appear to impact reward processing systems (Greene et al. 2018), suggesting that a better understanding of these systems in ASD is important both for elucidating the pathogenesis of the disorder and for evaluating potential novel ASD treatments.

2 Translational Evidence of Impaired Motivational Responses in Autism

Precise terminology is key to advance our understanding of how animal models can aid in the study of complex neuropsychiatric disorders such as ASD. In this chapter we use the prefered term “animal models for ASD” rather than “animal models of ASD” (Bale et al. 2019). Animal models for ASD have been able to recapiculate multiple aspects of ASD phenotypes and are thus well suited to aid in the understanding of ASD pathopysiology as well as potential mechanisms of action of novel therapeutic compounds (Resendez et al. 2020; Rodriguez-Romaguera et al. 2020). Although no definitive marker of ASD has been identified (Devlin and Scherer 2012), a large number of de novo single-gene mutations and copy number variants are associated with ASD, each within a subset of individuals (Pinto et al. 2014). Knockout (KO) and knock-in mice have been generated for many of the genetic mutations and copy number variants in ASD as well as for associated

neurodevelopmental disorders, such as Fragile X syndrome and tuberous sclerosis (for reviews, see Del Pino et al. 2018; Kazdoba et al. 2016). Other models have also used prenatal pharmacological manipulations that recapitulate impairments in fetal brain development that are associated with ASD-like symptoms (for a review, see Semenova et al. 2020). In particular, inflamatory models that use maternal immune activation in rodents cause lifelong behavioral deficits by inducing neuroinflamation in offspring, which replicates epidemiological evidence that implicates maternal infection as a risk factor for ASD (Atladottir et al. 2010; Estes and McAllister 2016). Neuroinflammation in offspring, in turn, may disrupt social motivation via effects on striatal DA functioning (Greene et al. 2019). In addition to pharmacological and geneticallly modified models for ASD, several inbred mouse strains also recapiculate ASD social deficit and repetitive behavior phenotypes (for a review, see Kazdoba et al. 2016). These inbred strains are very useful models in the study of idiopathic ASD because their ASD-like phenotypes are not caused by known genetic mutations.

Multiple rodent assays are available to study behavioral deficits associated with ASD. In this chapter we highlight research using assays to study social and nonsocial motivation phenotypes in animal models with genetic mutations and copy number variants associated with ASD. Reciprocal social interactions may be assessed by placing two mice in a confined arena and quantifying social sniffing and physical play (Terranova and Laviola 2005). Mutiple genetic mouse models for ASD display reduced reciprocal social interactions using this behavioral paradigm, including *Shank3* heterozygotes (Bozdagi et al. 2010), conditional *Pten* mutants (Kwon et al. 2006), *Engrailed2* null mutant (Brielmaier et al. 2012), and *Tsc1* heterozygotes (Tsai et al. 2012). Sociability is also commonly tested in the 3-chamber social assay. In this task, a mouse is tested for the amount of time spent exploring a novel mouse versus a novel object (Nadler et al. 2004). The novel mouse and the novel object are typically restricted to a laterally placed compartment with an empty center chamber that allows the mouse to cross from one chamber to the other. The difference between the amount of time spent in the side chambers quantifies preference for the novel mouse over the novel object. Decreased sociability has been observed in multiple genetic models for ASD that include conditional *Pten* KO mice (Kwon et al. 2006), haploinsuficient *Pten* mutant mice (Page et al. 2009), *Ctnap2* KO mice (Penagarikano et al. 2011), *Ub3a* triplication mice (Smith et al. 2011), $GABA_A$ receptor *Gabrb3* KO mice (DeLorey et al. 2008), 15q11–13 duplication mice (Nakatani et al. 2009), and 17p11.2 duplication mice (Molina et al. 2008).

In comparison, nonsocial stereotypical behaviors have been evaluated by assays that quantify the preference to engage in species-typical behaviors. Excessive motivation to engage in these behaviors recapitulates repetitive behavior and restricted interest phenotypes in ASD. Repetitive grooming behaviors are observed in several genetic mouse models for ASD, such as *Shank3* (Peca et al. 2011), *Cntnap2* (Penagarikano et al. 2011), *Neuroxin1α* (Etherton et al. 2009), and *Neuroglinin1* (Blundell et al. 2010). Marble burying is also a widely used assay to assess repetitive behaviors (Thomas et al. 2009). Increased marble burying has been reported in several genetic ASD models including *Tsc2* KO (Reith et al. 2013) and

monoamine oxidase (MAO) A and A/B KO mice (Bortolato et al. 2013). Repetitive behaviors induced by cognitive rigidity have also been assessed using reward-based tasks. For example, in the y-maze (or t-maze), a mouse learns that a food reward is placed in one of two arms. Following multiple trials of learning to associate reward with one maze arm, the food reward is then placed in the opposite arm to assess reversal learning. Mice with 15q11–13 duplication (Nakatani et al. 2009), MAO A and A/B KO mice (Bortolato et al. 2013), and mice with overexpression of eIF4E (Santini et al. 2013) all show defecits in this paradigm assaying reversal learning.

3 Neurobiological Mechanisms of Impaired Motivational Responses in Autism

Social motivation is subserved by neurobiological substrates that govern other motivated behaviors. The canonical dense ascending dopamine (DA) projections from ventral tegmental area to the striatum, orbitofrontal cortex, ventromedial prefrontal cortex, and anterior cingulate cortex form a DA pathway that is sensitive to rewards (Berridge et al. 2009). Reward-predictive DA bursts originating in the ventral tegmental area send signals to the striatum, including the nucleus accumbens, that reflect reward prediction error signals that facilitate learning and memory and that mediate approach behaviors towards salient goals (Schultz 2019). This DA system also mediates responses to social and nonsocial incentives (Gunaydin and Deisseroth 2014) and DA transmission in the nucleus accumbens influences social behaviors (Manduca et al. 2016). Preclinical evidence suggests that the neural circuits that mediate reward processing may have evolved, at least in part, to facilitate social affiliation and attachment (Trezza et al. 2011). Consistent with this conceptualization, social interaction recruits overlapping mesolimbic DA networks that are also active during the processing of nonsocial rewards such as food, money, and drugs of addiction (Morales and Berridge 2020), and reward processing brain mechanisms may serve to encode and consolidate positive memories of social experiences, facilitating social abilities hypothesized to be impaired in ASD (Keifer et al. 2021).

Numerous lines of evidence suggest that striatal DA dysfunction is implicated in the pathophysiology of ASD. The valproic acid model of ASD is one of the most widely used preclinical rodent models for ASD (Mabunga et al. 2015), in which prenatal valproic acid exposure causes ASD-like phenotypes and a cascade of neurobiological changes, including excitatory/inhibitory neural imbalances linked to increased basal DA in the frontal cortex (Narita et al. 2002), hyperactive mesocortical DA in response to stress (Nakasato et al. 2008), and changes in locomotor behavior akin to that observed in striatal DA-depleted animals (Shaywitz et al. 1976). Additionally, maternal immune activation in mice results in hyperdopaminergia in the ventral midbrain in offspring (Weber-Stadlbauer et al. 2021). Consistent with the clinical phenotype of ASD, the behavioral phenotypes

induced by prenatal valproic acid in rodents include decreases in socialization and social preference in the three-chamber social interaction assay (Dufour-Rainfray et al. 2010), as well as increases in nonsocial stereotypical behaviors such as self-grooming (Du et al. 2017), marble burying (Wu et al. 2018), and expression of repetitive behavior (impairment in reversal learning) in the y-maze (Markram et al. 2008).

Social interaction has been linked to differential expression of genes related to DA systems (Alugubelly et al. 2019), and preclinical models for ASD in rodents characterized by mutations in the DA transporter (DAT) or SHANK3 protein show mesocorticolimbic DA accumulation and reduced DA activity (Bariselli et al. 2016; DiCarlo et al. 2019). Clinical evidence suggests that reduced striatal functioning in ASD leads to impairments in effort-based decision making for rewards (Mosner et al. 2017). Additionally, de novo mutation in the human DAT gene (SLC6A3) is a candidate susceptibility gene for ASD (Neale et al. 2012). Common polymorphisms in both the DA D4 receptor gene and the DAT gene are related to challenging behaviors that occur in social contexts (Gadow et al. 2010a) and repetitive behaviors (Gadow et al. 2010b) in ASD. Polymorphisms of the DA D3 receptor gene are linked with striatal volumes and repetitive behaviors in ASD (Staal 2015). Consistent with clinical ASD phenotypes, mice with mutations in either DAT or *Shank3* exhibit decreased social preferences and an increase in repetitive rearing behaviors and self-grooming that is associated with impaired synaptic function in cortico-striatal circuits (Bariselli et al. 2016; DiCarlo et al. 2019; Peca et al. 2011).

Abnormalities in oxytocin neuropeptide signaling also play a critical role in ASD pathogenesis (Dolen 2015). Initial reports have demonstrated therapeutic effects from intranasal oxytocin administration for treating core ASD symptoms (Higashida et al. 2019; Parker et al. 2017; Sikich et al. 2021), and these effects have been associated with striatal responses to rewards in ASD (Greene et al. 2018). Oxytocin receptor activation also plays an important role in the activation of reward pathways during pro-social behaviors (Dolen et al. 2013). The reduced social preference found in *Shank3b* knockout mice is associated with reduced expression and activation of oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVN), and this deficit can be rescued by peripheral administration of an oxytocin receptor agonist (Resendez et al. 2020). PVN oxytocin neurons also send dense projections to the VTA, and oxytocin release within the VTA is necessary to drive activity of VTA-DA neurons that project to the nucleus accumbens that are involved in modulating social preference (Hung et al. 2017), thus demonstrating that oxytocin improves social deficits associated with ASD via direct effects on the mesolimbic DA system.

Finally, a small PET study found decreased fluorine-18-labeled fluorodopa (to visualize DA nerve terminals) in the anterior medial prefrontal cortex in individuals with ASD (Ernst et al. 1997), and a recent [^{11}C]SCH23390 PET study reported relations between striatal DA D1 receptor binding and ASD severity (Kubota et al. 2020). A recent PET-MR study of DA binding during reward processing in ASD using [^{11}C]raclopride, a D2/D3 DA receptor antagonist, found decreased phasic DA release to rewards in ASD in bilateral putamen and left caudate and that phasic DA release to rewards in ASD in the putamen predicted social functioning in the ASD

group (Zurcher et al. 2021). Furthermore, another PET-MR study found that mother–child bonding is associated with increased dopamine responses within the medial amygdala (Atzil et al. 2017). Taken together, these studies emphasize that social motivation impairments in ASD are regulated, at least in part, by neurobiological systems that mediate motivated behaviors.

4 Studying Motivational Responses in Syndromic Developmental Disorders Associated with Autism to Understand Idiopathic Autism

Although most individuals with ASD do not have identifiable genetic abnormalities, a number of single-gene disorders and chromosomal abnormalities are associated with ASD (de la Torre-Ubieta et al. 2016), and a distinction is often made between "syndromic" ASD (i.e., ASD is one of many diagnoses recognized as part of a syndrome) and "idiopathic" ASD (i.e., ASD is recognized to result from unknown causes (Miles et al. 2005)). However, genomic advances and analyses of large-scale ASD genetic databases have called into question the distinction between syndromic and idiopathic ASD and whether individuals with ASD with known genetic abnormalities are phenotypically distinguishable from those with unknown causes (Bishop et al. 2017). In this regard, studying genetically defined neurodevelopmental disorders that are associated with ASD may shed light on the pathogenesis of ASD more broadly (Geschwind and State 2015), and research that identifies reward-based impairments in syndromic developmental disorders associated with ASD may aid our understanding of the contribution of these impairments to the pathogenesis of idiopathic ASD.

Prader–Willi syndrome (PWS) is an example of a genetic disorder with substantial symptoms overlap with ASD. Further, PWS symptoms strongly suggest the involvement of mesolimbic DA systems. PWS is caused by the lack of expression of imprinted genes in the 15q11-q13 region (Bittel and Butler 2005). It is characterized by intellectual disability and strongly elevated appetite (hyperphagia) as well as a range of other behavioral, cognitive, and social impairments (Salles et al. 2020). The hyperphagia that characterizes PWS suggests dysregulation of motivational systems, and hyperactivation in response to food stimuli has been observed in the nucleus accumbens (Shapira et al. 2005), medial PFC (Miller et al. 2007), and insula (Shapira et al. 2005) in those with PWS. Additionally, Holsen and colleagues (Holsen and Thompson 2004) found higher eye blink rates and a relation between eye blink rates and compulsive behavior in PWS, suggesting dysfunction in this indirect measure of DA and GABA mechanisms. One of the genes implicated in PWS, *Magel2*, is highly expressed in the regions of the brain that control appetite. In a mouse model for PWS that lacks expression of the Magel2 gene, Luck et al. (2016) found abnormal behaviors and biomarkers reflecting DA dysfunction. Interestingly, motivational dysregulation in PWS is specific to food and is not observable in response to other

types of rewards, highlighting the context-specificity of reward processing impairments in this disorder (i.e., an external nonsocial context that is specific to food availability).

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that affects multiple organ systems and is caused by loss-of-function mutations in the tumor-suppressor genes TSC1 or TSC2 that encode proteins that negatively regulate mTOR complex 1 (mTORC1) (Henske et al. 2016). Up to 40% of individuals with TSC have ASD (Numis et al. 2011) and approximately 50% of individuals with TSC have some degree of intellectual disability (Joinson et al. 2003). Mechanistic target of rapamycin (mTOR)-inhibiting agents has shown promise in the treatment of TSC-associated epilepsy and other neurodevelopmental manifestations of the disorder (Salussolia et al. 2019). Loss of Tsc1 and activation of mTORC1 in DA neurons causes somatodendritic hypertrophy, reduces intrinsic excitability, alters axon terminal structure, and impairs striatal DA release (Kosillo et al. 2019). These changes lead to a selective deficit in cognitive flexibility that was preventable by genetic reduction of the mTOR-binding protein Raptor, thereby establishing a critical role for Tsc1-mTORC1 signaling in modulating the functional properties of DA neurons. Kosillo et al. (2019) selectively deleted Tsc1 from mouse DA neurons to test whether activation of mTORC1 signaling in DA neurons produced ASD-related phenotypes. They found that this deletion led to deficits in reversal learning in mice that underwent an odor-based reinforcement learning paradigm, establishing a central role for Tsc1-mTORC1 signaling in regulating the functional properties of striatal DA neurons as well as reward-based cognitive inflexibility in TSC.

22q11.2 deletion syndrome (22q11.2DS), also referred to as DiGeorge syndrome or velo-cardio-facial syndrome, is associated with diverse physical, behavioral, social, and cognitive impairments (Ousley et al. 2007). Approximately 15–50% of those with 22q11.2DS have ASD and approximately 0.3–1% of those with ASD have 22q11.2DS (Fiksinski et al. 2021), a 10–40-fold increase relative to the general population (Ousley et al. 2017). Individuals with 22q11DS have been shown to demonstrate relations between striatal gray matter volume and social impairments (Campbell et al. 2006) and individuals with 22q11DS are hemizygous for the catechol-O-methyltransferase (COMT) gene that plays a role in DA degradation (McDonald-McGinn et al. 2015). Though research directly addressing reward processing in 22q11.2DS is sparse, the available findings suggest the possibility of impaired striatal DA functioning during reward processing within a social context in 22q11DS (Fallgatter and Lesch 2007).

Fragile X syndrome is the most common inherited cause of intellectual disability, occurring in 1/4,000 males and 1/8,000 females (Crawford et al. 2001). It is caused by a mutation of the *Fmr1* gene on the long arm of the X chromosome (locus Xq27.3; Verkerk et al. 1991). The *Fmr1* full mutation affects cognition, adaptive behavior, social communication, anxiety, and motor skills (Lightbody and Reiss 2009). Individuals with Fragile X syndrome demonstrate ASD-like social impairments that are likely due to interactions of the *Fmr1* gene with other genes and environmental factors during brain development (Brodkin 2008). Dalton et al. (2008) reported that participants with Fragile X syndrome activated the right insula

(as well as other regions) to faces more than an ASD group or a control group, suggesting abnormal salience attribution to faces in Fragile X syndrome. A small investigation of four patients with parkinsonism carrying the Fragile X permutation found initial evidence of decreased DA striatal binding (Ceravolo et al. 2005), and an fMRI study in awake transgenic Fragile X rats found decreased activation in the mesolimbic/habenular reward circuit as well as decreased behavioral preference for a rewarding odor (Kenkel et al. 2016). Finally, indirect indications of midbrain DA involvement in Fragile X syndrome include evidence of high rates of co-morbidity with tremor disorders (Berry Kravis et al. 2003), higher blink rates (Roberts et al. 2005), and preclinical evidence that the FMRP protein is a key messenger regulating DA modulation (Wang et al. 2008).

5 A New Nosology to Describe Motivational Impairments in Autism and Related Neurodevelopmental Disorders

This chapter has summarized clinical and preclinical evidence that ASD and related neurodevelopmental disorders is characterized by reward processing impairments. Additionally, clinical studies indicate that reward processing impairments in ASD are context-dependent: within the same individual reward processing may be simultaneously blunted in the context of certain (e.g., social) stimuli and heightened in the context of other (e.g., nonsocial) stimuli. This is perhaps not surprising given that ASD is a heterogenous disorder and given that the etiology of ASD is not well understood (Hervas 2016). This stands in contrast to other forms of psychopathology where reward processing impairments are typically either heightened, for example in manic states (Ashok et al. 2017), or blunted, for example in major depressive disorder (Auerbach et al. 2019). One notable exception is substance use disorders that are typically characterized by both heightened motivational responses to drug cues and blunted motivational responses to more adaptive stimuli (Bozarth 1990; Piantadosi et al. 2021).

To characterize the complexities of these motivational deficits, we propose that reward processing impairments in ASD and related neurodevelopmental disorders may be described as either "anhedonic" or "hyperhedonic," depending on the context (e.g., "anhedonic" while processing social stimuli and "hyperhedonic" when processing restricted interest stimuli (Carter et al. 2020)). Although the term "anhedonia" is widely used in psychiatry (American Psychiatric Association 2013), its converse, "hyperhedonia," is far less commonly used: only a few studies have described manic states (Pizzagalli et al. 2008) and impulse control disorders (Loas et al. 2012) as hyperhedonic. Although we are not suggesting that heightened motivational states in ASD necessarily share features with mania, we believe that adopting these terms to describe reward processing impairments in ASD acknowledges the mechanistic and phenotypic overlap between anhedonic and hyperhedonic processes in neurodevelopmental disorders, including ASD, and other psychiatric

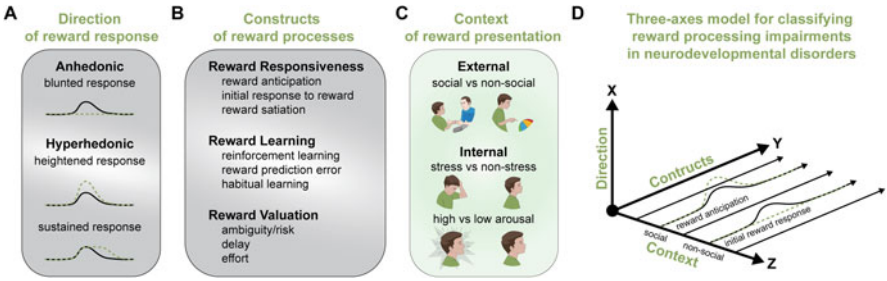

Fig. 1 A three-axes model for classifying reward processing impairments in ASD and related neurodevelopmental disorders. (**a**) The direction of reward responses may be anhedonic (blunted) and hyperhedonic (heightened and sustained). (**b**) The constructs and subconstructs of reward processes as defined in The Positive Valence System Domain of the Research Domain Criteria (RDoC) from the National Institute of Mental Health. (**c**) The context of reward presentation can be external (e.g., social vs nonsocial) and/or internal (e.g., stress vs non-stress, high vs low arousal). (**d**) This proposed three-axes model integrates the Direction of reward response on axis X, the Constructs of reward responses on axis Y, and the Context of the reward presentation in axis Z to classify reward processing impairments

disorders and will allow insights from research in other disorders to inform ASD pathogenesis. The adoption of these terms in ASD and related neurodevelopmental disorders also highlights that blunted and heightened reward-based responses may be rooted in similar neurobiological systems and is consistent with the NIMH Research Domain Criteria (RDoC) initiative (Insel et al. 2010) that aims to establish a neurobiologically valid framework for classifying mental illness by employing common constructs across different DSM-based disorders (Whitton et al. 2021).

In addition to using the terms "anhedonia" and "hyperhedonia," other descriptors are also needed to describe impaired reward processing phenotypes commonly observed in ASD and related neurodevelopmental disorders. For example, evidence is accumulating that reward processing impairments in ASD are most commonly observed during reward anticipation (i.e., "reward wanting") but are not as common during hedonic responses to rewards (i.e., "reward liking") (Keifer et al. 2021), suggesting that reward processing research in ASD should delineate which components of reward processing are impaired, as has commonly been the approach in research in other disorders (e.g., Dichter et al. 2012). To address this, we propose that reward processing impairments in ASD and related neurodevelopmental disorders may be best described in terms of a three-axes model (see Fig. 1) that incorporates: (1) *Direction of reward response*: whether a response is anhedonic (i.e., blunted) or hyperhedonic (i.e., heightened or sustained); (2) *Constructs of reward processes*: whether reward liking, reward wanting, or other reward-based processes are impaired; and (3) *Context of reward*: the conditions in which the impairment is present, including external contexts such as social or nonsocial situations, as well as internal contexts such as whether an individual is under a stress or non-stress state (including the discomfort associated with medical conditions that commonly co-occur in ASD (Lai et al. 2014)), or under a high or low arousal state (including

sleep disturbance that is common in ASD (Johnson and Zarrinnegar 2021)). There are likely additional relevant axes, including whether responses are evident during the presentation of a stimulus or during the withholding of a stimulus (i.e., the omission of an expected reward during a "negative" punishment task that may elicit frustrative non-reward responses (Carlezon Jr. et al. 2019; Missig et al. 2020; Phillips et al. 2019).

This model is not meant to be constrained by these three axes but is rather an initial framework to describe reward processing impairments more precisely in ASD and related neurodevelopmental disorders. The goal is for this nosology to aid in the translation of preclinical research to clinical studies, in the application of findings from research in other psychiatric disorders to ASD and related neurodevelopmental disorders, and research on novel treatments given that interventions that monotonically affect reward processing brain circuits may not be sufficient to improve impaired hedonic processes (e.g., Auerbach et al. 2019).

In summary, the social motivation theory of autism emphasizes the importance of understanding the contribution of impaired reward processing to the core symptoms of ASD (Chevallier et al. 2012b). Despite over a decade of research addressing this framework, the aspects of reward processing (e.g., reward responsiveness, reward learning, reward valuation), the kinds of rewards affected (e.g., social or nonsocial rewards), and the influence of contextual factors on reward processing impairments in ASD are not well understood. Additionally, future research is needed to investigate the extent to which impaired motivational responses may be a useful biomarker of treatment response in ASD (e.g., Greene et al. 2018).

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Anhedonia in Neurodegenerative Diseases

Vicky Turner and Masud Husain

Contents

Abstract Neurodegenerative diseases are increasingly recognised to be an important cause of brain disorders, particularly in late age. Associated with a wide range of pathologies, they lead to progressive loss of neurons in different regions of the nervous system. Although anhedonia is common in a variety of neurodegenerative diseases, to date it has not been extensively studied in most of these conditions. Here we review the current literature on studies assessing the association between anhedonia and neurodegenerative diseases including Parkinson's Disease, Dementia with Lewy Bodies, Parkinson's Plus Syndromes, Alzheimer's Disease, Vascular Dementia, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis and Huntington's Disease. Much of the research has been conducted in Parkinson's disease where it is evident that there are strong links between apathy (loss of motivation) and anhedonia, although the two syndromes can be dissociated. Intriguingly, drugs that improve apathy can also lead to amelioration of anhedonia in some cases.

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Curr Topics Behav Neurosci (2022) 58: 255–278
https://doi.org/10.1007/7854_2022_352
Published Online: 19 April 2022

Overlaps between the two syndromes may also exist across other neurodegenerative conditions, including Frontotemporal Dementia in which imaging has revealed atrophy of both common brain regions associated with anhedonia and apathy, as well as a set of unique brain regions associated with anhedonia. A transdiagnostic perspective might be helpful to investigate whether a common network of brain regions is dysfunctional with anhedonia across neurodegenerative conditions.

Keywords Alzheimer's disease · Amyotrophic lateral sclerosis · Apathy · Dementia with Lewy bodies · Depression · Frontotemporal dementia · Huntington's disease · Parkinson's disease · Parkinson's plus syndromes · Vascular dementia

1 Introduction

With increases in life expectancy, neurodegenerative diseases constitute an important and increasing cause of global health burden, accounting for more than a quarter of all neurological disorders worldwide (Feigin et al. 2020). Although cognitive and motor impairments have traditionally been associated with this group of diseases, it has become apparent that neuropsychiatric symptoms are a key feature of most neurodegenerative conditions (Aalten et al. 2007). Surprisingly, there has been relatively little research on the syndrome of anhedonia in these diseases. When it has been investigated, the evidence suggests that anhedonia can be a frequent accompaniment of common conditions, such as Alzheimer's disease, vascular dementia and Parkinson's disease (Table 1).

Traditionally defined as a reduction in the ability to experience pleasure (Ribot 1896), the concept of anhedonia has recently incorporated views that also include a motivational component – a loss of motivation to seek pleasure (Treadway and Zald 2011). Several lines of evidence, in both animals and humans, have led to the proposal that pleasure is not a unitary construct, but consists instead of two distinct components: anticipatory and consummatory pleasure. The anticipatory factor refers to the motivation to seek pleasure or 'wanting', while the consummatory factor captures in-the-moment hedonic response or 'liking' (Berridge and Kringelbach 2013, 2015). An important consideration that has emerged from the study of anhedonia in neurodegenerative disorders is its nosological position with respect to two related – and intensively studied – neuropsychiatric syndromes that are associated with loss of pleasure and motivation: depression and apathy.

Given the fact that anhedonia is considered to be one of the core symptoms of major depressive disorder, it is perhaps not surprising that there is a close relationship between the two. It is nevertheless of considerable interest to determine whether aspects of depression can be dissociated from anhedonia in neurodegenerative conditions, particularly given recent views on the motivational components of anhedonia (Treadway and Zald 2011). The relationship between apathy, a syndrome defined by lack of motivation to act, and anhedonia also raises similar important

Table 1 Prevalence of anhedonia in neurodegenerative diseases

Disease	Prevalence	How anhedonia was measured	Sample size	Source
Parkinson's disease	7%	SHAPS	45	(Pluck and Brown 2002)
	40%	PAS	25	(Isella et al. 2003)
	45.7%	SHAPS	626	(Lemke 2005)
	74%	SHAPS	46	(Kaji and Hirata 2011)
	10%	SHAPS	100	(Fujiwara et al. 2011)
	16.3%	SHAPS	86	(Miura et al. 2012)
	12.3%	SHAPS	318	(Nagayama et al. 2012)
	12%	SHAPS	254	(Spalletta et al. 2013)
	9%	SHAPS	49	(Loas et al. 2014)
	15%	SHAPS	117	(Matsui et al. 2013)
	8%	SHAPS	34	(Pomponi et al. 2014)
	5%	SHAPS	57	(Mrochen et al. 2016)
	39%	SHAPS	318	(Nagayama et al. 2017)
	75%	SHAPS	155	(Assogna et al. 2019)
Dementia with Lewy bodies	76%	Structured interview	26	(Rockwell et al. 2000)
	25%	Structured interview	71	(Chiu et al. 2017)
Alzheimer's disease	40.3%	Structured interviews and medical records	67	(Reichman and Coyne 1995)
	37%	Structured interview	26	(Rockwell et al. 2000)
	61%	Semi-structured interview	1,155	(Lopez et al. 2003)
	35.6–80%	Structured interview (anhedonia was measured as part of an 'apathy-related symptom cluster' that included anhedonia, anergia and restriction of activities)	137	(Saz et al. 2009)
	4%	Structured interview	241	(Chiu et al. 2017)
Vascular dementia	40–66.7%	Structured interview	56	(Saz et al. 2009)
	5–21%	Minimum uniform dataset	270	(Lavretsky et al. 2008)
	34.2%	Structured interview and medical records	38	(Reichman and Coyne 1995)
Amyotrophic lateral sclerosis	1%	Medical records	112	(Martínez et al. 2018)

questions. At the heart of such considerations is the issue of construct validity. What really defines anhedonia? Does it share elements with apathy or other components of major depressive disorder, as currently defined? If so, can it still be considered an independent syndrome? Are there different neuroimaging correlates of anhedonia and apathy in neurodegenerative diseases? Can anhedonia be treated successfully using similar therapies across different diseases?

We are only at the beginning of endeavours to answer such questions. For example, attempts to distinguish anhedonia and apathy at the behavioural, cognitive

or structural brain imaging level have only just commenced, while treatments targeting dopaminergic systems have been attempted in only a very few studies. Although physical and cognitive deficits in neurodegenerative diseases might contribute to patients' apparent anhedonia, clinical experience suggests levels of anhedonia do not necessarily correlate well with levels of physical disability or cognitive impairment. Nonetheless, few studies have controlled for such confounding factors. Here we perform a transdiagnostic evaluation of the existing literature to critically appraise what is currently known, pointing out gaps in our knowledge which, if addressed in future investigations, might lead to a better understanding of anhedonia, across neurodegenerative conditions.

2 Parkinson's Disease

The largest body of work on anhedonia in neurodegenerative diseases typically has been on people with Parkinson's disease (PD). Although defined by motor symptoms, individuals with PD also often display non-motor symptoms including neuropsychiatric disorders. The prevalence of anhedonia in PD has been estimated to vary widely between 5 and 75% across different studies (Table 1). A recent meta-analysis confirms that overall anhedonia scores are significantly higher in PD than in healthy controls (Trøstheim et al. 2020). Furthermore, its presence appears to be negatively correlated with quality of life (Matsui et al. 2013) and also significantly associated with fatigue in PD patients (Solla et al. 2014).

The large variation in prevalence rates of anhedonia across studies might be attributable to several factors such as differences in sample sizes, cultural backgrounds, sample selection, disease severity in the patients tested and presence of other comorbidities that might influence anhedonia, e.g. co-existing chronic conditions unrelated to PD. Differences in the instruments used to assess anhedonia (Table 2) might also potentially play a role although the vast majority of published reports have used the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995). One study has employed the Physical Anhedonia Scale (PAS) (Isella et al. 2003) but other researchers have not deployed it in PD, presumably because it focuses solely on physical anhedonia symptoms.

Few studies of anhedonia in PD have used large samples, but even in those that have prevalence rates varied greatly, for example 12% in 318 patients (Miura et al. 2012) and 46% in 626 patients (Lemke et al. 2005). Although the SHAPS has been validated in the local language for Italian (Santangelo et al. 2009a) and Japanese (Nagayama et al. 2017) populations, cultural differences may also play an important contribution to estimates of prevalence, depending on people's willingness and sensitivities to admit to certain symptoms. This is particularly pertinent, given that one common issue across assessment tools is that they rely on self-reported patient data which has both advantages and disadvantages. Specifically, self-report instruments such as the SHAPS can be administered quickly and allow for rapid data collection, but there is a risk that patients may not be able to assess their current

Table 2 Measures used for anhedonia and apathy across diagnoses

Disease	How anhedonia was measured	How apathy was measured	Sample size	Source
Parkinson's disease	SHAPS	AES	45	(Pluck and Brown 2002)
	MADRS	LARS	95	(Dujardin et al. 2014)
	SHAPS	Apathy scale	50	(Kaji and Hirata 2011)
	PAS	Apathy scale	25	(Isella et al. 2003)
	SHAPS TEPS	Apathy scale	50	(Jordan et al. 2013)
	SHAPS	AMI	102	(Ang et al. 2018)
	SHAPS	Apathy scale	14	(Nagayama et al. 2019)
	SHAPS	Subscale derived from HAM-D, BDI and MADRS scales	60	(Antosik-Wójcińska et al. 2017)
	SHAPS	Apathy scale	37	(Thobois et al. 2013)
Parkinson's plus syndrome	SHAPS	AES	149	(Lansdall et al. 2017)
Alzheimer's disease	Semi-structured interview	Semi-structured interview	1,155	(Lopez et al. 2003)
Frontotemporal dementia	SHAPS	Cambridge behavioural inventory-revised	28	(Shaw et al. 2021a)
	SHAPS	DAS	87	(Shaw et al. 2021b)

symptoms accurately or be prepared to divulge them. Using self-reported scales often requires intact cognition and due to the nature of neurodegenerative diseases, patients may not always have the capacity to complete these questionnaires. Alternative methods of measuring anhedonia such as carer ratings or laboratory tests measuring odour intensity and hedonic tone may be considered. However, use of caregiver reports in conjunction with patient self-report has not been presented in published investigations in PD.

Another potentially important confounding factor is disease severity which is not always reported in studies of anhedonia in PD. Ideally, scales assessing general disease severity, such as the widely used Unified Parkinson's Disease Rating Scale (UPDRS) or cognitive assessments, should be included as a confounder variable in analyses. In one investigation, patients with higher levels of anhedonia showed more severe motor deficits and restrictions in activities in daily living (Lemke et al. 2005). Additionally, a relationship between anhedonia and motor deficits in PD was established, but most of the patients included only experienced mild motor deficit defined as a score of 3 or lower on the Hoehn and Yahr Scale (Nagayama et al. 2017). In contrast, in a large scale Italian study, motor symptoms, disease duration and disease severity did not correlate with anhedonia in patients with PD (Santangelo et al. 2009a). Consistent with this, no significant relationship was found between physical anhedonia, motor symptoms and disease duration in an earlier, smaller-scale investigation, also on Italian PD cases (Isella et al. 2003). The

conflicting evidence on anhedonia and motor symptoms indicates that anhedonia is unlikely simply to be a reaction to motor symptoms experienced in PD, but they may be associated.

2.1 Anhedonia and Its Relationship with Depression in Parkinson's Disease

Several studies have examined the relationship of anhedonia to depression in PD. Given that anhedonia can be one of the defining features of Major Depressive Disorder (MDD), it would not be a surprise to find the two conditions would be strongly related, but can anhedonia occur without depression? The first study to attempt answering this question explored depression and its relationship with anhedonia and apathy in 65 PD patients with depression and 60 patients without depression (Santangelo et al. 2009b). Mean SHAPS, Apathy Evaluation Scale and Hamilton Depression scale scores were higher in the depressed group of PD patients, indicating higher rates of anhedonia, apathy and depressive symptoms in patients who were depressed. The primary aim of this study was to examine depressive symptoms and cognition and therefore did not explore correlations between the three symptoms, but it did provide evidence that the three symptoms could be strongly related as indexed by the scores on the three scales used to assess patients.

One Japanese study assessing anhedonia and its relationship with depression showed that PD patients who had a higher score on the SHAPS also showed higher BDI values, also demonstrating that the two syndromes are highly related (Nagayama et al. 2017). In another Japanese cohort of 100 PD patients matched with 111 healthy controls it was found that anhedonia, indexed by the SHAPS, was also significantly related to depression as assessed by the Self-Rating Questionnaire for Depression (Fujiwara et al. 2011). However, some patients without depression displayed anhedonia, demonstrating also that anhedonia can be dissociated from full-scale depression.

Does the severity of depression play a role in levels of hedonic tone? One study compared levels of anhedonia in PD cases with Major Depressive Disorder (MDD), Minor Depressive Disorder (MIND) and no depression. Patients completed SHAPS and BDI questionnaires, and depression severity was diagnosed using a structural psychiatric interview. Results showed that patients with MDD showed the highest levels of anhedonia followed by MIND and no depression, as measured by mean SHAPS score and using a cut-off SHAPS score of >2 to indicate anhedonia (Spalletta et al. 2013). In addition, correlations between SHAPS and BDI scores were assessed in the three depression groups and showed that reduced hedonic tone was correlated with depression severity in patients with MDD and no depression, but anhedonia was not correlated with depression in the MIND category. These findings demonstrate that anhedonia is related to depression severity but suggests that it may be more complex and multidimensional in PD patients with MIND.

Is there a specific component of anhedonia that is related to depression in PD patients? Physical anhedonia was assessed against depression and other non-motor symptoms in PD patients and healthy controls (Isella et al. 2003). PD patients had significantly higher levels of anhedonia but in this case physical anhedonia was not correlated with depression as measured by the Geriatric Depression Scale. However, this was not replicated in a different study of PD patients using alternative instruments to measure anhedonia (Loas et al. 2014). This work used several scales to assess hedonic tone in order to explore the relationship between anhedonia and depression in PD (Loas et al. 2014). Forty-nine PD cases were assessed for anhedonia using the Temporal Expectation of Pleasure Scale (TEPS), SHAPS and the revised-PAS, while the BDI was used to rate depression. The TEPS measured anticipatory and consummatory anhedonia, the SHAPS covered social interaction, food and drink, sensory experience and interest/pastimes, whereas the revised-PAS measured physical anticipatory and physical consummatory anhedonia. Results showed that physical consummatory anhedonia was present only in PD patients, and the SHAPS was the only anhedonia scale where scores differed according to depression severity determined by the BDI).

This investigation also aimed to assess anhedonia in subtypes of depression termed non-endogenomorphic and endogenomorphic. The latter has been considered to be characterised by pervasive anhedonia, comprising both consummatory and anticipatory anhedonia; whereas non-endogenomorphic depression has been postulated to consist of only anticipatory anhedonia (Klein 1984). PD patients with endogenomorphic depression displayed higher levels of anhedonia measured by the SHAPS than patients with non-endogenomorphic depression (Loas et al. 2014). As the SHAPS measures both consummatory and anticipatory anhedonia, the results did not confirm the hypothesis that non-endogenomorphic depression was solely related to the anticipatory anhedonia domain. However, this investigation was first to use multiple scales to measure hedonic tone to explore the relationship between anhedonia and depression in PD to provide evidence that the relationship between these two variables is complex and needs further clarification.

2.2 Anhedonia and Its Relationship to Apathy in Parkinson's Disease

An important issue – both from a theoretical and a clinical perspective – is the relationship between anhedonia and apathy. Most conceptual frameworks of apathy have characterised it as a loss of motivation to initiate or persevere with goal-directed behaviour (Marin 1991; Starkstein and Brockman 2011). Historically, anhedonia has been considered to be a loss of pleasure (Ribot 1896), so at first glance these two syndromes might seem to be very different. However, recent work has suggested that one component of anhedonia might be the loss of motivation to seek pleasure (anticipatory anhedonia) while another might be the hedonic experience of gaining

pleasure (consummatory anhedonia) (Treadway and Zald 2011). The relationship between anhedonia and apathy might therefore be far closer than initially envisaged. This would also be consistent with some evidence that anhedonia and apathy might share some common underlying mechanisms (Husain and Roiser 2018).

In idiopathic PD, the evidence suggests that anhedonia is strongly linked to apathy (Assogna et al. 2011). The first study to provide evidence on this relationship assessed anhedonia using the SHAPS and apathy using the Apathy Evaluation Scale in 45 PD patients and 17 similarly disabled osteoarthritis control cases in the UK (Pluck and Brown 2002). Participants were split into high apathy or low apathy groups and correlations with SHAPS scores were explored. Overall, PD patients did not display higher levels of anhedonia than the osteoarthritis group, but individuals in the high apathy group displayed higher levels of anhedonia than patients in the low apathy group. Furthermore, in this particular study, no significant relationship between apathy and depression was found in PD patients, which suggests that anhedonia and apathy might share similar mechanisms that are not found in depression.

Another investigation, this time in 95 patients in France, reported that apathy indexed by the Lille Apathy Rating Scale (LARS) was significantly associated with anhedonia (assessed by the Montgomery and Asberg Depression rating scale, MADRS) and fatigue (Dujardin et al. 2014), also supporting the view that anhedonia and apathy might be strongly linked without depression. The relationship between anhedonia, apathy and depression was also examined in a study conducted on 50 PD patients in Japan (Kaji and Hirata 2011). Japanese versions of the SHAPS, Apathy Scale and the Hamilton Depression Scale were employed, and participants were compared to pre-determined cut-off threshold scores in the three scales. Figure 1 outlines the prevalence and overlap of anhedonia, apathy and depression in this report. The investigators found that nearly all cases with apathy displayed anhedonia; and nearly all patients with depression also displayed apathy and anhedonia, but a large portion of patients experienced anhedonia and apathy without depression. A strong relationship between SHAPS and Apathy Scale scores was also found in this

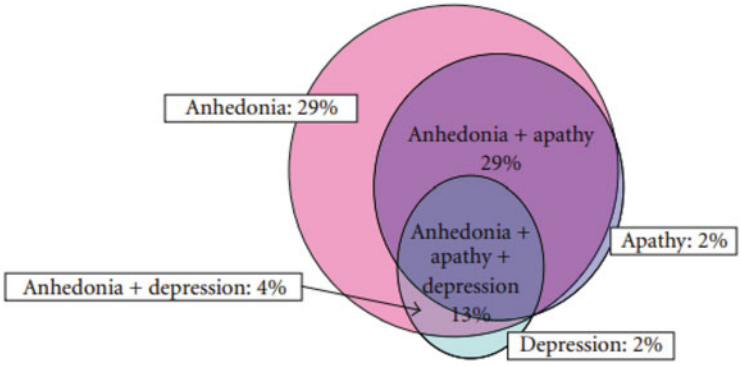

Fig. 1 Prevalence and overlap of anhedonia, apathy and depression in PD (Kaji and Hirata 2011)

cohort. Of the patients that were not depressed, 29% of patients reported an overlap of both anhedonia and apathy. It was concluded that anhedonia and apathy share a common mechanism (possibly of disturbances of dopamine in the reward system) and that the two symptoms are core features of PD, independent of depression scores.

Contrary to these conclusions, an Italian study on 25 PD patients found no relationship between anhedonia as measured by the PAS and apathy, indexed by the Apathy Scale (Isella et al. 2003), suggesting that physical anhedonia and apathy are not related. The PAS is a self-rated questionnaire that asks patients to respond to statements of various pleasant situations involving direct sensory experiences (Chapman et al. 1976), whereas the more commonly used SHAPS questionnaire assesses the dimensions of both physical and social anhedonia. The results of this investigation suggest that *physical* anhedonia might be a separate syndrome to apathy. But PD patients reported higher mean PAS and Apathy Scale scores than controls. Thus, the two symptoms appear to be common symptoms in PD and is possible that social anhedonia has a stronger relationship with apathy (Kaji and Hirata 2011), but this has not specifically been explored in detail to date.

Anticipatory and consummatory anhedonia in PD and their relationship to apathy has been investigated in PD and healthy controls (Jordan et al. 2013). Fifty PD patients and 42 healthy older adults completed the SHAPS, TEPS and Apathy Scale to assess anhedonia and apathy. Anhedonia was thus measured using two scales: the SHAPS is believed to measure global anhedonia whereas the TEPS was included along with the SHAPS to explore whether a specific domain of anhedonia (anticipatory or consummatory) was related to apathy. PD patients reported higher mean scores on the SHAPS, TEPS Consummatory subscale and Apathy Scale compared to controls, indicating anhedonia and apathy are prevalent in PD. Patients with increased Apathy Scale scores had greater global anhedonia (measured by the SHAPS scores) and anticipatory anhedonia (measured by the TEPS Anticipatory subscale scores) than PD patients without apathy, independent of diagnosis, age, education or depressive symptoms (Jordan et al. 2013). These findings suggest that a relationship between anhedonia and apathy exist, and this relationship is characterised by anticipatory pleasure and behavioural drive more than consummatory pleasure.

Most conceptual frameworks of apathy consider it not be a unitary syndrome of loss of motivation but instead composed of several dissociable dimensions, including behavioural, cognitive, social and emotional domains (Levy and Dubois 2006; Ang et al. 2017). Each of these may have differential impacts on anhedonia. Assessment of how these domains of apathy are related to anhedonia in 102 PD patients and 147 healthy controls was carried out using the Apathy Motivation Index (AMI). Patients who had higher levels of social and behavioural apathy – but not emotional apathy – were more anhedonic and depressed, measured by the SHAPS and Geriatric Depression Scale. These results suggest that apathy and anhedonia might have a strong relationship in behavioural and social domains (Ang et al. 2018). However, overall, PD patients had relatively preserved emotional motivation. The multidimensional nature of apathy and its relationship to aspects of anhedonia have not been extensively investigated in other neurodegenerative diseases.

2.3 Treatment of Anhedonia in Parkinson's Disease

There are no treatments that specifically target anhedonia in PD or any other neurodegenerative diseases. Dopamine is important for anticipatory but not the consummatory experience of pleasure (Berridge and Robinson 2003), and there is some evidence that treatment with dopaminergic medication can lead to an improvement in anhedonia. Pramipexole, a dopamine agonist at D2 and D3 dopamine receptors, appears to reduce anhedonia in PD patients. One investigation assessed over 600 PD patients treated with pramipexole as well as levodopa (Lemke 2005; Lemke et al. 2006). Prior to the study commencing, anhedonia, as measured by a German version of the SHAPS, was present in 45.7% of PD patients, while 80% were classified as being depressed. A significant difference in SHAPS scores was found between PD patients who were depressed and non-depressed (determined by depression scores on the Short-Parkinson's-Evaluation-Scale). Depressed patients reported a higher rate of anhedonia than non-depressed patients. Following treatment with pramipexole, anhedonia scores on the SHAPS scale significantly decreased from a mean score of 2.5 to 0.72 and the incidence of anhedonia (determined by a cut-off $\geq$3 on the SHAPS) reduced from 45.7% of patients at baseline to 25.5% after 9 weeks. In PD patients with moderate-severe depression, anhedonia reduced in prevalence from 74.3% to 45.3% of patients, while in non-depressed patients it decreased from 34.6% to 18.3% after 9 weeks.

The effect of pramipexole was replicated in an observational study examining the frequency of anhedonia with respect to medications used to treat PD (Fujiwara et al. 2011). Of all the drugs used, only pramipexole showed a significant impact. Seventy-two per cent of PD patients treated with pramipexole showed normal hedonic tone. Further, SHAPS scores of the patients on pramipexole were significantly lower than patients not on the drug. Together, these findings suggest pramipexole might be effective at reducing rates of anhedonia in PD patients. However, not all studies have reported significant efficacy of pramipexole on anhedonia.

A 12-week randomised control trial of pramipexole compared to placebo was conducted on 296 PD patients with mild-to-moderate disease severity, on stable levodopa and mild-to-moderate depressive symptoms (assessed by scores on the geriatric depression scale and the UPDRS part 1 depression score) (Barone et al. 2010). The primary efficacy outcome measure was change on BDI scores, measuring depression, from baseline to 12 weeks. Two hundred and eighty seven patients (139 on pramipexole and 148 on placebo) were included in the analysis, with BDI scores for patients on pramipexole showing a small beneficial effect, reducing from a mean of 18.7 at baseline to 13.1 at 12 weeks, compared with scores reducing from 19.2 to 15.0 in the placebo group. The study also explored the impact of pramipexole on anhedonia using SHAPS scores but found no treatment effect as determined by median change in SHAPS scores and did not report the SHAPS scores at baseline or 12 weeks.

Recently, PD patients have been treated with istradefylline, an adenosine A2A receptor antagonist used for treatment of motor symptoms. The drug was given to 14 PD patients for 12 weeks, measuring anhedonia, apathy and depression using the SHAPS, Apathy Scale and BDI. On istradefylline, SHAPS, Apathy Scale and BDI scores significantly reduced from baseline scores at 4-, 8- and 12-weeks, with mean SHAPS scores at week 12 about 50% reduced from baseline scores, indicating that istradefylline reduces anhedonia (Nagayama et al. 2019). As apathy and depression rates dropped as well as anhedonia, this trial also provided evidence for the overlapping relationship between the three symptoms.

In selected PD cases subthalamic nucleus deep brain stimulation (STN-DBS) can lead to improvement of motor symptoms, but evidence assessing the impact of STN-DBS on psychiatric symptoms, including anhedonia in PD is limited. In one report, STN-DBS had no significant effect on anhedonia or depression although L-Dopa did (Witt et al. 2006). However, this study was carried out in a chronic setting where medications may have a longer-term benefit than STN-DBS. Another investigation assessed the impact of STN-DBS only on anhedonia, apathy and depression in 60 PD patients who were evaluated 5 days pre-treatment to 6 months post-treatment (Antosik-Wójcińska et al. 2017). Anhedonia, apathy and depression (measured by SHAPS; a subscale for apathy derived from HAM-D, BDI and MADRS scales; and BDI and MADRS) had a notable reduction in the first 30 days following STN-DBS. Anhedonia reduced by 9%, apathy by 32% and depression by 23% on MADRS and 7% on BDI, and this level of reduction was maintained after 6 months.

There is also some limited evidence that treatment for apathy can also impact upon anhedonia. Many PD patients who are treated with STN-DBS have their dopaminergic medicine dose decreased substantially because deep brain stimulation improves their motor deficits. But this can come at a cost, with development of apathy as the dopaminergic medication dose is dropped. Thirty-seven PD patients who underwent subthalamic stimulation and decrease in dopaminergic treatment took part in a 12-week prospective, placebo-controlled, randomised double blind trial using piribedil, a selective D2/D3 dopamine receptor agonist to treat apathy (Thobois et al. 2013). Scores on the Apathy scale reduced by 35% in patients on the drug, and results also showed a trend towards improvement in anhedonia measured by the SHAPS. Taken together, there is some evidence that dopamine agonists such as pramipexole and piribedil, or the adenosine A2A receptor antagonist istradefylline can improve anhedonia and apathy in PD.

3 Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is characterised by dementia including attentional, executive and visuospatial impairments often associated with visual hallucinations and Parkinsonian motor features (McKeith et al. 2017). Patients with DLB also suffer from neuropsychiatric complications, including anhedonia, although

specific evidence for the latter is limited in published studies. DLB patients have been compared to those with Alzheimer's disease (AD) patients with respect to frequency, severity and symptoms of depression that included pervasive anhedonia as a symptom. Pervasive anhedonia determined by structured interviews with patients and carers was present in 25% of DLB patients and 4% of AD patients (Chiu et al. 2017). These results are in line with a previous study on anhedonia in DLB and AD, which confirmed a significantly higher rate of anhedonia as measured by patient and informant structured interviews: 76% in 26 DLB patients, compared to 37% in AD patients (Rockwell et al. 2000).

In another study, DLB patients were compared to patients with other forms of Parkinsonism when measuring anhedonia using the SHAPS. Results revealed DLB patients had the highest mean SHAPS score indicating that DLB patients are more anhedonic than patients with other forms of Parkinsonism (Santangelo et al. 2009a). However, the sample size of DLB cases in this study was small, with only 14 DLB patients included. Furthermore, this group by definition had marked cognitive impairment, which may influence overall mood and anhedonia in this patient group.

There is limited evidence on the relationship between anhedonia and depression in DLB. One study assessed the frequency and severity of depression in DLB and AD patients using DSM-IV criteria (Chiu et al. 2017). Twenty per cent of DLB patients were diagnosed with major depression compared to 9% of AD patients. However, the frequency of minor depression was not significantly different between the two patient groups (31.6% and 28.2%). The relationship between anhedonia and depression was not directly examined in this study, but models of multivariable risk estimates showed that anhedonia had the greatest value for differential diagnosis of depressive symptoms between DLB and AD, suggesting that anhedonia and depression are closely linked in these two patient groups. Another study evaluated depressed mood in 26 DLB patients using patient and informant structured interviews and showed the rate of depression was 66% and anhedonia was 76% (Rockwell et al. 2000). Patients were separated into two groups according to disease severity (measured by the Mini Mental State Examination, MMSE), with depression reported more frequently in the more severe DLB group. The authors, however, did not examine the relationship between depressed mood and anhedonia. The limited evidence on anhedonia and depression in DLB does not reveal much about correlations between the two symptoms. Furthermore, there have been no studies looking at the rate of apathy and its relationship with anhedonia in DLB patients to date.

4 Parkinson's Plus Syndromes

Parkinson's plus syndromes (PPS), sometimes referred to as atypical Parkinsonian syndromes, are neurodegenerative diseases that feature some of the symptoms and signs of PD but with additional features that separate them from idiopathic PD (Armstrong and McFarland 2019). They include progressive supranuclear palsy (PSP), multisystem atrophy (MSA), corticobasal syndrome (CBS) and vascular

Parkinsonism (VP). In general, the evidence base regarding anhedonia in these PPS is quite limited. One very large Italian study of patients with different forms of Parkinsonism recruited individuals with PSP, MSA, VP as well as idiopathic BD and DLB (Santangelo et al. 2009a). Although this investigation did not report rates of anhedonia in the different patient groups it documented that mean SHAPS scores were highest in DLB (5.3), followed by PSP (3.1), VP (2.4), MSA (2.3) and then PD (1.8). Anhedonia also correlated with frontal dysfunction measured by the Frontal Assessment Battery in PSP and VP patients. The Frontal Assessment Battery is a brief tool that is used to determine dementias with a frontal dysexecutive phenotype from AD. Domains assessed include conceptualisation, mental flexibility, programming, sensitivity to interference, inhibitory control and environmental autonomy. This study did not clarify which subdomains were impaired and correlated with anhedonia. In addition, when all groups were combined, apathy and depression were significantly related to SHAPS scores, as well as increasing age and cognitive impairment.

Rates of anhedonia in PSP has been explored further in patients with two frequent variants of PSP, Richardson's Syndrome (PSP-RS) and PSP with predominant parkinsonism (PSP-P) (Assogna et al. 2019). Twelve PSP-RS and 11 PSP-P patients underwent neuropsychological evaluations for anhedonia and other variables including depression and alexithymia and were compared to 155 PD patients. The prevalence of anhedonia, measured by the SHAPS, was 12.5% in both PSP patient groups and 75% in the much larger PD group. This difference was not formally significant but, as the authors suggest, this may have been down to small sample size. Another factor might have been the scale used. The SHAPS focuses on consummatory anhedonia whereas there is evidence for anticipatory anhedonia being affected in degenerative parkinsonian syndromes. An alternative scale such as the TEPS could be used in future studies to measure anticipatory anhedonia in PSP.

Another study examined 149 patients diagnosed with either PSP or CBS as well as individuals with two types of frontotemporal dementia – see section below. They were assessed with neuropsychological, behavioural and imaging tools with a primary focus on apathy and impulsivity (Lansdall et al. 2017). Anhedonia measured by the SHAPS was higher across all patient groups compared to controls, but the syndrome was not compared between groups. Nevertheless, a significant relationship between anhedonia, apathy and depression was identified through principal component analysis using scores from the SHAPS, AES and BDI. These findings again suggest a strong overlap between these constructs but did not investigate how and whether they might be dissociable.

5 Alzheimer's Disease

Alzheimer's disease (AD), the most common cause of dementia, is characterised by cognitive decline, often beginning with memory decline but eventually involving multiple cognitive domains. Neuropsychiatric symptoms are increasingly

appreciated to be a common feature in AD (Zhao et al. 2016). The reported prevalence rates of anhedonia in AD vary widely, between 4 and 61% (Table 1). As with PD, these highly varying figures could be due to differences in sample selection or sizes and different instrument used to measure anhedonia.

One important factor that can influence prevalence rates is disease severity. Patients with AD can be rated from mild to severe depending on the level of cognitive impairment and disruption to activities of daily living. Results of several investigations suggest that the levels of anhedonia increase with disease severity. In one large study which analysed psychiatric symptoms in 1155 patients with probable AD, 61% were considered to have anhedonia when assessed using semi-structured interviews (Lopez et al. 2003). The rate of anhedonia increased with disease progression: 50% in mild AD, 65% in moderate cases and 72% severe AD (Lopez et al. 2003). In a different investigation of 137 patients with AD, anhedonia was evaluated through observation and with an 'apathy-related symptom cluster' based on the results that included three negative-type symptoms: anergia, restriction of activities and anhedonia. Anhedonia and observed slowing of activity was shown to be significantly different between patients with mild/moderate AD (36%) and severe AD (80%) (Saz et al. 2009).

Other studies have compared anhedonia in AD patients to those with DLB. In one investigation which used semi-structured interviews and controlled for disease severity, age, gender, education and depressive symptoms, AD cases were found to have lower levels of anhedonia compared to DLB patients (4% and 25% respectively) (Chiu et al. 2017). Another also reported rates of anhedonia were lower in AD patients (37%) compared to DLB patients (76%) using structured interviews (Rockwell et al. 2000). Patients from the two groups were separated into subgroups according to disease severity, as measured by the MMSE, with depressed symptoms showing more frequently in the severe disease group. However, they did not assess the impact of disease severity on rates of anhedonia.

Little is known about anhedonia in mild cognitive impairment (MCI). People with this diagnosis show evidence of mild impairment on cognitive testing, are not affected in activities of daily living but are at higher risk of developing AD or another form of dementia in the future. In one study, using semi-structured interviews conducted by a psychiatrist, people with MCI were compared to patients with mild probable AD (Lopez et al. 2005). Forty per cent of the MCI group were anhedonic compared to 50% of AD cases. Anhedonia, but not dysphoria, has also been found to be a risk factor for dementia in cognitively normal elderly individuals (Lee et al. 2019). The study also found that the presence of anhedonia was associated with an approximately five-fold higher risk for MCI and dementia.

Although anhedonia is widely reported in AD, its relationship with depression and apathy is poorly understood. Rates of depression and apathy are well reported with 19–78% of AD patients in 30 studies having depression and 19–88% of AD cases across 25 investigations displaying apathy (Zhao et al. 2016). Two studies have explored the relationship between anhedonia and depression and whether they are separate syndromes in AD. Completing semi-structured interviews to determine the presence of anhedonia, apathy and depression, anhedonia was found to be

associated with major depression in mild dementia but no association was found in patients with moderate or severe dementia (Lopez et al. 2003). In addition, anhedonia, apathy and a lack of energy were more frequent in patients with moderate and severe cognitive impairment than those with mild dementia. This suggests there might be overlap or possibly common mechanisms underlying anhedonia and apathy in AD, but the evidence is not substantial.

A preliminary study has examined anhedonia and depression in AD and their impact on cognition, with patients being split into four groups: anhedonia and depression, anhedonia only, depression only, and neither of the two syndromes (Natta et al. 2013). In this investigation, anhedonia was measured using the Social-Emotional Withdrawal Scale on the assessment of Negative Symptoms in AD (SANS-AD) and depression was assessed with the HAM-D. The group displaying anhedonia and depression had a greater adverse impact on working memory compared to the other groups, with the anhedonia only group showing poorer results than the depression only group despite no overall differences in cognition between groups (Natta et al. 2013). The results of these studies suggest that anhedonia can be separable from depression, and its presence might independently be a risk factor for cognitive impairment in AD. To the best of our knowledge, there are currently no studies that have examined specifically the relationship between anhedonia and apathy in AD. Further clarification of the relationship between anhedonia, apathy and depression might have important implications for both diagnosis and treatment.

6 Vascular Dementia

Vascular dementia (VD) is the second most common type of dementia. Associated with a wide range of pathological changes that impact on the micro- and macrovasculature of the brain, vascular cognitive impairment (VCI) and VD can present in a range of ways from insidious, slow progression in small vessel cerebrovascular disease (SVD) or subcortical ischemic vascular disease (SIVD) through to step-wise deterioration following strokes in multi-infarct dementia (MID) (van der Flier et al. 2018; ter Telgte et al. 2018). Anhedonia has been reported in SVID in people with and without cognitive impairment. One study used the Minimum Uniform Dataset to assess and measure rates of anhedonia in people with SVID (Lavretsky et al. 2008). Anhedonia was more prevalent in demented patients (22%) than in people with cognitive impairment (12%) and individuals who were cognitively normal (5%). In another investigation, anhedonia in VD was compared to other forms of dementia using an 'apathy-related symptom cluster' to measure anhedonia, anergia and restriction of activities. Fifty six patients with probable VD were separated into groups of mild/moderate VD ($n = 30$) and severe VD ($n = 26$) with patients in the severe VD group showing higher levels of anhedonia (67%) compared to the mild/moderate group (40%) (Saz et al. 2009).

The relationship between anhedonia, depression and apathy has not been well investigated in VD. In one study, anhedonia was assessed as a symptom of depression in 38 patients with MID (Reichman and Coyne 1995). Inclusion criteria for MID patients was imaging evidence of a clinically significant stroke, as well as displaying focal neurological symptoms. Anhedonia and depression were grouped into one variable ('depressed mood/anhedonia') and was frequently observed in the MID group (34.2%) in patients who otherwise did not meet the criteria for major depression (Reichman and Coyne 1995). An important finding was that the subjective symptoms of depression (diminished self-esteem, thoughts of death, guilty feelings) were not significantly associated with depressed mood/anhedonia, although fatigue was. However, it is unclear from the results of this study how dissociable anhedonia is from depression in VD. With respect to apathy and anhedonia, we are unaware of any studies that have systematically investigated the relationship between these syndromes in VD.

7 Frontotemporal Dementia

Frontotemporal dementia (FTD) is often a younger-onset dementia syndrome characterised by progressive decline in behaviour, personality and/or language function (Hodges and Piguet 2018). The literature on anhedonia in FTD is extremely limited, but one study recently published has provided an in-depth overview. Anhedonia was measured using the SHAPS alongside other clinical and brain imaging data at two timepoints in 87 FTD patients, 34 AD patients and 51 healthy controls (Shaw et al. 2021b). Lack of insight is common in FTD (Mendez et al. 2005). Therefore, carers were also asked to complete questionnaires on patients' symptoms. Results showed patients rated themselves as having lower levels of anhedonia compared to carers, suggesting under-estimation of symptoms in patients. To assess the prevalence of anhedonia in different diagnoses of FTD, patients were separated using diagnostic criteria into a behavioural variant (bvFTD) group, semantic dementia (SD) and progressive non-fluent aphasia group (PNFA). Patients with bvFTD and SD displayed significantly higher levels of anhedonia relative to the PNFA, AD and healthy controls groups, with no significant difference between bvFTD and SD cases.

Importantly, this study also provided an assessment of the relationship between anhedonia, depression and apathy. Apathy is a prominent feature in FTD (Massimo et al. 2015) and patients often suffer also with other neuropsychiatric symptoms including depression (Blass and Rabins 2009). In FTD patients, increased anhedonia was associated with greater apathy (measured by the Dimensional Apathy Scale, DAS), higher levels of self-reported depression (measured by the Depression and Anxiety Scale, DASS) and greater functional impairment (Shaw et al. 2021b). Although there were strong associations between anhedonia and depression and apathy, neuroimaging revealed distinctly different patterns of regional atrophy associated with these symptoms.

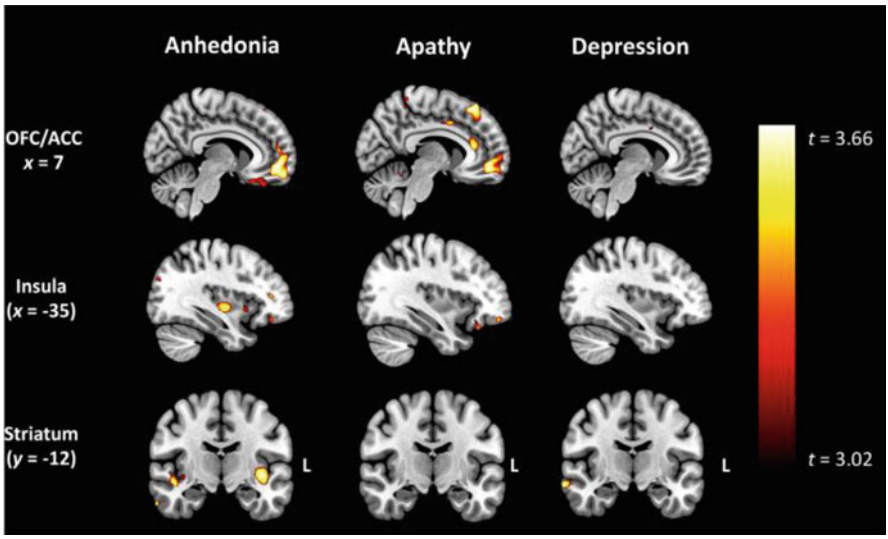

Fig. 2 Grey matter correlates of anhedonia (SHAPS), apathy (DAS) and depression (DASS) across the entire patient cohort ($n = 105$) (Shaw et al. 2021b)

Imaging data on anhedonia in neurodegenerative diseases are exceptionally scarce. In fact, to the best of our knowledge, this study is the only one that has examined both apathy and anhedonia in the same patient group to investigate brain correlates of each syndrome. Similar analyses might profitably be applied across other diseases in future studies. MRI scans of 154 participants were available for analysis: 29 AD, 50 behavioural-variant FTD, 8 PNFA, 18 SD and 49 controls, and were carried out within 6 months of SHAPS completion (Shaw et al. 2021b). Whole-brain correlation analyses were explored on patient groups between grey matter intensity and scores of the SHAPS, DAS and DASS to assess anhedonia, apathy and depression, respectively. Figure 2 outlines the grey matter atrophy correlates of anhedonia, apathy and depression. Lower SHAPS scores, indicating greater anhedonia, were associated with grey matter intensity decrease in bilateral orbitofrontal, medial prefrontal and paracingulate cortices, as well as insular and lateral temporal regions, and the right putamen to a lesser degree. Increased apathy scores were associated with grey matter intensity decrease in a predominantly right-sided network of frontopolar, orbitofrontal and medial prefrontal cortical regions, including the anterior cingulate cortex, right parietal regions, occipital cortices and the right cerebellum. In contrast, higher levels of depression scores were associated with a relatively restricted set of regions on the right lateral temporal cortices (including the posterior middle and super temporal gyri, left precuneus and lateral occipital cortex).

Analyses revealed no significant overlap between SHAPS scores and depression severity on the DASS. However, there was a region of overlap between SHAPS and DAS scores that was identified in the right hemisphere. Figure 3 shows that this covered the right prefrontal cortex, orbitofrontal cortex, paracingulate cortex and

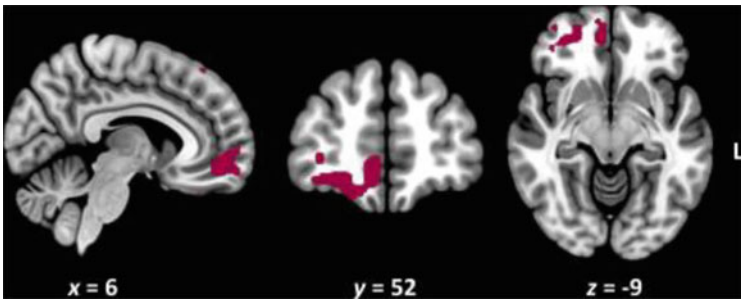

Fig. 3 Regions of grey matter intensity decrease common to anhedonia and apathy (Shaw et al. 2021b)

frontal pole. Thus, overall there was evidence of both common and unique brain regions associated with anhedonia and apathy.

In this study levels of anhedonia did correlate significantly with cognitive impairment or disease duration, suggesting that it is not simply a by-product of disease severity. As mentioned, behavioural data using the SHAPS, DAS and DASS showed associations between anhedonia, apathy and depression, but these constructs diverged at the brain level, at least with respect to patterns of atrophy (Fig. 2). The findings coincide with previous evidence in neuropsychiatric conditions whereby similar behavioural features can emerge due to distinct pathophysiological mechanisms (Whitton et al. 2015).

An additional study was conducted in 28 SD patients exploring the impact of lateralisation of temporal lobe atrophy on anhedonia, measured by the SHAPS (Shaw et al. 2021a). Eight SD patients presenting with right-predominant (SD-R) profiles of temporal love atrophy and 20 left-predominant (SD-L) profiles were compared with 30 AD patients and 30 controls on SHAPS scores. The SHAPS scale was modified to include carer ratings of anhedonia at time of symptom onset and current time for patients due to the nature of SD with some patients displaying a lack of insight, with controls completing only the self-rated SHAPS scales. Results at the current time showed SD-R patients had significantly higher levels of anhedonia when compared to SD-L patients and AD patients, with these groups not differing from controls. Carer ratings revealed SD-R patients displayed significantly higher rates of anhedonia than AD patients. Analyses of anhedonia from symptom onset to current time were carried out using carer reported scores and revealed that increased rates of anhedonia were most prevalent in SD-R patients, followed by SD-L and AD. This study was important at highlighting a possible unique role of the right temporal lobe on anhedonia rates in SD, which offers an insight into the role of hemispheric lateralisation on mechanisms of pleasure in the brain. Longitudinal studies on the evolution of anhedonia, and its potential association with psychiatric symptoms, disease course and disease severity are necessary to address the impact of anhedonia within different types of FTD.

8 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also referred to as motor neurone disease, is a neurodegenerative disorder of the motor system impacting motor activity under voluntary control (Elman and Grossman 2007). Many individuals with ALS also develop cognitive deficits (Abrahams et al. 2005) and neuropsychiatric symptoms, in particular depression (Rabkin et al. 2005). A subset of ALS patients with cognitive deficits may go on to develop clinical dementia, which presents in a pattern similar to FTD characterised by impairment in language, executive function, memory and visuospatial skills (Elman and Grossman 2007). The literature on neuropsychiatric features in ALS typically focuses on depression but two studies have addressed anhedonia in this disease.

One of these assessed non-motor symptoms in 112 patients with ALS and found only 1% reported anhedonia (Martínez et al. 2018). A second study reported on psychopathology in 27 ALS cases, assessing anhedonia as part of the Depressive Mood Scale. None of the patients appeared anhedonic, but those who were recently diagnosed with ALS (in the previous 6 months) presented a lack of expressiveness (Bungener et al. 2005). The results of these studies suggest that anhedonia is not characteristic of ALS, but these investigations did not use validated assessment tools to measure anhedonia which was not one of the main outcome variables. Due to the emerging similarities between ALS and FTD as well as the high prevalence of depression in this disease, it would seem worthwhile to measure anhedonia in ALS in future studies.

9 Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterised by progressive motor dysfunction, psychiatric symptoms and cognitive deterioration (Walker 2007). HD develops as a result of an expanded trinucleotide CAG repeat on the huntingtin gene on chromosome 4 (MacDonald 1993), and typically has a mid-adult onset with a disease duration of 15–20 years. Neuropsychiatric symptoms are prevalent across different stages of HD, but there is limited evidence available on anhedonia in HD. Anhedonia has been studied in the context of hedonic olfaction in HD, with patients showing lower hedonic ratings and a narrower hedonic range compared to healthy controls (Hayes et al. 2007). Currently there are no studies assessing the relationship between anhedonia, depression and apathy in HD.

Apathy, on the other hand, has been extensively studied and has been shown to be the most frequently reported symptom, being present in 28% of a cohort of HD patients (van Duijn et al. 2014), but this was not examined in the context of its relationship with anhedonia. An on-going study assessing hedonic olfaction in HD and healthy controls aims to correlate hedonic olfaction with anhedonia, apathy and

depression, measured by patient-rated subjective questionnaires (Marxreiter et al. 2016). Results have not yet been published, but the authors hope it will provide evidence on anhedonia and correlates with other psychiatric symptoms in HD. Due to the apparent overlap of anhedonia with depression and apathy in other neurodegenerative diseases, the relationship between these three symptoms might profitably be considered in future research of HD outcomes.

10 Conclusions

In conclusion, a transdiagnostic assessment of the literature provides evidence that anhedonia is a frequent symptom in patients with neurodegenerative diseases. Most studies focus on PD patients although reported rates of anhedonia vary widely in this patient group. There is limited evidence in other neurodegenerative diseases, but the evidence suggests that anhedonia is a frequent symptom across these conditions. To date, findings suggest a strong relationship between anhedonia and depression, which might not be surprising given the fact that anhedonia is a core symptom in many people with major depressive disorder. However, perhaps more intriguingly, anhedonia frequently overlaps with apathy, with the evidence for this being strongest in PD (Fig. 1) and FTD. Treatment with dopaminergic D2/D3 receptor agonists in PD can concomitantly improve features of both apathy and anhedonia. Moreover, imaging in FTD shows that atrophy of a common brain region in the right frontal lobe is associated with both anhedonia and apathy (Fig. 3). These links might relate to motivational dysfunction common to both syndromes. On the other hand, apathy and anhedonia can be dissociated, both at the behavioural level and with respect to patterns of atrophy in FTD (Fig. 2). These observations set the stage for more intensive, hypothesis-driven investigation of the cognitive mechanisms and brain networks involved in anhedonia – and the related condition of apathy – to understand common and unique features of these two important syndromes that cut across a range of neurodegenerative conditions.

Acknowledgments This work was funded by The Wellcome Trust and NIHR Oxford Biomedical Research Centre.

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Part III
Reward Processing Systems in Anhedonia

Pleasure, Reward Value, Prediction Error and Anhedonia

Karel Kieslich, Vincent Valton, and Jonathan P. Roiser

Contents

Abstract In order to develop effective treatments for anhedonia we need to understand its underlying neurobiological mechanisms. Anhedonia is conceptually strongly linked to reward processing, which involves a variety of cognitive and neural operations. This chapter reviews the evidence for impairments in experiencing hedonic response (pleasure), reward valuation and reward learning based on outcomes (commonly conceptualised in terms of "reward prediction error"). Synthesising behavioural and neuroimaging findings, we examine case-control

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Curr Topics Behav Neurosci (2022) 58: 281–304
https://doi.org/10.1007/7854_2021_295
Published Online: 14 February 2022

studies of patients with depression and schizophrenia, including those focusing specifically on anhedonia. Overall, there is reliable evidence that depression and schizophrenia are associated with disrupted reward processing. In contrast to the historical definition of anhedonia, there is surprisingly limited evidence for impairment in the ability to experience pleasure in depression and schizophrenia. There is some evidence that learning about reward and reward prediction error signals are impaired in depression and schizophrenia, but the literature is inconsistent. The strongest evidence is for impairments in the representation of reward value and how this is used to guide action. Future studies would benefit from focusing on impairments in reward processing specifically in anhedonic samples, including transdiagnostically, and from using designs separating different components of reward processing, formulating them in computational terms, and moving beyond cross-sectional designs to provide an assessment of causality.

Keywords Anhedonia · Decision making · Hedonic response · Prediction error · Reward

1 Introduction

Anhedonia is usually defined as a loss of interest or pleasure in previously rewarding activities. It is a cardinal symptom of depression and a core negative symptom in schizophrenia, and it is also often present in Parkinson's disease and other neurological disorders. Its clinical manifestation overlaps with several other symptoms, such as apathy, fatigue, anergia or avolition. Anhedonia is an important symptom to understand because it is associated with poor clinical outcomes: anhedonic patients are at higher risk for non-response to both psychological and pharmacological treatments (McMakin et al. 2012; Craske et al. 2016), established treatments may have little impact on anhedonia (Fig. 1), and there are no interventions specifically targeting this symptom (Argyropoulos and Nutt 2013). It is also associated with

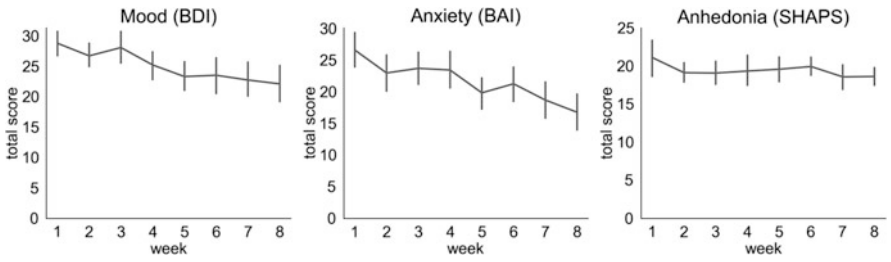

Fig. 1 Anhedonia is relatively unaffected by cognitive-behavioural therapy, even as the broader spectrum of depressive symptoms improves; adapted from Nord et al. (2019). Weekly mood, anxiety and anhedonia self-report scores, shown over a course of 8 weeks of therapy. Error bars represent standard error of the mean. *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *SHAPS* Snaith-Hamilton Pleasure Scale

suicidal ideation independently of depression (Ducasse et al. 2018) and suicide within 1 year (Fawcett et al. 1990).

In order to develop effective treatments for anhedonia we need to understand the neurobiological mechanisms underlying it. This is complicated by the fact that anhedonia does not represent a unitary construct as its conceptualisation has evolved from "inability to experience pleasure" to "loss of interest or pleasure in previously rewarding activities", adding a motivational component. But experiencing pleasure and being motivated involve multiple distinct neurocognitive mechanisms, which may be differently affected in different patients, and may therefore require different treatments (Treadway and Zald 2011; Husain and Roiser 2018). To understand the neurobiology of anhedonia and develop targeted treatments, it is therefore important to deconstruct it into its component cognitive and neural processes.

2 Anhedonia and Reward Processing

Cognitively, anhedonia can be conceptualised as a disruption in reward processing. Reward processing involves a variety of cognitive operations in which information about reward is used to guide behaviour. This includes: computing and making decisions based on reward value; anticipating reward; initiating and sustaining action necessary to obtain reward; experiencing hedonic response (pleasure); and learning based on reward outcomes (commonly conceptualised in terms of "reward prediction error"). Disruption to any of these processes (Fig. 2) could potentially drive anhedonia (Husain and Roiser 2018).

One of the main benefits of studying anhedonia through the conceptual framework of reward processing is that the cognitive and neural mechanisms of reward processing are relatively well understood (Berridge et al. 2009). Describing how the different subcomponents of reward processing are altered in anhedonia could help explain the mechanistic heterogeneity within this symptom and provide specific targets for treatment.

While some of these processes are relatively straightforward to measure, others can only be studied indirectly. The most common approaches are to use cognitive tests which engage them, or record physiological responses which they elicit (including functional neuroimaging and psychophysiology). More recently, computational accounts of different stages of reward processing have been developed

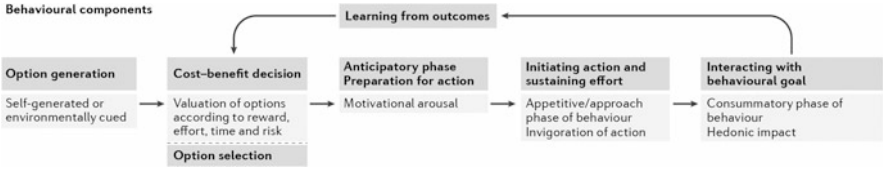

Fig. 2 Components of reward processing, disruption to any one of which could potentially drive anhedonia; adapted from Husain and Roiser (2018)

(Dreher and Tremblay 2009). Such accounts express what happens at the different stages of reward processing in mathematical form, and allow us to exploit the full richness of data (for example, by capturing how responses change on a trial-by-trial basis during learning). Computational modelling additionally provides insight into processes that are not directly observable (for example, physiological correlates of reward prediction error).

While anhedonia is considered a transdiagnostic symptom (Husain and Roiser 2018) and disrupted reward processing a transdiagnostic research domain (Insel et al. 2010), most studies examined reward processing in case-control designs investigating individual disorders in which anhedonia is present (Halahakoon et al. 2020). Only a minority of studies focused on anhedonia specifically, attempted to measure anhedonia levels, included anhedonic subsamples, or studied anhedonia transdiagnostically (Lambert et al. 2018; Whitton et al. 2021). This chapter examines the evidence from these case-control studies in the context of depression (which form the largest body of literature) and schizophrenia, and highlights the studies which focused specifically on anhedonia.

3 Pleasure

The term anhedonia was classically understood as "inability to experience pleasure", but it is not clear that patients with anhedonia actually have attenuated hedonic responses.

3.1 Self-Report Questionnaires

The most common way to assess hedonic capacity in anhedonic individuals has been to use self-report questionnaires, such as the Snaith-Hamilton Pleasure Scale (Snaith et al. 1995), Temporal Experience of Pleasure Scale (Gard et al. 2006), Chapman's Physical Anhedonia Scale (Chapman et al. 1976), or – the most recently developed – Dimensional Anhedonia Scale (Rizvi et al. 2015). In these questionnaires, patients with depression, schizophrenia and other disorders consistently report diminished experience of pleasure compared to healthy controls (Watson and Naragon-Gainey 2010). However, all these questionnaires ask patients to rate the degree of pleasure experienced from theoretical or imagined rewards. It is therefore difficult to ascertain whether lower scores really indicate a lower ability to experience pleasure, or the fact that the internal value of these imagined rewards is diminished (possibly due to a disruption in valuation processing, as discussed in the following section). Lower scores could also reflect recollection bias or general negative bias in depression, or cognitive impairments (Roiser and Sahakian 2013). The same limitations apply to qualitative studies, in which patients with depression (Watson et al. 2020) and schizophrenia (Gee et al. 2019) have reported lower experience of pleasure.

3.2 Ecological Momentary Assessments

Studies using ecological momentary assessments (EMA), asking people to rate their levels of enjoyment in response to various daily events several times a day, have generally found that depressed patients did not report lower reactivity to positive events, despite having higher scores of anhedonia on self-report questionnaires (Peeters et al. 2003; Bylsma et al. 2011; Thompson et al. 2012). One such study (Wu et al. 2017) did find lower levels of reported pleasure in patients with depression. However, this study assessed the experience of pleasure by asking participants which of the recently-reported activities they had been most looking forward to, and was therefore not necessarily an assessment of momentarily experienced pleasure but instead of recollection of anticipation.

Interestingly, in some EMA studies, patients with depression even reported *greater* brightening of mood following pleasant events than did healthy controls, after accounting for baseline mood (Peeters et al. 2003; Bylsma et al. 2011). This surprising and apparently paradoxical finding might be reconciled by studies finding that mood does not depend on rewarding outcomes per se, but is instead driven by the difference between expected and actual outcomes, in other words the prediction error (Eldar et al. 2016). Notably, in the above-mentioned EMA studies, depressed participants experienced fewer rewarding events. It is possible that they engaged in fewer rewarding activities because they valued them as less rewarding than did healthy controls – suggesting an impairment in valuation rather than hedonic capacity, as discussed below. However, when they did experience rewarding events, the "in-the-moment" experience of reward may have been relatively normal, as suggested by lab-based studies discussed below. Combined with more negative expectations, such preserved "in-the-moment" hedonic responses would correspond to greater prediction errors, resulting in greater improvement in mood than in healthy controls (albeit likely only transitory). If this explanation is correct, an important question is why reward values were not updated following the positive experience (which would suggest differences in some aspect of reward learning). Either way, the findings of these studies point to impairments in other components of reward processing than hedonic capacity.

3.3 Laboratory Assessments

Laboratory assessments of pleasure have yielded similar results to EMA. Specifically, when patients were asked to report the pleasantness of various primary rewards presented to them in laboratory conditions (such as sweet tastes and pleasant odours, which are intrinsically rewarding without requiring learning; Rizvi et al. 2016), most studies found no differences between healthy controls and patients with depression (Amsterdam et al. 1987; Berlin et al. 1998; Swiecicki et al. 2009; Chentsova-Dutton and Hanley 2010; Dichter et al. 2010; Arrondo et al. 2015a) or

schizophrenia (Berlin et al. 1998). Notably, even those studies which specifically examined patients with high levels of self-reported anhedonia (Chentsova-Dutton and Hanley 2010) or melancholic depression (Amsterdam et al. 1987) – who exhibit high levels of anhedonia by definition – did not identify any abnormality. This pattern of results is consistent with the notion that anhedonia, in contrast with its etymology and historical definition, is not associated with diminished ability to experience pleasure per se. Instead, lower levels of enjoyment reported by anhedonic patients on questionnaires may be better explained by disruptions in other components of reward processing.

However, the literature is not entirely consistent and there are some unresolved questions. Findings of no differences in pleasantness ratings are somewhat complicated by the observation that, while depressed patients did not differ from healthy controls in their pleasantness ratings of sweet tastes, they exhibited higher threshold for sweet taste perception (Berlin et al. 1998). This could suggest that while anhedonic patients experience pleasure to a similar degree to healthy individuals overall, they might need to accumulate more evidence to reach the same experience. This would also be consistent with some computational accounts of anhedonia, which have found lower drift rate (i.e., the speed of reaching decision threshold) in depression (Robinson and Chase 2017).

3.4 Physiological Responses

Few studies have attempted to measure hedonic reactions through physiological responses, or facial responses. One such study (Steiner et al. 1993) found that depressed patients responded to sweet tastes with muted and shorter facial expressions compared to controls (interestingly there was no difference for aversive tastes). There is also some evidence of lower physiological responses (such as heart rate changes) during the delivery of pleasurable stimuli in healthy individuals with high levels of self-reported anhedonia (Ferguson and Katkin 1996), but studies in clinically-defined anhedonic groups are lacking.

A parallel line of evidence comes from neuroimaging studies of responses to pleasant stimuli. McCabe et al. (2009) used fMRI to measure hemodynamic responses to pleasant stimuli (both picture and taste of chocolate) in patients with remitted depression. They found that despite giving the same ratings to the pleasant stimuli as healthy controls, the remitted depressed group showed attenuated hemodynamic responses to the stimuli in the ventral striatum, a region linked to reward responsiveness. However, because the stimuli were presented on screen and delivered at the same time, this study design does not allow anticipation and consummation of reward to be assessed separately. It is therefore possible that the blunted responses reflected lower sensitivity to anticipated reward or disruption in some other component of reward processing. In a subsequent study (McCabe 2016), the researchers attempted to disentangle anticipatory and consummatory responses to pleasant stimuli by examining whether the neural responses parametrically varied

with participants' pleasantness ratings, and how much they reported they "wanted to have them". Interestingly, hemodynamic responses in the ventral striatum in remitted depressed patients were parametrically modulated by the ratings of wanting, *not* pleasantness.

In summary, the extant literature does not provide strong evidence for lower hedonic experience or associated physiological responses in clinical anhedonia. However, definitive studies are lacking. Future studies should use designs that can disentangle hedonic responses from other components of reward processing because, as discussed in the next section, there is evidence that these subcomponents associate negatively with anhedonia.

4 Reward Value

If the ability to experience pleasure is really intact in anhedonia, what might account for consistently reported lower levels of experienced pleasure in both self-report questionnaires and qualitative studies? One possible explanation is that the internal value assigned to potentially rewarding activities is decreased. Lower valuation would also lead to lower reward seeking, potentially explaining why anhedonic individuals exhibit lower interest and engage in fewer rewarding activities.

Reward value has been defined as "the subjective desire or preference for some quantity of one resource over another" (Redish et al. 2016), although several approaches to defining and measuring value exist, often with slightly different meanings (O'Doherty 2014). According to the neuroeconomics literature, value of a certain quantity of reward is determined by how much benefit an individual *expects* to derive from it (e.g. because it will elicit pleasure or cover a physiological or social need). This value can be discounted by the expected costs associated with obtaining the reward, the probability that the reward will occur, or length of time until the reward will be obtained (Zald and Treadway 2017). Reward value is a theoretical concept – as a latent construct it is not directly observable – but it can be inferred, either from behavioural (in particular, choices or reaction times) or physiological (in particular, neuroimaging) responses to potential or anticipated reward. Over the past decade an influential method of inferring reward value has been to use computational modelling (discussed in Huys and Browning 2022).

4.1 Behavioural Studies

We can infer how much an individual values a reward based on how frequently they choose one reward over another; the costs they are willing to overcome to obtain it (by measuring e.g. how much physical effort or money they are willing to expend); or with how much vigour and speed they approach the reward. By varying reward magnitudes, we can also assess how sensitive individuals are to increasing rewards.

Several behavioural tasks using such approaches have been developed and used to infer whether and to what extent individuals with depression and schizophrenia value rewards less than control participants. However, only a limited number of these studies have actually focused specifically on individuals with anhedonia, or indeed even included measures of anhedonia (Halahakoon et al. 2020).

Effort Tasks In one group of tasks, such as the Effort Expenditure for Rewards Task (Treadway et al. 2009), which was reverse translated from prior animal studies (Salamone et al. 2016; see Treadway and Salamone 2022), or the Incentive-Force Task (Prévost et al. 2010), participants' valuation of rewards of various magnitudes is inferred from their willingness to engage in physical effort to obtain them. Several studies using such "value-based choice" tasks have found that, compared to healthy controls, people with depression and schizophrenia are less willing to expend greater effort for larger or more probable rewards. While in some studies depressed participants expended less effort overall (Treadway et al. 2012; Hershenberg et al. 2016), in most studies participants with depression (Cléry-Melin et al. 2011; Yang et al. 2014; Zou et al. 2020) and schizophrenia (Barch et al. 2014; Chang et al. 2019; Fervaha et al. 2013; Gold et al. 2013; McCarthy et al. 2016; Treadway et al. 2015; Yang et al. 2021; Zou et al. 2020) did not differ from healthy controls in their overall willingness to expend effort; instead, anhedonic individuals were less willing to expend greater effort when the magnitude or probability of reward were high. Although some studies in depression (Yang et al. 2021) and schizophrenia (Docx et al. 2015) reported divergent results, overall the pattern is remarkably consistent (although this may be due in part to publication bias; Halahakoon et al. 2020).

Importantly, the degree of responsiveness to increasing potential reward was found to correlate negatively with self-reported anhedonia (Sherdell et al. 2012; Yang et al. 2014) or broader negative symptoms (Gold et al. 2013; Barch et al. 2014; Strauss et al. 2016; Moran et al. 2017), even in studies where there was no overall group difference (Sherdell et al. 2012; Strauss et al. 2016). This pattern suggests that lower valuation of increasing rewards is related to anhedonia specifically, rather than depression or schizophrenia per se. However, this interpretation is complicated by the fact that the association with self-reported anhedonia is not a universal observation (Cléry-Melin et al. 2011; Treadway et al. 2012; Fervaha et al. 2013; Hershenberg et al. 2016; Chang et al. 2019). One possibility is that divergent results are due to differences in the questionnaires used to assess anhedonia as some of them may measure a different construct than the effort tasks (Horan et al. 2006). Here, a useful alternative could be the recently developed Positive Valence Systems Scale (Khazanov et al. 2019), which measures the Research Domain Criteria's "positive valence systems" subdomain (Insel et al. 2010) and may relate to differences in effort valuation more closely.

Risk-Taking Tasks Lower ability of rewards to incentivise choices in depression and schizophrenia has also been observed, although less consistently, in risk-taking paradigms, such as the Cambridge Gambling Task (Rogers et al. 1999), in which reward value is indexed by the amount of money or points participants are willing to stake at different odds. Two prospective studies found that, compared to healthy

controls, adolescents with depression failed to increase their stake when the odds of winning were very high (Forbes et al. 2007; Rawal et al. 2013). In other words, as in the effort-based paradigms, they were less incentivised by higher probability of reward. In one study, lower "reward seeking" was correlated with self-reported anhedonia and negatively correlated with the frequency of extracurricular activities (Rawal et al. 2013), and it predicted the onset of new depression after 1 year in both studies (Forbes et al. 2007; Rawal et al. 2013). However, a very large prospective study in adolescents, using the Cambridge Gambling Task, did not find strong evidence for lower reward seeking in depression (the association did not survive adjustment for gender), either cross-sectionally nor longitudinally (Lewis et al. 2021). Importantly, this study included a nationally representative sample, longer follow-up period and adjusted for a number of potential confounders, increasing confidence in this negative finding. Other studies using this task, performed in elderly patients with depression (Clark et al. 2011; Dombrovski et al. 2012) and adolescents with schizophrenia (MacKenzie et al. 2017) also failed to find any association. These inconsistencies may have arisen because the Cambridge Gambling Task conflates reward seeking with risk taking, which may not be altered in depression, and punishment avoidance, which is heightened in depression (Eshel and Roiser 2010), potentially masking associations. As such risk-taking paradigms may not be specific measures of reward valuation, and because of equivocal findings yielded by them, their interpretation remains tentative. Notably, though, when differences have been detected, the pattern of results has largely agreed with the findings from effort-based paradigms.

Reward Bias Tasks The above findings are complemented by evidence from tasks that assess the ability to develop "reward response bias", which have shown that patients with depression exhibit lower responsiveness to reward even when information is not explicitly provided. In these tasks, such as the Probabilistic Reward Task (Pizzagalli et al. 2005) and its adaptations (Aylward et al. 2020), correct responses to one stimulus are rewarded more frequently than correct responses to the other. When uncertain about which stimulus has been presented, healthy participants are more likely to respond as if the more frequently rewarded stimulus has been presented, termed the reward response bias. In several studies, individuals with depression have been found to be less likely to develop reward bias than control participants (Henriques and Davidson 2000; Pizzagalli et al. 2005, 2008; Vrieze et al. 2013; Aylward et al. 2020), suggesting that they are less sensitive to implicit reward information. Computational support for this interpretation was provided by a meta-analysis by Huys et al. (2013) (discussed in detail below). Some studies reported that lower reward response bias was associated with high levels of anhedonia or was specific to the melancholic subtype of MDD (Fletcher et al. 2015), and predicted poor antidepressant response (Vrieze et al. 2013). In a larger sample, Lawlor et al. (2020) did not find evidence of a lower reward bias in depression, but a subsequent meta-analysis by Halahakoon et al. (2020) nonetheless concluded that lower reward bias in depression is a consistent finding; moreover, its effect size was the largest of the reward processing impairments assessed in the meta-analysis.

Interestingly, using computational analysis, Lawlor et al. (2020) showed that even in the absence of lower reward bias, participants with depression were slower to accumulate the evidence required to make decisions. This result does not necessarily contradict the notion of lower reward sensitivity in depression, but indicates that the mechanisms behind it may be more nuanced.

In contrast to depression, patients with schizophrenia have not been found to show lower reward response bias (Heerey et al. 2008; Barch et al. 2017). This could mean that reward valuation in schizophrenia might be impaired only when information about possible options is explicitly provided and requires conscious evaluation, while decision making based on implicit reward information is intact. Several authors (Culbreth et al. 2018; Strauss et al. 2014) proposed that apparent lower reward valuation in schizophrenia may therefore be due to impairments in executive function – well established in schizophrenia – specifically the ability to integrate and maintain reward value representations (see also Moran et al. 2022). Such findings demonstrate that lower reward valuation may arise by different mechanisms in different patients across disorders (as discussed in the final section).

Response Vigour Tasks Another possible method to index reward value is to examine the vigour individuals are willing to expend, as opposed to choices (as assessed in the studies discussed above). However, there is little evidence that reward-related vigour is impaired in depression (Halahakoon et al. 2020), despite symptoms such as psychomotor slowing and fatigue.

Summary Although not all studies agree, there appears to be reasonably consistent evidence from a range of different behavioural paradigms that individuals with depression and schizophrenia value rewards less than healthy controls. In particular, stimuli associated with high probabilities and magnitudes of reward appear to incentivise their behaviour less. In depression, this has been confirmed and quantified by a recent meta-analysis of studies investigating behavioural differences in reward processing between individuals with depression and healthy controls (Halahakoon et al. 2020). However, the precise cognitive mechanisms underlying lower reward valuation in depression and schizophrenia remain to be elucidated, and it remains unclear whether this is specific to anhedonia or relates to other symptoms present in depression and schizophrenia.

4.2 Neuroimaging Studies

Complementing behavioural tasks, differences in reward valuation can be studied by measuring neural responses elicited by stimuli associated with reward. The most commonly used neuroimaging paradigm is the Monetary Incentive Delay task (Knutson and Heinz 2015), which requires quick responses to cues in order to obtain associated rewards (typically monetary). Responses are required after a delay, which allows the separation of neural responses to anticipation and consummation. As summarised by several meta-analyses, mostly non-overlapping, numerous studies

have found that individuals with depression (Zhang et al. 2016; Keren et al. 2018; Ng et al. 2019), schizophrenia (Leroy et al. 2020) and sometimes specifically with anhedonia (Arrondo et al. 2015b), exhibited lower hemodynamic responses during reward anticipation than did controls, particularly in the striatum, a region known to play a causal role in reward processing from animal experiments (Berridge et al. 2009). Most convincingly, this pattern was observed in a large longitudinal study in adolescents, where lower ventral striatum response during reward anticipation predicted anhedonia (but not low mood without anhedonia) in previously healthy adolescents 2 years later (Stringaris et al. 2015), in addition to cross-sectional associations.

While such findings are consistent with the hypothesis that anhedonia is driven by lower reward valuation, their interpretation is not entirely straightforward. First, lower responses were not always specific to reward anticipation or a single region within striatum: they were equally often (and sometimes only) observed following reward delivery and in both ventral and dorsal striatum, as well as other brain regions (Borsini et al. 2020). This pattern makes it difficult to ascertain whether they relate to reward valuation specifically or reflect a general alteration in reward processing. Second, because they used tasks not designed to capture behavioural differences, they were often not accompanied by differences in behaviour (here, the invigoration of responding with greater potential reward; Halahakoon et al. 2020; Nielson et al. 2021). This makes it difficult to interpret whether lower neural responses indicate impairment, compensation or relate to some group difference unrelated to reward processing (Robinson et al. 2013). Interestingly, in one study, striatal responses to reward correlated with EMA of positive affect immediately prior to scanning (Forbes 2009). Third, as hemodynamic responses in striatum were often not specific to reward processing (Dombrovski et al. 2015), interpreting them as such may be a fallacious reverse inference (Poldrack 2006). Finally, as the tasks typically used in these studies did not require making any decisions (although there are exceptions; Huang et al. 2016), it is difficult to relate the neuroimaging findings to the behavioural literature where most differences were observed in decision making.

Despite the aforementioned limitations and inconsistencies, the behavioural and neuroimaging literatures largely agree and are consistent with lower reward valuation in anhedonia, at least when assessed within the context of depression and schizophrenia.

5 Learning and Reward Prediction Error

One possible explanation for why rewards are valued less in anhedonia could be that individuals are less able to learn about them. According to reinforcement learning theory (see Kangas et al. 2022), reward value is not static but can be updated following experience, using the difference between obtained and predicted reward, termed the reward prediction error. There is strong evidence that prediction errors drive reward learning, are represented in several brain regions (including the ventral

striatum) and correspond to dopamine release in the ventral striatum (Bayer and Glimcher 2005; Steinberg et al. 2013). It has been proposed that dysfunction in the way that reward prediction errors are computed or signalled in the brain could be one mechanism driving anhedonia. Being less able to compute or utilise prediction errors would lead to weaker internal representations of reward values, which might then manifest as lower interest in engaging in rewarding activities as well as lower anticipated pleasure.

Like reward value, reward prediction error is a latent construct that cannot be directly observed. However, parameters governing the influence of prediction errors can be estimated, by using computational models; and using the same models, physiological responses corresponding to modelled reward prediction errors can be measured.

5.1 Neuroimaging Studies

Findings from neuroimaging studies using such an approach to examine reward prediction errors and anhedonia are inconsistent. While some studies reported lower reward prediction error signals in the ventral striatum in patients with depression and schizophrenia (Murray et al. 2008; Gradin et al. 2011; Ermakova et al. 2018; Kumar et al. 2018; Katthagen et al. 2020), other studies reported discrepant results (Culbreth et al. 2016; Rutledge et al. 2017). Problematically, the responses corresponding to reward prediction errors are typically not specific to a single region but distributed across prefrontal cortex, insula, hippocampus and striatum, and sometimes accompanied by differences in behaviour (in some studies, clinical participants exhibited lower exploration, slower reaction times, slower learning, worse choice accuracy or worse overall task performance), which complicates the interpretation of differences observed (Strauss et al. 2014). Overall, the idea that anhedonia is driven by attenuated reward prediction error signals is not convincingly supported by neuroimaging findings.

5.2 Behavioural Studies

The evidence from behavioural studies is also mixed. By computationally analysing behavioural data from a reinforcement learning task, Chase et al. (2010) found that the learning rate, a parameter governing the extent to which prediction errors update value, negatively correlated with anhedonia in depressed participants, suggesting anhedonia is associated with impaired reward learning. A similar result in participants with depression was reported by Brown et al. (2021) who additionally found that the lower learning rate observed in depressed participants was normalised following successful cognitive-behavioural therapy. These findings are consistent with several other studies in which depression, including anhedonic depression, was

associated with slower learning from rewarding outcomes (Must et al. 2006; Thoma et al. 2015; Kumar et al. 2018). However, discrepant findings have also been reported (Gradin et al. 2011; Rothkirch et al. 2017), and a meta-analysis of case-control studies of reinforcement learning in depression (Halahakoon et al. 2020) only identified a relatively modest effect size.

Problematically, in many of the tasks which are commonly used to measure reward learning, such as the Iowa Gambling Task (Bechara et al. 1994), it is difficult to separate reward learning and reward valuation. Given the consistent findings of impaired reward valuation in anhedonia, presented above, it is possible that what is ostensibly "learning" on these tasks could be driven by problems with valuation (making the subjective value of options more similar to one another).

Several studies which used computational approaches to analyse behavioural data from various reinforcement learning tasks provided support for this idea. By reanalysing behavioural data from the Probabilistic Reward Task (Pizzagalli et al. 2005), Huys et al. (2013) tested whether individuals with depression were less likely to develop a response bias because they value rewards less, or because they are less able to learn about reward. Using computational models with separate parameters for reward sensitivity (in this model represented by the inverse temperature parameter, which influences the steepness of the softmax choice function – see Huys and Browning 2022 for a detailed explanation) and learning rate, the authors showed that anhedonia is specifically associated with lower inverse temperature, rather than lower learning rates, compared to healthy controls. Interestingly, a dopamine agonist drug, pramipexole, increased the development of reward bias by enhancing learning but *not* reward value, calling into question whether it would be an effective intervention to improve reward valuation and thereby anhedonia.

Similar conclusions came from a study by Gold et al. (2012) in schizophrenia, which analysed a different probabilistic choice task using computational modelling to understand the decisions of patients with schizophrenia following an initial learning phase. Participants with schizophrenia who had severe avolition (another negative symptom, related to anhedonia) did not seem to prefer stimuli that frequently yielded rewards over those associated with frequently avoiding losses (both of which outcomes would elicit positive prediction errors), suggesting an impairment in the representation of value. However, prediction error processing per se was apparently intact, as this group did prefer stimuli associated with frequent gains over those which yielded frequent losses.

Consistent with these findings, in an EEG study using a probabilistic learning task Cavanagh et al. (2019) reported that depression was associated with smaller reward positivity (an event-related potential elicited by rewards) and delta-band response, but this did not affect reward prediction error signals or lead to impaired reward learning; therefore the authors suggest that this may instead reflect lower reward valuation in depression.

Taken together, the evidence from the studies discussed in this section suggests that learning from rewarding outcomes is probably intact in anhedonia and that the impairments observed in anhedonic individuals may be, at least in part, explained by impairments in the representation of value.

6 Directions for Future Research

As discussed in the preceding sections, a growing body of literature has linked anhedonia to impaired reward processing, in particular decision making based on reward value. However, there are inconsistencies across behavioural paradigms, neuroimaging findings and samples, which in some cases lack satisfying explanations, suggesting that our understanding of the mechanisms underlying the observed differences may be incomplete. This section outlines the key open questions and approaches which may help resolve them.

6.1 Characterising Reward Processing Alterations Using Suitable Paradigms and Computational Approaches

A key challenge for the field to move forward is to explain why anhedonic individuals value rewards less. They could be less sensitive to information about reward magnitude; they could perceive costs required to obtain rewards to be higher or discount reward values more dramatically; they could discount uncertain or delayed rewards more; they could perform integration of this information in a suboptimal way etc. Often, the paradigms used to study reward processing do not allow these processes to be easily dissociated, but it is important to do so, because different processes may suggest different causal pathways and treatment targets (Prévost et al. 2010; Husain and Roiser 2018).

A promising way to gain deeper insight into these issues is to computationally model the reward-related behaviour being studied, which allows a more fine-grained analysis of the behavioural responses recorded, as well as insights into processes which are not directly observable using traditional analyses. The usefulness of computational approaches for dissociating component processes of reward processing is exemplified by the studies by Huys et al. (2013) and Gold et al. (2012) (discussed above), which suggested that impairments on reinforcement learning tasks may be driven by impairments in reward valuation and not learning.

Computational approaches have several other advantages which may help elucidate the mechanisms underlying altered reward processing more precisely (see Huys and Browning 2022). One notable advantage is that they can link behavioural and neuroimaging findings and help us understand what neuroimaging differences mean. Using this approach, Rutledge et al. (2017) showed that striatal hypoactivation in depression is unrelated to reward prediction error. Combining value-based choice tasks with computational modelling and neuroimaging may be a particularly fruitful endeavour (Forbes et al. 2020; Rupprechter et al. 2021).

6.2 Understanding Heterogeneity Across Disorders Using Transdiagnostic Assessments

Our understanding of altered reward processing as a mechanism of anhedonia is limited by the fact that most studies examine it within the context of diagnostic categories such as depression or schizophrenia, without focusing on specifically anhedonic individuals – many studies do not even assess anhedonia levels (Halahakoon et al. 2020). The assumption is that because anhedonia is a prominent diagnostic symptom of these disorders, the studied participants will be sufficiently anhedonic. However, the inherent heterogeneity of the diagnostic categories – some participants with the diagnosis of depression or schizophrenia may have no anhedonia at all – may mask important associations and lead to inconsistencies between studies (Müller et al. 2017). Future studies of reward processing impairments should focus on anhedonic individuals specifically, measure the presence, type and level of anhedonia using well-validated tools, and examine reward processing impairments as functions of these measures in addition to case-control comparisons.

Given the presence of anhedonia across disorders, transdiagnostic studies may be informative. Several recent studies comparing reward processing in different disorders (Culbreth et al. 2018; Lambert et al. 2018; Whitton et al. 2015; Yang et al. 2021) have yielded insights into the commonalities and differences in reward processing in different disorders. For example, it has been suggested that, in depression, lower willingness to expend effort for higher reward magnitudes may relate to lower reward sensitivity, whereas in schizophrenia it may be due to impaired ability to integrate and maintain reward value representations (Culbreth et al. 2018). In addition to such broad comparisons between disorders, it would be informative to examine whether there are dissociable patterns of reward processing impairments in anhedonic individuals irrespective of diagnostic classification. Computational approaches have been increasingly used to this end (Marquand et al. 2016; Husain and Roiser 2018).

6.3 Improving the Validity and Reliability of Reward Processing Measures

As studying the components of reward processing relies either on self-report or requires inference from behavioural or physiological responses, it is important to make sure that these tools are psychometrically valid and reliable (Mkrtchian et al. 2021b). Most of the behavioural paradigms used to assess reward processing are yet to be psychometrically validated or have varying test-retest reliability (Reddy et al. 2015). Furthermore, they have typically been developed to capture within-individual effects but often perform less well in assessing individual differences, which is a problem that applies also to the computational analysis of reward-processing behaviour (Eckstein et al. 2021).

Another issue is that the behavioural paradigms used to assess reward processing typically rely on monetary rewards (Halahakoon et al. 2020). However, monetary rewards may not necessarily be valued equivalently across participants with different socioeconomic backgrounds, and there are well-known relationships between socioeconomic status and incidence of psychopathology (Kessler et al. 1997). Studies using other types of reward, including social or primary rewards, would be informative. Researchers using monetary rewards should assess income levels and take this into account when performing analysis.

Self-report questionnaires have their own set of limitations. As mentioned above, they rely on conscious evaluation of hypothetical scenarios and are thus potentially affected by working memory impairments or a variety of different biases (such as recollection bias, anchoring effects and demand characteristics). These problems may explain why they are often not found to correlate well with behavioural and neuroimaging measures, or even with EMA (Gold and Strauss 2012; Moran et al. 2017). Future studies should nonetheless always include them and examine their associations with the observed findings, as self-reported questionnaires still capture important aspects of the subjective experience of anhedonia. However, researchers should take advantage of recent and well-validated questionnaires (see Wang et al. 2022), and these could be usefully complemented by EMA as well as assessments of psychosocial functioning.

6.4 Addressing Causality with Longitudinal and Intervention Studies

Nearly all work on reward processing and anhedonia has been cross-sectional (Halahakoon et al. 2020; Nielson et al. 2021). More longitudinal studies would help ascertain whether the association between disruptions in reward processing and anhedonia is casual and could therefore be used as a risk marker and target for intervention, including prevention. The existing longitudinal studies support the notion that disrupted reward processing is a causal factor in the development of anhedonia, but do not provide a completely consistent picture (Forbes et al. 2007; Lewis et al. 2021; Rawal et al. 2013; Stringaris et al. 2015).

Evidence of causality could also come from intervention studies, for example assessing whether direct manipulation of the reward system, e.g., pharmacologically or with deep-brain stimulation, alters reward processing and consequently improves anhedonia. There have been only a few intervention studies which focused specifically on the reward system and anhedonia, but the results to date are promising. For example, deep-brain stimulation of the ventral striatum normalised its responses to reward and improved depression symptoms in one study (Bewernick et al. 2012). Similarly, ketamine was found to specifically improve anhedonia over-and-above general depressive symptoms, and the level of improvement was specifically

correlated with increased in striatal metabolism (Lally et al. 2014) and normalisation of fronto-striatal connectivity (Mkrtchian et al. 2021a).

7 Conclusion

This chapter has presented evidence that depression is associated with disrupted reward processing. In contrast to the historical definition of anhedonia, there is surprisingly limited evidence for impairment in the ability to experience pleasure. However, this is largely based on self-reports of pleasure in response to various pleasurable stimuli; definitive studies measuring neurophysiological responses to pleasure are lacking, particularly studies with designs that can disentangle hedonic responses from other processes such as anticipation. There is some evidence that learning about reward, and reward prediction error signals, are impaired in depression, but the literature is inconsistent. The strongest evidence is for an impairment in how reward value is represented and used to guide choices. Several computational accounts of these processes have also been proposed, which may facilitate our understanding of the specific cognitive mechanisms that underlie anhedonia. Future studies would benefit from focusing on impairments in reward processing specifically in anhedonic samples, including transdiagnostically, and from using designs separating different components of reward processing, formulating them in computational terms, and moving beyond cross-sectional designs to provide an assessment of causality.

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Anticipation: An Essential Feature of Anhedonia

Anthony G. Phillips and Soyon Ahn

Contents

Abstract The following essay addresses the evolution of the term "anhedonia" as a key construct in biological psychiatry, especially as it pertains to positive emotional and motivational states central to mental health and well-being. In its strictest definition, anhedonia was intended to convey an inability to experience "pleasure" derived from ingestion of sweet tastes or the experience of pleasant odors and tactile sensations, among a host of positive sensations. However, this definition has proved to be too restrictive to capture the complexity of key psychological factors linked to major depression, schizophrenia, and substance use disorders it was originally intended to address. Despite the appeal of the elegant simplicity of the term anhedonia, its limitations soon became apparent when used to explain psychological constructs including aspects of learning, memory, and incentive motivation that are major determinants of success in securing the necessities of life. Accordingly, the definition of anhedonia has morphed into a much broader term that includes key roles in the disturbance of motivation in the form of anergia, impaired incentive motivation, along with deficits in associative learning and key aspects of memory, on which the ability to predict the consequences of one's actions are based. Here we argue that it is this latter capacity, namely predicting the likely consequences of

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Curr Topics Behav Neurosci (2022) 58: 305–324
https://doi.org/10.1007/7854_2022_317
Published Online: 19 April 2022

motivated behavior, which can be termed "anticipation," that is especially important in the key deficits implied by the general term anhedonia in the context of neuropsychiatric conditions.

Keywords Amygdala · Dopamine · Dorsal striatum · Incentive motivation · Positive and negative contrast effects · Prefrontal cortex · Preparatory and consummatory behaviors · RDOC · Ventral striatum

1 Dopamine and Anhedonia

The origin of the dopaminergic hypothesis of anhedonia can be traced to a seminal article in *Science* by Wise and colleagues entitled "*Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food"* (Wise et al. 1978), that proposed the bold conjecture that the disruptive effects of neuroleptic drugs, which act as dopamine (DA) receptor antagonists, on operant responding for food reflected a "reward" deficit. It was explicitly assumed that the loss of positive reinforcing properties arose because of an inability to experience the hedonic properties of food and by implication, other biologically significant stimuli (Wise 1982, 1985). The use of operant responding procedures to build a case for DA and anhedonia was fortuitous, because it provided a simple means to refute the initial version of this hypothesis. Support for the conclusion that DA systems in the brain mediate the rewarding (reinforcing) properties of incentive stimuli such as food was based solely on the resemblance of the pattern of operant behavior observed following treatment with DA receptor antagonists to an extinction curve induced by removal of food reward. This in turn gave rise to the assumption that neuroleptic drugs disrupt operant responding solely by disrupting hedonic properties of primary rewards, thereby creating a state of anhedonia.

Following the lead of Salamone (1987), several groups including the Phillips' lab mounted vigorous arguments against this so-called anhedonia hypothesis of DA function. In one series of experiments, we trained rats to lever-press for either brain-stimulation reward or food on a variable interval schedule (VI-60 s or VI-4 min) (Phillips and Fibiger 1979). Subsequently, these rats experienced extinction with or without treatment with the DA antagonist haloperidol. Following the logic of the anhedonia hypothesis, DA receptor blockade should not reduce responding further during extinction as no hedonic properties of food reward were present. However, the rate of responding was greatly reduced when haloperidol and extinction were combined, relative to extinction alone. In addition, a second major assumption of the anhedonia hypothesis posited that reduced operant behavior should only be observed *after* an animal had experienced degraded reward effects. However, when we tested rats on a VI-4 min schedule of food reinforcement, which ensured extended bouts of operant responding prior to receiving the first reinforcement, treatment with the DA antagonist haloperidol caused a significant suppression in lever presses relative to

the extinction plus vehicle control. These data along with similar findings by Tombaugh and colleagues (1979, 1980, see also Peciña 1997) indicated that the effects of neuroleptics on operant behavior cannot be accounted for solely in terms of a unitary process, such as impaired perception of the positive hedonic properties of food and other natural rewards.

2 Dopamine and Preparatory Behaviors as Distinct from Consummatory Behaviors

Ethological approaches to parsing motivated behavior into individual components draw on important distinctions between preparatory and consummatory behaviors (Craig 1918; Woodworth 1918; Konorski 1967). In the context of feeding, consummatory behaviors constitute events occurring after contact with food, in turn giving rise to biting, chewing, and swallowing. The term ingestive behavior is also used interchangeably with consummatory responses. Preparatory behaviors, also called appetitive acts, include the many motor responses that enable an organism to obtain access to food and other biologically significant stimuli such as water, sexual partners, warmth, and safety. A careful examination of the extensive literature concerning the neurochemical correlates of these separate aspects of motivated behaviors indicates that DA systems are preferentially involved in preparatory/appetitive stages of reward seeking, not in the consummatory behaviors per se (Blackburn et al. 1992). Notable examples include the disruption of hoarding behavior by the DA receptor antagonist pimozide (Blundell et al. 1977) and its abolition by lesions of DA soma in the ventral tegmental area (VTA). Importantly, similar lesions of the VTA do not affect food or water intake significantly (Fibiger et al. 1974; Heffner and Seiden 1983). Autoshaped behavior is another form of preparatory responding (Woodruff and Williams 1976) that is attenuated by both pimozide and haloperidol (Beninger et al. 1981). Furthermore, as noted above, instrumental responding for food reward clearly falls into the category of preparatory/appetitive behavior and is attenuated by low or moderate doses of pimozide (Tombaugh et al. 1979; Wise and Schwartz 1981), as well as lesions of the mesocorticolimbic DA system. In light of this important distinction between preparatory/appetitive as distinct from consummatory phases of reward-seeking behavior, our group undertook a series of three different studies to gain further insights into the role of DA in these different aspects of motivated behavior. To reiterate, these objective measures draw a sharp distinction between events related to incentive motivation and hedonic sensory experience arising from contact with biologically significant stimuli (i.e., positive reinforcers/rewards). Later versions of the anhedonia hypothesis are adapted to reflect these new insights (Wise 1982, 1985).

The advent of in vivo brain microdialysis, coupled with the use of high pressure liquid chromatography with electrochemical detection for precise analysis of DA and its metabolites, revealed significant increases in DA efflux in the nucleus

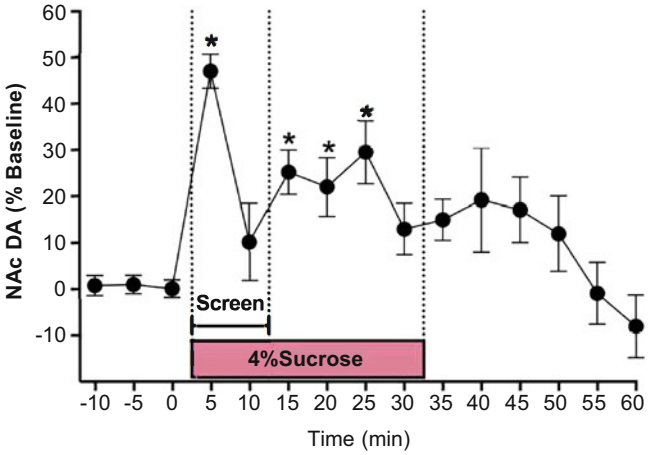

Fig. 1 A significant increase in dopamine efflux in the nucleus accumbens is elicited by anticipation of access to a sucrose solution and is maintained by subsequent consumption. *Dashed lines* highlight the initial preparatory phase in which sucrose was presented behind a perforated screen (Samples 4 and 5) and the consummatory phase, when rats were given access to the sucrose following removal of the screen (Samples 6–9). * Indicates significant difference from baseline ($p < 0.05$). Redrawn from Vacca et al. (2007)

accumbens (NAc) during lever-pressing for food and consumption of food pellets or sweet liquids (Hajnal and Norgren 2001; Hernandez and Hoebel 1988). The finding that consumption of high-palatability as compared to low-palatability foods elicited greater efflux of DA in the NAc (Hajnal et al. 2004; Norgren et al. 2006; Smith 2004) may appear to reflect the hedonic properties of these reward stimuli; but this simple assumption fails to consider the contribution of other factors such as those related to incentive motivation. Data from the Phillips lab (Fig. 1), utilizing a simple protocol which separated an initial period of reward anticipation from the subsequent consumption of a sucrose solution, show a significant increase in DA efflux in the NAc during a 10-min period, *prior to the ingestion* of a palatable sucrose solution (Vacca et al. 2007). Some influential animal models of depression place great emphasis on a reduction in sucrose preference as evidence of anhedonia induced by various stress protocols including chronic mild stress (Willner et al. 1992). However, a recent study by Salamone and colleagues (Pardo et al. 2015) shows that sucrose preference is insensitive to reductions in DA signaling, a finding that further questions the putative relationship between DA transmission and "anhedonia".

As a direct test of the hypothesis that DA plays an especially important role in preparatory responses, we examined the effects of DA receptor blockade or vehicle treatment on behavioral responses to food-related conditional stimuli encountered prior to presentation of food, thereby signaling delivery of food. If these disruptions of DA function had a significant effect on the preparatory responses of lever-pressing for a subsequent food reward, prior to ingestion of the food pellet, again this would refute the assumption that impaired DA function degrades the value of food reward

by creating a state of anhedonia. We adopted Weingarten's (1984) "conditioned feeding" paradigm where food was provided only during several daily pairings of the discriminative stimulus with a discrete meal. Presentation of this cue elicited bouts of preparatory responses. Conditioned preparatory responses to a conditioned stimulus (CS+) signaling delivery of a meal were attenuated in rats by the DA receptor antagonist pimozide (Blackburn et al. 1987). In contrast, these animals displayed normal consummatory behaviors following the delivery of food. Similarly, in a separate experiment, the 20-min free-feeding intake of liquid diet by rats that had been deprived of food for 23 h was unaffected by doses of pimozide as high as 0.6 mg/kg. Once more, these findings were consistent with the involvement of DA in the production of preparatory behaviors elicited by incentive stimuli.

In a related study, changes in the activity of DA systems in relation to preparatory and consummatory feeding responses were investigated in rats conditioned by presenting a CS+ with food delivery, the unconditioned stimulus (US) (Blackburn et al. 1989). When sacrificed after exposure to the CS+ alone on a test trial, the ratio of the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) to DA (DOPAC/DA ratio) was increased significantly in the NAc. Smaller increases were observed in the dorsal striatum, but these were not statistically significant. In contrast, no increases were observed in the DOPAC/DA ratio in either brain region following consumption of meal for 7 min. These findings confirm again that activation of DA release in the NAc is associated with anticipation of a meal, when the rat is engaged in preparatory feeding behaviors. In contrast, this study did not find evidence for similar activation of DA release during of short bouts of consummately feeding behavior.

Migler (1975) conducted similar experiments with monkeys and found results in accord with the involvement of DA in preparatory behavior. A panel-tone stimulus combination served as a CS+, signaling the delivery of a food pellet. Monkeys typically took the pellet in the first few seconds of panel illumination while undrugged, but when drugged with the DA receptor antagonist chlorpromazine they often delayed responding until after the panel was no longer illuminated. Clody and Carlton obtained comparable results with rats (Clody and Carlton 1980).

Salamone and colleagues (1994) propose that dopaminergic activity in the NAc is related to behavioral activation, exertion of effort, and possibly cost–benefit analyses relating effort to value of reward stimuli (Salamone et al. 2003, 2005). Remarkably, consumption of large quantities of food was not accompanied by increased DA efflux, which stands in contrast from the perspective of the anhedonia hypothesis. Salamone et al. also observed a significant relationship between response rates of individual rats and the magnitude of DA efflux in the NAc (Salamone et al. 1994). It must be noted in passing that consumption to satiety of a large meal of a palatable food such as fruit loops, onion rings (Ahn and Phillips 1999) or sucrose (Hajnal and Norgren 2002) is accompanied by a significant increase in DA efflux in both the NAc and medial prefrontal cortex.

3 Emergence of Anticipation as a Key Construct in the Anhedonia Story

By the turn of the current century, a consensus had emerged around the concept of incentive motivation and its primary role in the initiation and subsequent vigor of approach behaviors (aka preparatory/appetitive responses discussed above) required to secure the various goal objects necessary for both survival and daily quality of life (Berridge and Robinson 1998, 2003; Berridge 2001). Closely linked to this conjecture was the hypothesis that the mesocorticolimbic DA innervation of forebrain structures, in particular the prefrontal cortex and NAc, played a key role in incentive motivation (Berridge and Robinson 1998; Fibiger and Phillips 1986; Robbins et al. 1989; Ikemoto and Panksepp 1999; Redgrave et al. 1999; Mogenson and Phillips 1976). Consistent with the importance of CS+ in the initiation of approach behavior, visual and olfactory stimuli associated with natural rewards such as food or sexually receptive conspecifics were shown to evoke significant increases in DA efflux in the NAc prior to changes observed during consummatory behavior (Ahn and Phillips 1999; Fiorino et al. 1997; Ahn and Phillips 2002). Depletion or antagonism of DA function in the NAc eliminated or diminished Pavlovian CSs effects on instrumental responding (i.e., Pavlovian to instrumental transfer (Cardinal et al. 2002; Parkinson et al. 2002)) and additionally, shifted response choice away from those requiring greater effort relative to food reward (Salamone et al. 1994, 2003).

A rapprochement between more cognition-based motivational hypotheses, as distinct from those based on reinforcement learning theory, in the context of explaining goal-directed behaviors was provided by Dickenson's insight that performance of an instrumental task is controlled by two distinct processes. In an elegant series of experiments, Dickinson and colleagues (1995) demonstrated that an animal's performance during the initial phase of learning is based on an "action-outcome" expectancy (aka anticipation), by which an organism gains knowledge that an instrumental action will lead to a specific biologically significant outcome. With this unique insight, Dickenson provided an empirical definition of anticipation. After repeated experience of confirmed outcome expectancies, a second process gains prominence when response-control gradually shifts to a habit-based process. Of critical importance was the further insight that instrumental performance is only sensitive to manipulations that degrade the incentive value of the outcome, during the initial action-outcome stage. These observations highlighted the remarkable ability of rats to obtain information linking current incentive value to an action-outcome contingency and in the process gain the ability to anticipate the probable consequence of their preparatory/appetitive behaviors. This outcome devaluation and Pavlovian-to-instrumental transfer protocol, also provided further insights into the neural mechanisms subserving action-outcome control of instrumental behavior, as exemplified by the effect of lesions to the basolateral amygdala causing impairment in the capacity of rats to encode the relation between a specific action and the value of an outcome (Corbit and Balleine 2005).

In the context of this essay, the question arises as to whether DA activity in the NAc region is related to action-outcome or habit-based based stages of instrumental responding. Although neither the core nor shell region of the NAc has been implicated in action-outcome associations (Balleine and Killcross 1994; Corbit et al. 2001; De Borchgrave et al. 2002; Kelley et al. 1997), deficits in the acquisition of instrumental responding have been reported following blockade of the NMDA class of glutamate receptors in the NAc core (Yin et al. 2004). Using mice, with a knockdown of the DA transporter and chronically elevated levels of DA, Yin et al. examined DA function during early action-outcome as distinct from later habit-based stages of instrumental responding and failed to observe deficits early in training when instrumental responding was still sensitive to tests of outcome devaluation (Yin et al. 2006). Notably, rats with bilateral 6-OHDA lesions of the nigrostriatal DA system remained sensitive to reward devaluation despite extensive training sessions (Faure 2005). Accordingly, the nigrostriatal DA system, and more specifically, its innervation of the dorsal striatum may play a critical role in the transition from an action-outcome stage to a habit-based stage of instrumental conditioning.

Intrigued by Dickenson and Balleine's important insights, we sought further information about the possibility of dynamic changes in DA transmission at these different stages of instrumental behavior (Ahn and Phillips 2007). Brain microdialysis experiments with probes located in the NAc or mediodorsal (MD) striatum were performed early (5th day) when outcome-expectancy is evident and at a later habit-based stage of instrumental learning (16th day). Importantly this protocol had previously been used to confirm that 120 (but not 360) reinforced responses were sensitive to outcome devaluation and therefore represented an action-outcome stage of instrumental learning (Dickinson et al. 1995). Given the finding that NAc lesions completely abolished Pavlovian to instrumental transfer, consistent with DA function in a conditioned appetitive state, we hypothesized that DA efflux in the NAc may be comparable during both early action-outcome and later habit-based stages of instrumental responding. DA levels in the MD striatum were also measured as a control for generalized activity and we predicted that no significant changes in DA efflux would be associated with instrumental responding. This study also included a "within-trial" extinction condition to confirm the hypothesis that presentation of a Pavlovian CS+ paired previously with food pellets would accompany increased DA efflux in the NAc but not MD striatum. DA efflux in the NAc was increased significantly during both early and later training stages (Day 5 and 16, respectively) of an instrumental response for food on an RI 30-s schedule of reinforcement (Fig. 2) confirming previous reports of increased DA release in the NAc during fixed interval or ratio schedules of food reinforcement (Salamone et al. 1994; Richardson and Gratton 1996; Cousins et al. 1999).

As noted above, responses emitted during the early phase of training on interval schedules have been characterized as goal- or outcome-directed (Dickinson et al. 1995; Adams and Dickinson 1981; Balleine and Dickinson 1992). Contrary to our main hypothesis that dopaminergic activity in the NAc would be increased

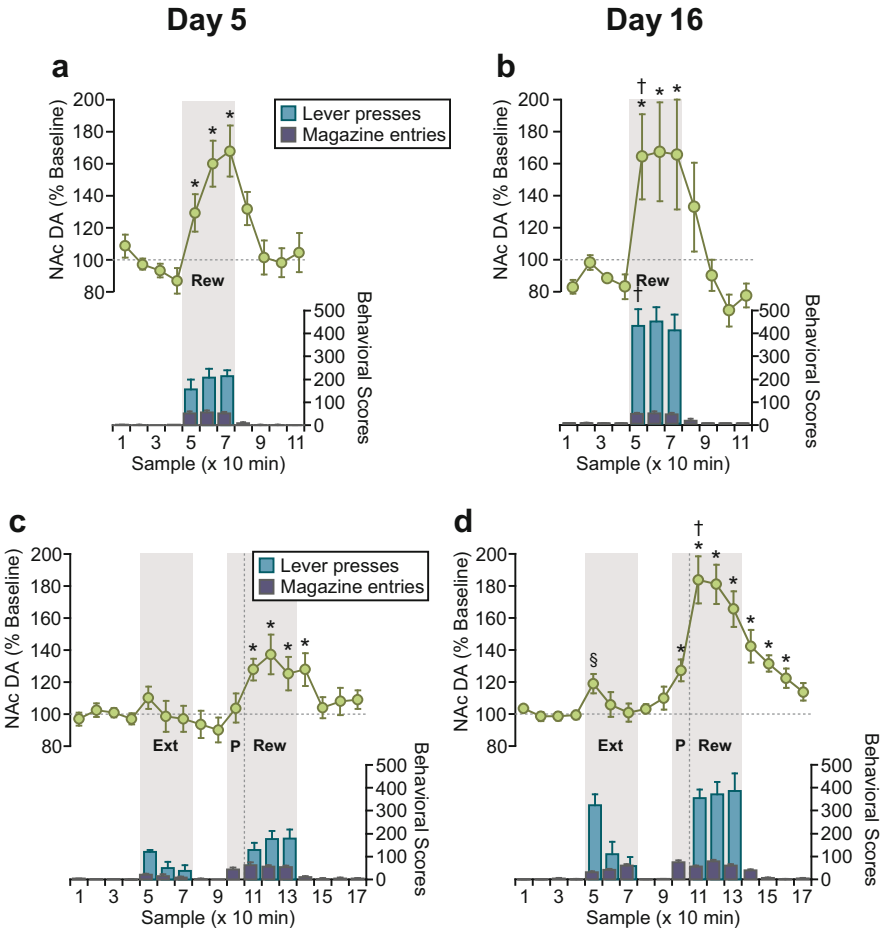

Fig. 2 DA efflux in the NAc in relation to the outcome-expectancy (**a**, **c**, *Day 5*) and habit-based (**b**, **d**, *Day 16*) phases of instrumental responding for food reward. In the reward (*Rew*) phase, food pellets and an auditory conditioned stimulus (CS+) were delivered on a random interval (RI) 30-s schedule. In the extinction (*Ext*) phase, the CS+ was activated on an RI 30-s schedule in the absence of pellets. Five pellets delivered noncontingently served to signal the availability of pellets and prime (*P*) responding. *,§ Indicate significant differences from baseline value (*Sample 4*) ($p < 0.05$). † Indicates significant difference from the corresponding data point on *Day 5* ($p < 0.05$). Redrawn from Ahn and Phillips (2007)

selectively when instrumental behavior was controlled by outcome-expectancy, we failed to observe a selective increase in DA efflux when rats had limited as compared to extended training experience (Figs. 2a, c vs. b, d, respectively). Indeed, the magnitude of DA efflux was significantly greater after extended training during the habit-based phase of response control. These increases in DA efflux were site-

specific, as no significant changes in MD striatal DA efflux were observed throughout the different phases of this experiment.

In light of the earlier finding that lesions of the BLA impaired the establishment of action-outcome expectancies, it would be of interest to determine whether selective increases in DA efflux in the BLA might occur only during the early phase in the acquisition of new instrumental behavior (Corbit and Balleine 2005). Kahnt and Schoenbaum recently reviewed the literature on the relation between neural recordings or reduced function in the orbitofrontal cortex (OFC) in several mammalian species including humans with respect to a selective form of expectancy called outcome inference (Kahnt and Schoenbaum 2021). Outcome inference arises solely from mental simulations and unlike directly experienced expectancies appears to be under the direct control of the OFC. Accordingly, it would also be of interest to examine the role of DA in the OFC in the context of outcome inference.

Performance on instrumental tasks is often conducted under non-rewarded or extinction conditions to evaluate the control of behavior by Pavlovian incentive stimuli, un-confounded by unconditioned reward stimuli. As shown in Fig. 2c, d, DA efflux in the NAc was increased significantly, but only during the initial 10-min of the extinction trial on day 16, but not on day 5, consistent with previous reports of increased DA efflux in the NAc elicited by a CS+ (Phillips et al. 1993; Datla et al. 2002). Systemic administration of DA receptor antagonists during Pavlovian pairings of a CS+ with food reward blocks Pavlovian to instrumental transfer (Beninger and Phillips 1981; Dickinson et al. 2000). Collectively, these findings suggest that a phasic increase of DA efflux in the NAc shown to occur after treatment with amphetamine (Taepavarapruk and Phillips 2003; Brebner et al. 2005) may mediate the facilitatory effects of a Pavlovian CS+ on instrumental responding. It is also of interest to note that the inclusion of an extinction session before a reinforced phase of instrumental responding attenuated the magnitude of DA efflux in the NAc observed when food reward was available on day 5, but not on day 16 (Fig. 2c, d). This finding may be attributed to attenuation in the secondary reinforcement property of the CS+ associated with the delivery of food reward or possibly, an influence of frustrative non-reward engendered by extinction. In either case, it is apparent that these effects of extinction are restricted to the early outcome-expectancy phase of instrumental training.

Our data are also relevant to the relationship between response output and DA activity (Dickinson et al. 1995). As shown in Fig. 2a, b, although the rate of lever presses was twice as high on day 16 compared to day 5, the magnitude of DA efflux did not differ significantly between the 2 days. In Fig. 2c, on day 5, initial response rates during the extinction and reward phases of the test were comparable during the first 10 min (Samples 5 and 11), yet the corresponding magnitude of DA efflux during the reward phase was three times greater than the extinction phase. A similar pattern was observed on day 16 (Fig. 2d). Thus, different rates of responding were associated with similar magnitudes of DA efflux, and similar rates of responding were associated with different magnitudes of DA activity. Accordingly, no positive correlations between rate of lever press responding and magnitude of DA efflux in

the NAc were observed after limited and extended training. Finally, with respect to the appealing hypothesis that dopaminergic activity in the NAc is related to behavioral activation (Salamone et al. 2003, 2005), it must be emphasized that although our data challenge this hypothesis, it cannot be refuted simply on the basis of the lack of a correlation between magnitude of DA efflux and intensity or degree of behavioral activation. One approach to refute this hypothesis would be to suppress DA efflux in the NAc pharmacologically, by local infusion of the DA D2 agonist quinpirole at doses which would enhance autoreceptor inhibition. If this modulation of DA efflux resulted in comparable suppression of lever-pressing during both extinction and reinforced operant responding, despite differential initial levels of DA efflux, this would challenge the conjecture that the degree of behavioral activation reflects the absolute level of extracellular DA in the NAc.

The integrity of the dorsolateral striatum has been shown to be required for habit formation in instrumental learning, and furthermore, rats with damage to this region of the striatum reverted to a state in which instrumental actions were goal-directed (Yin et al. 2005). This finding implies that the system involving the dorsolateral striatum responsible for habit formation can inhibit the circuit that mediates action-outcome or goal-directed instrumental actions. This in turn raises the possibility that the increase in NAc DA efflux observed (Ahn and Phillips 2007) after extended training provides a representation of instrumental incentive learning that is held in check by activity in the dorsolateral striatum.

In summary, these findings showing elevated DA efflux in the NAc during extinction in the presence of a Pavlovian CS+ are consistent with a role for the NAc in incentive motivation (Berridge and Robinson 1998; Fibiger and Phillips 1986; Robbins et al. 1989; Balleine and Killcross 1994; Phillips et al. 1993). Rats received 60 food pellets during the microdialysis experiments on days 5 and 16, and the magnitude of DA efflux was significantly greater after extended training sessions. These data refute the hypothesis that dopaminergic activity in the NAc is a simple reflection of either reward value or reinforcement of instrumental responses (Wise 2004). The use of a "within subject" design revealed an unappreciated effect of extended training of instrumental responding on the magnitude of DA efflux in the NAc. Importantly, this does not appear to be related to motor responding per se. Instead, it may reflect another important factor, namely the "uncertainty" inherent in a variable interval schedule of outcome presentation. If this is the case, then extended training appears to be required to learn that the probability of receiving a beneficial outcome during the 30-min test session is always unpredictable. This degree of uncertainty may be related to optimal conditions for activating midbrain DA neurons (Fiorillo 2003), resulting in a sustained increase in DA release in the NAc throughout a period of random reinforcement. Such patterns of DA release may contribute to the maintenance of high levels of motivation required to ensure access to objects essential for survival.

4 Novel Insights from Preclinical Studies of Contrast Effects on the Role of Incentive-Anticipation in Mood Disorders

When considering the impact of the concept of anhedonia on the field of biological psychiatry, there can be little argument that the greatest legacy is its heuristic value, as witnessed by the extensive body of work contained within the present volume. While the use of this concept in clinical diagnosis remains relevant, we would argue that its ongoing importance continues to be found in the rich body of preclinical studies linking the significance of anhedonia, as redefined, to specific neural systems. This work in turn has led to refined preclinical models of neuropsychiatric disorders, especially those related to mood disorders, including specific aspects of depression.

One of the most seminal findings in the study of motivation and reward, and perhaps one of the most underappreciated, is the phenomenon of successive contrast effects (Flaherty 1996). These effects are bivalent as revealed by both negative and positive contrasts, reflecting in turn a significant suppression (−) or enhancement (+) in reward-seeking behaviors when a subject experiences an unanticipated change in the value of an expected reward. These phenomena are displayed in species that ascend the phylogenetic scale from bees to humans and have been implicated in adaptation to significant changes in the environment, which in turn can shape the evolution of species (McNamara et al. 2013). In his insightful treatise, Flaherty commented that successive negative contrast "provides a model for the characterization of the neurobiology and psychopharmacology of disappointment" (Flaherty 1996, p. 173). We have noted that both successive negative and positive contrast provide measures of affect specifically disturbed in mood disorders and therefore have a great deal to offer in studying basic cognitive, behavioral, and neural processes related to anxiety and depression (Barr and Phillips 2002). Data from the Phillips lab illustrate both successive positive and successive negative contrast in the context of instrumental lick responses for two different concentrations of sucrose solution, namely 4% or 32% (Barr and Phillips 2002; Vacca and Phillips 2005; Genn et al. 2004; Phillips et al. 2008). The control group has access to a 32% concentration throughout the experiment. Positive contrast is expressed by the unexpected access to a 32% sucrose solution by rats that previously experienced a less sweet 4% solution for many days. Compared to the group maintained on a 32% solution (32%–32%) the mean lick rate for rats in the 4%–32% condition exceeds that of the control group (Fig. 3a). Importantly this effect is still evident 4 days after the switch in reward value. Successive negative contrast is readily observed by switching the reference value of sucrose solution from 32% to 4% (Fig. 3c). Both phenomena imply that repeated experience with a specific incentive value, in this case expressed as the sweetness of sucrose for which preference curves have been generated (32% significantly preferred over 4%), gives rise to memory for an expected value of the initial incentive stimuli. Positive contrast occurs immediately when a stimulus with significantly greater incentive value is encountered; one that

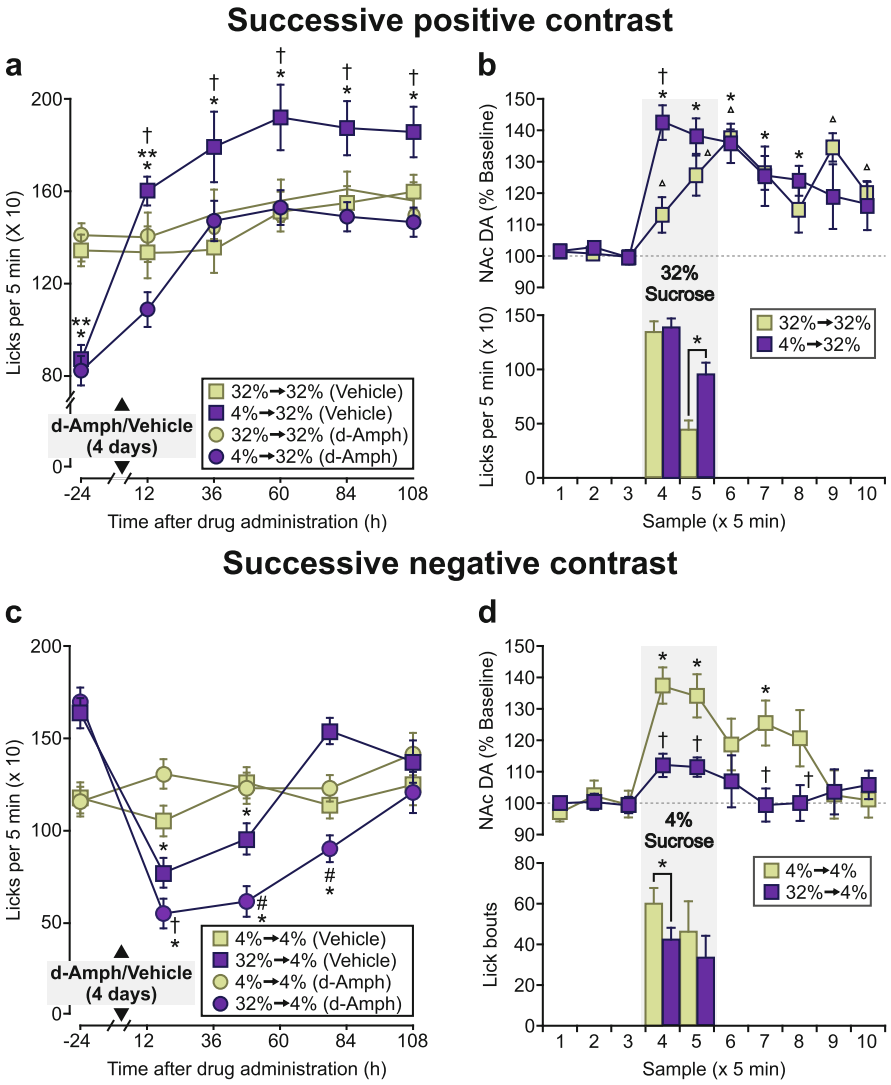

Fig. 3 Successive contrast effects in rats as indicated by licking for 4% and 32% sucrose solutions. **a, b**, Rats that experienced an upshift in sucrose concentration (*4% → 32%*) displayed increased licking and enhanced DA efflux in the NAc compared to rats that remained on 32%. **c, d**, Rats that experienced a downshift in sucrose concentration (*32% → 4%*) exhibited decreased licking and reduced DA efflux compared to rats that remained on 4%. **a, c**, Treatment with escalating doses of d-amphetamine (*d-Amph*) over 4 days enhanced both positive and negative contrast effect on sucrose licking. Redrawn from Vacca and Phillips (2005), Phillips et al. (2008), Barr et al. (2002), and Genn et al. (2004)

has greater positive valence than anticipated. On the other hand, successive negative contrast is generated when the newly experience incentive properties of the sucrose solution are less sweet (4%) than that anticipated by the memory of the 32% solution.

In related neurochemical studies, we measured changes in DA efflux in the NAc in the critically important 10-min period when the value of the sucrose concentration was switched from 4% to 32% (positive contrast) or maintained at 32%. As shown in Fig. 3b, we observed an immediate and significant increase in DA efflux in the group switched unexpectedly from 4% to 32% sucrose, relative to the group maintained on the 32% solution (Genn et al. 2004). As predicted, in a separate study, DA efflux in the NAc was significantly suppressed following an unexpected decrease in sucrose concentration from 32% to 4% (negative contrast; Fig. 3d).

It is well established in both preclinical and clinical studies that discontinuation of access to psychostimulant drugs such as cocaine and d-amphetamine gives rise to aversive affective states in both experimental animals and humans (Koob et al. 1997). Evidence of anhedonia in post-drug withdrawal is best characterized by disruption in responding for brain-stimulation reward (Leith and Barrett 1976, 1980; Markou and Koob 1991; Wise and Munn 1995). In an extensive series of experiments, Barr and Phillips confirmed reduced motivation to obtain natural rewards, including a sucrose solution after the termination of an escalating-dose schedule of d-amphetamine administration (Barr et al. 1999; Barr and Phillips 1999). For a comprehensive summary of these findings, including the effect of withdrawal from this 4-day treatment with d-amphetamine on successive negative contrast, see Barr et al. (2002). Key features of the effect of post-amphetamine withdrawal on both behavioral and neurochemical correlates of successive negative contrast are summarized in Fig. 3c, d. Note particularly the significantly greater suppression in lick rate in rats induced by amphetamine withdrawal in the 32%–4% sucrose condition relative to the control 32%–4% (Vehicle) group. The powerful effect of amphetamine withdrawal on successive positive contrast is shown in Fig. 3a (compare groups 32%–4% (Vehicle) to 32%–4% (d-Amph)). As noted previously, Fig. 3b confirms a significant increase in DA efflux in the NAc in the group for which the sucrose concentration was increased from 4% to 32%.

In addition to providing new perspectives on the neural correlates of mental disorders such as depression, models combining psychostimulant drug withdrawal along with successive negative and positive contrast paradigms could also contribute to the development of new therapeutics for the treatment of mood disorders and substance use disorders. Accordingly, we look forward to their use future studies on the effects of novel drug candidates including fast-acting antidepressants such as ketamine and its metabolites (Aleksandrova et al. 2017).

5 Anhedonia, Anticipation, and the RDoC Classification System

It is now widely recognized that individual dimensions of mental illness arise from altered neural processes within specific brain circuits that may be shared across diagnostic categories (Insel et al. 2010). The US National Institute of Mental Health

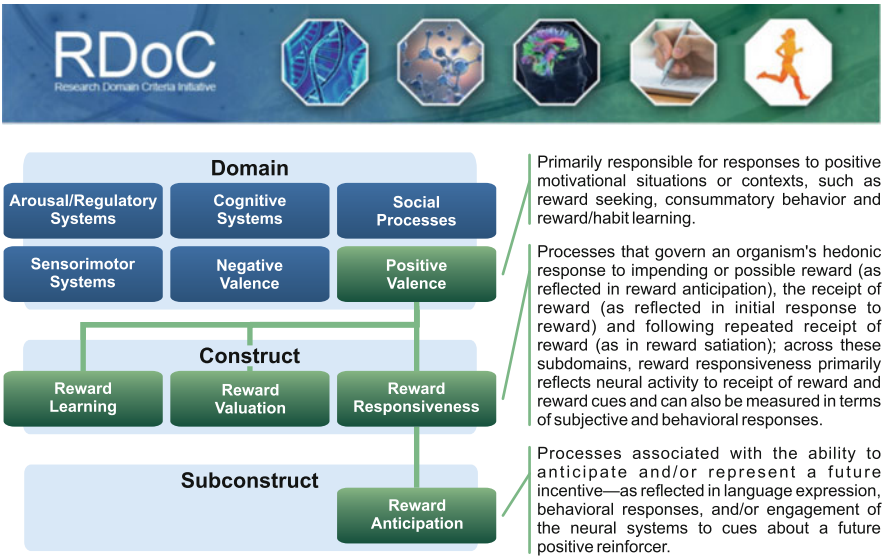

Fig. 4 The Research Domain Criteria (RDoC) classification system is a categorization of psychological/psychiatric concepts at three levels of organization. Highlighted (*in green*) are concepts of *Positive Valence (Domain*), *Reward Responsiveness (Construct),* and *Reward Anticipation (Subconstruct)*. Banner and definitions were obtained from https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix

(NIMH) now promotes the use of the influential Research Domain Criteria (RDoC) which include as key domains – arousal/regulatory systems; cognitive systems; social processes; sensorimotor systems; and negative and positive valence systems – in the belief that they provide a more objective and scientific alternative to the diagnostic categories contained in the Diagnostic and Statistical Manual of mental disorders. Furthermore it is assumed that the use of the more focused and objective RDoC domains will foster greater reliance on neurobiological data, which in turn will facilitate new drug development for the treatment of mental illness (Casey et al. 2014) (Fig. 4). As will become quite apparent from a close perusal of this book, these objectives are shared by those who champion the use of terms such as "Anhedonia" and "Anticipation" to provide more objective bases for the understanding, diagnosis, and treatment of major psychiatric disorders.

The case for recognizing the important overlap between the RDoC classification system and the expanded view of anhedonia championed here is readily apparent from the prominence given to two of the six key Domains that constitute the RDoC categorization system; namely the Positive Valence Systems and Cognitive Processes (Fig. 4). Note especially that the Positive Valence Systems include "Reward Anticipation" as a subconstruct, defined as "Processes associated with the ability to anticipate and/or represent a future incentive-as reflected in language expression, behavioral responses, and/or engagement of the neural systems to cues about a future positive reinforcer." This rich description of the precise factors "responsible for

responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior and reward/habit learning" provides much needed clarity as we seek to understand how factors such as anhedonia – broadly defined – can contribute to a better understanding of the motivational and cognitive dysfunctions that are of paramount importance to the diagnosis and treatment of many psychiatric disorders (Mittal and Wakschlag 2017).

6 Concluding Remarks

In her 1971 hit "Anticipation," Carley Simon struck all the right notes by defining this concept in a manner that can be readily understood, conveying *the central role of imagining what's to come* as we move throughout the day. The third verse in particular says it all:

> And I tell you how easy it feels to be with you
> How right your arms feel around me.
> But I rehearsed those words just late last night
> When I was thinking about how right tonight might be.
>
> Anticipation, anticipation
> Is making me late
> Is keeping me waiting.

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Vigor, Effort-Related Aspects of Motivation and Anhedonia

Michael T. Treadway and John D. Salamone

Contents

Abstract In this chapter we provide an overview of the pharmacological and circuit mechanisms that determine the willingness to expend effort in pursuit of rewards. A particular focus will be on the role of the mesolimbic dopamine system, as well the contributing roles of limbic and cortical brains areas involved in the evaluation, selection, and invigoration of goal-directed actions. We begin with a review of preclinical studies, which have provided key insights into the brain systems that are necessary and sufficient for effort-based decision-making and have characterized novel compounds that enhance selection of high-effort activities. Next, we summarize translational studies identifying and expanding this circuitry in humans. Finally, we discuss the relevance of this work for understanding common motivational

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Curr Topics Behav Neurosci (2022) 58: 325–354
https://doi.org/10.1007/7854_2022_355
Published Online: 4 May 2022

impairments as part of the broader anhedonia symptom domain associated with mental illness, and the identification of new treatment targets within this circuitry to improve motivation and effort-expenditure.

Keywords Decision-making · Depression · Dopamine · Effort · Motivation

1 Introduction

Motivation is one of the key constructs used in the psychological sciences. But since psychological constructs are complex and multifaceted, it is worthwhile to ponder the meaning and usage of the term. Does motivation refer solely to an internal state, a subjective desire, or the verbal expression of a goal? Is motivation simply subsumed into another construct, such as emotion? Are avolition and anhedonia synonymous, or are they experimentally and psychometrically dissociable from each other?

Psychological research and theory over the last century have emphasized that motivation refers to much more than a subjective internal state or desire; motivation also is inextricably linked to the instigation, maintenance, and persistence of action (Salamone et al. 2017). While goal-directedness is clearly a vital aspect of motivation, the importance of activational aspects, variously described through the years with terms like energy, arousal, or exertion of effort, has been evident in psychological research and theory for almost a century (Duffy 1941, 1963; Cofer and Appley 1964; Salamone 1988; Salamone et al. 2017). It has been recognized for decades that work requirements are a critical aspect of instrumental performance (Collier and Jennings 1969), and thus, the ability to exert high levels of effort is adaptive because it enables organisms to overcome work-related response costs that separate them from reinforcers. If behavioral neuroscience research has yielded any fruits over the last several decades, certainly one is that complex functions can be parsed into dissociable aspects by manipulations of neural function (Salamone and Correa 2002, 2012; Berridge and Robinson 2003). Studies at the basic science and preclinical levels have focused on identifying neural circuits and chemical transmitters that regulate behavioral activation, exertion of effort, and effort-related choice, and dissociate them from neural circuits controlling primary motivational processes that underlie reinforcement (Salamone and Correa 2002, 2012). From these studies, more formal animal models have emerged (Salamone et al. 2018). In parallel, there has been an ongoing emphasis on psychiatric symptoms in humans related to a lack of behavioral activation, such as anergia, avolition, apathy, and fatigue (Demyttenaere et al. 2005; Fava et al. 2014; Cooper et al. 2014; Ghanean et al. 2018). Furthermore, there has been an explosion of work on response vigor and effort-related decision-making (ERDM) in humans over the last decade (e.g. Wardle et al. 2011; Treadway et al. 2012; Barch et al. 2014). This chapter will review and integrate preclinical and clinical studies related to this important area of research and

discuss its implications for understanding the pathophysiology and of motivational impairments as well as potential treatment strategies.

2 Neurochemistry and Pharmacology of Behavioral Activation and Effort-Related Processes: Preclinical Foundations

Motivational stimuli can induce goal-directed instrumental behaviors that culminate in consummatory activities, but they also have activating effects. Motivation researcher and theorist Charles Cofer (1972, p. 34) emphasized that motivational stimuli "energize responses, either in general or specifically" to control the vigor and efficiency of behavior. Classical studies involving rodent research across multiple laboratories have demonstrated that forebrain dopamine (DA) systems are important for behavioral activation (Koob et al. 1978; Salamone 1986, 1988; Kelley et al. 2005; Robbins and Everitt 2007). For example, exposing food-restricted animals to scheduled but non-contingent presentation of food or other reinforcers can induce a variety of activities (e.g., locomotion, drinking, licking, wheel-running), and considerable evidence indicates that mesolimbic DA is involved in this schedule-induced activity. Nucleus accumbens DA depletions impair a variety of schedule-induced activities, including wheel-running (Wallace et al. 1983), drinking (Robbins and Koob 1980; Wallace et al. 1983), and locomotion (McCullough and Salamone 1992). Nevertheless, the effects of DAergic manipulations on indices of behavioral activation are dissociable from actions on primary food motivation. Depletions of DA in nucleus accumbens that reduced spontaneous and amphetamine-induced locomotion failed to suppress food intake (Koob et al. 1978). Local injections of DA D1 and D2 receptor antagonists injected into the core or shell subregions of accumbens blunted locomotor activity but did not reduce food intake (Baldo et al. 2002). These observations are supported by a recent chemogenetic study reporting that activation of DA neurons projecting to nucleus accumbens substantially increased locomotor activity but did not reduce total food consumption (Boekhoudt et al. 2017). Taken together, these studies illustrate how the effects of DAergic manipulations on indices of behavioral activation in food-related tasks do not depend in any simple or direct way on changes in primary food motivation or appetite. In fact, the preponderance of evidence demonstrates that one can experimentally dissociate the effects of dopaminergic manipulations on instrumental response rate and exertion of effort in response to work requirements, vs. effects on primary or unconditioned food motivation or reinforcement (Aberman and Salamone 1999; Salamone and Correa 2002, 2012; Kelley et al. 2005; Mingote et al. 2005; Salamone et al. 2007, 2017, 2018).

The dissociation between the exertion of effort vs. primary or unconditioned food motivation and reinforcer preference is clearly evident in rodent studies of effort-related choice behavior (also known as EBDM). With this type of procedure,

animals are given a choice between a preferred reinforcer that can only be obtained by a high degree of work (e.g., multiple lever presses) vs. a less preferred reinforcer obtained by minimal effort. One of the most commonly used tasks of this type is the concurrent fixed ratio 5 chow feeding choice task (FR5/chow choice task; Salamone et al. 1991). Animals must select between lever pressing for preferred high carbohydrate pellets vs. approaching and consuming a concurrently available standard lab chow. Interference with DA transmission dramatically shifts choice behavior, decreasing lever pressing but substantially *increasing* chow intake. This outcome is sometimes referred to as a *low-effort bias*, and it can be produced by systemic injections of low doses of nonselective, D1 selective, or D2 selective antagonists (Salamone et al. 1991, 2002; Sink et al. 2008), local infusion of D1 or D2 antagonists into nucleus accumbens core or shell (Nowend et al. 2001; Farrar et al. 2010), or neurotoxic depletions of DA in the accumbens but not neostriatum (Salamone et al. 1991; Cousins et al. 1993). More recently, this shift in effort-based choice was shown to be produced by systemic or intra-accumbens injections of tetrabenazine (TBZ; Nunes et al. 2013; Yohn et al. 2016a), which depletes DA by blocking DA storage via inhibition of the vesicular monoamine transporter type-2. Studies using TBZ to induce a low-effort bias are increasingly being used in animal models of pathological motivation (Yohn et al. 2016a; Rotolo et al. 2019, 2020, 2021; see below). In summary, studies employing the FR5/chow choice task demonstrate that rats exposed to the pharmacological conditions listed above remain directed toward the acquisition and consumption of food. Rather than showing a general loss of food reward, rats with diminished DA transmission re-direct their food seeking away from working on the lever, and instead approach and consume the freely available chow.

Several behavioral tests have been used in rats to assess effort-based choice. In addition to the FR5/chow choice task, progressive ratio (PROG)/chow choice tasks have been developed (Schweimer et al. 2005; Randall et al. 2012). Because of the challenge presented by the gradually increasing work requirement, rats on this task lever press less than on the FR5 task, reaching a break point within a 30-minute session, which in turn triggers a timeout that inactivates the lever. This task functions essentially as a type of effort discounting task, and untreated animals typically shift from lever pressing to consuming large quantities of the alternative low-effort option (concurrently available chow). Although this task is sensitive to DA antagonists and DA depletion (Randall et al. 2012, 2014), the PROG/chow choice task is particularly useful for assessing the effects of drugs that enhance selection of high-effort PROG lever pressing by increasing DA transmission by blocking the DA transporter (e.g., bupropion, lisdexamfetamine, GBR12909, MRZ-9547; Sommer et al. 2014; Randall et al. 2015; Yohn et al. 2016b, c, d). Furthermore, individual differences in selection of PROG lever pressing vs. chow were significantly related to the degree of DA D1 receptor signaling in nucleus accumbens core as marked by expression of phosphorylated DARPP-32 (Thr34) (Randall et al. 2012). Consistent with these findings, Trifilieff et al. (2013) used a random ratio/chow feeding choice task to assess the effects of adult overexpression of DA D2 receptors in nucleus accumbens in mice. They found that enhanced D2 receptor function in the accumbens but not the neostriatum selectively increased ratio responding without altering consummatory

behavior, the representation of the value of the reinforcer, or behavioral flexibility. These results, together with those obtained from experiments involving DA antagonism and depletion, indicate that accumbens DA transmission exerts a bi-directional regulation over the selection of high-effort instrumental activities.

Tests of effort-based choice using other instrumental behaviors, choices, and reinforcer options have dramatically expanded this line of research. A T-maze barrier task was developed in which rats or mice have a choice between climbing a barrier in one arm to obtain a high magnitude of reinforcement vs. entering another arm with no barrier to obtain a lower magnitude reward (Salamone et al. 1994). Similar to the results obtained from operant procedures, rats and mice treated with DA D1 or D2 antagonists, as well as neurotoxic or pharmacological depletion of DA with TBZ, show a shift from choosing the barrier arm vs. the no-barrier arm (Salamone et al. 1994; Cousins and Salamone 1994; Mott et al. 2009; Mai et al. 2012; Pardo et al. 2012). There also are discrete-trial effort discounting procedures that employ either different FR lever pressing requirements or a T-maze with a barrier in order to control the effort component (Floresco et al. 2008; Bardgett et al. 2009). DA antagonists with various selectivity profiles alter ratio discounting in a manner consistent with the low-effort bias demonstrated using other procedures (Floresco et al. 2008; Bardgett et al. 2009; Hosking et al. 2015).

2.1 Brain Circuitry Involved in Effort-Based Choice

Although much of the review above has focused on the effects of DAergic manipulations, especially those affecting the mesolimbic DA innervation of nucleus accumbens, it is clear that effort-based decision-making is regulated by neural circuits that connect limbic, cortical, and striatal areas and involve multiple transmitters. EBDM across multiple tasks is affected by lesions, inactivation, or pharmacological manipulation of frontal cortical areas, including anterior cingulate cortex (Walton et al. 2003) and medial orbitofrontal cortex (Münster et al. 2018, 2020). Depletions of anterior cingulate DA by injections of 6-hydroxydopamine also were able to shift T-maze barrier choice performance (Schweimer and Hauber (2006). Hart et al. (2017) observed that excitotoxic lesions of anterior cingulate cortex decreased PROG lever pressing for sucrose pellets, but did not affect intake of concurrently available chow. The effects of anterior cingulate lesions in this study were not mediated by decreased appetite, changes in food preference, or a failure to update reinforcement value. Disconnection studies involving manipulation of different components of the circuitry on opposite sides of the brain have shown that effort-based choice and exertion of effort are regulated by connections between basolateral amygdala and anterior cingulate cortex (Floresco and Ghods-Sharifi 2007), anterior cingulate cortex and nucleus accumbens core (Hauber and Sommer 2009), and accumbens core and lateral ventral pallidum (Mingote et al. 2008), as well as medial orbitofrontal cortex and ventral tegmental area (Münster et al. 2020).

DA interacts with the neuromodulator adenosine in neostriatum and nucleus accumbens. Caffeine and other methylxanthines such as theophylline and theobromine act as minor stimulants via their actions as nonselective antagonists of adenosine receptors (Ferré et al. 2008; Randall et al. 2011; Pardo et al. 2012). Adenosine A2A receptors are highly expressed in nucleus accumbens and neostriatum (Ferré et al. 2004), and there are cellular interactions between DA D2 and adenosine A2A receptors that are co-localized on the same accumbens and neostriatal medium spiny neurons (Ferré 1997; Svenningsson et al. 1999). Adenosine A2A receptor antagonists have been studied for their potential antiparkinsonian effects (Ferré 1997; Morelli and Pinna 2002; Correa et al. 2004), and istradefylline (Nourianz) has been approved for use in several countries. Particularly relevant for the present review, drugs that act on adenosine A2A receptors induce substantial effects on instrumental behavior and effort-related choice. Local intra-accumbens injections of the A2A agonist CGS 21680 shifted effort-related choice, decreasing FR5 lever pressing and increasing chow intake (Font et al. 2008), but infusions into neostriatum dorsal to the accumbens did not. Caffeine, theophylline, and several adenosine A2A receptor antagonists (MSX-3, MSX-4, Lu AA47070, istradefylline) can reverse the low-effort bias induced by systemically administered DA D2 antagonists (Farrar et al. 2007; Worden et al. 2009; Mott et al. 2009; Collins et al. 2012; Nunes et al. 2010; Santerre et al. 2012; Randall et al. 2012; Pardo et al. 2020), and MSX-3 and preladenant reverse the effects of TBZ (Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2015a; Salamone et al. 2018). Intra-accumbens injections of MSX-3 reversed the effects of intra-accumbens injections of the D2 antagonist eticlopride in rats responding on the FR5/chow concurrent-choice task (Farrar et al. 2010). Furthermore, A2A receptor knockout mice are resistant to the effort-related effects of haloperidol (Pardo et al. 2012). Studies using signal transduction markers of DA D2 transmission (e.g., cFos, phosphorylated DARPP-32) indicate that adenosine A2A receptor antagonists reverse the signal transduction effects of D2 receptor antagonism and TBZ in accumbens medium spiny neurons (Farrar et al. 2010; Santerre et al. 2012; Nunes et al. 2013).

While the role of DA in EBDM is well characterized, the involvement of other monoamines remains less clear. DA antagonism and depletion produces a low-effort bias that is consistently reversed by drugs that facilitate DA transmission (Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2015a, b, 2016a, b, c), and drugs that block DA transport (DAT) enhance selection of high-effort PROG lever pressing (Randall et al. 2015; Yohn et al. 2016b, c, d; Rotolo et al. 2019, 2020, 2021). Knockdown of DAT in mice enhanced selection of high-effort lever pressing vs. chow in mice (Cagniard et al. 2006), and chemogenetic activation of VTA DA neurons enhanced PROG lever pressing (Boekhoudt et al. 2018). In contrast, the serotonin transport (SERT) inhibitor fluoxetine reduced lever pressing and wheel-running in rats tested on EBDM tasks (Presby et al. 2021). Fluoxetine and citalopram failed to reverse the effort-related effects of TBZ (Yohn et al. 2016a,b; Carratalá-Ros et al. 2021), and fluoxetine failed to stimulate PROG lever pressing (Yohn et al. 2016d). The results with drugs that act on norepinephrine or its transporter (NET) are mixed. The NET inhibitor desipramine does not reverse the

effort-related effects of TBZ (Yohn et al. 2016a), and neither desipramine nor the more selective NET inhibitor atomoxetine stimulates exertion of effort in rats tested on choice tasks (Yohn et al. 2016d; Hosking et al. 2015). Fitzpatrick et al. (2019) showed that chemogenetic inactivation of VTA DA neurons impaired effort-based motivation and indices of response speed and vigor in mice, while inactivation of locus coeruleus NE neurons affected attentional processes, but not effort or response vigor. However, studies that employed a force-based effort task in monkeys reported that locus coeruleus NE neurons showed enhanced firing during force exertion (Varazzani et al. 2015), and administration of the alpha 2 receptor agonist clonidine reduced exertion of effort (Borderies et al. 2020). Thus, questions remain about the precise role of NE in different aspects of effort-related function (e.g., repetitive response maintenance vs. force output, physical or cognitive effort, task engagement, species differences).

In addition to neuropharmacological and neurochemical manipulations, several studies have identified stress and inflammation as physiological factors that affect effort-based choice. Restraint stress induced a low-effort bias as measured with an effort discounting task in rats (Shafiei et al. 2012), and corticotropin-releasing hormone appears to mediate these stress-related effects (Bryce and Floresco 2016; Hupalo et al. 2019; Dieterich et al. 2020). Social defeat stress also induces a low-effort bias in rats (Dieterich et al. 2020, 2021a, b). Pro-inflammatory cytokines have been implicated in motivational symptoms in humans such as anergia and fatigue (Miller 2009; Dantzer 2009; Felger and Treadway 2017; Bekhbat et al. 2022). Animal studies have involved administration of the pro-inflammatory cytokines interleukin (IL)-1β and IL-6. In rats tested on the FR5/chow choice task, a low-effort bias was induced by administration of IL-1β (Nunes et al. 2014; Yohn et al. 2016b) and IL-6 (Yohn et al. 2016e) at doses that did not alter food preference or induce fever. A behaviorally effective dose of IL-6 also decreased extracellular DA in nucleus accumbens as measured by microdialysis (Yohn et al. 2016e). These findings highlight the cross-talk between peripheral inflammatory responses and central neurotransmission, and also point to possible treatment strategies.

Food is by far the most commonly used reinforcer in rodent studies, including the ones described above. Nevertheless, multiple environmental conditions and activities can serve as reinforcers. A recent series of effort-based choice studies has exploited this by using running wheel (RW) activity as the high-effort reinforcer. Correa et al. (2016) developed a maze task in which mice can choose between wheel-running vs. intake of sucrose pellets. Under baseline or control conditions mice spent more time running and less time eating, but injections of low doses postsynaptic doses of haloperidol reduced time running but actually *increased* time spent consuming sucrose. Mice with adenosine A2A receptor knockout were resistant to the haloperidol-induced shift from RW activity to sucrose intake. Using another version of the maze that involved three options (RW, sucrose, sniffing an odor), haloperidol again reduced time engaged in RW activity, but increased sucrose intake and had no effect on sniffing the odor (Correa et al. 2020). Postsynaptic doses of haloperidol in the low-to-moderate dose range had no effect on sucrose intake or preference in parallel preference tests. TBZ also shifted preferences in the 3-choice

maze, reducing time spent engaged in RW activity but increasing sucrose intake at doses that had no effect on independent measures of appetite or open field locomotion (López-Cruz et al. 2018; Carratalá-Ros et al. 2020). The pattern of effects induced by TBZ was not mimicked by motivational manipulations, such as making the RW aversive or harder to move (Carratalá-Ros et al. 2020). At doses that had no effect on their own, the adenosine antagonist caffeine reversed the effects of TBZ on T-maze performance, and also blunted the TBZ-induced expression of pDARPP-32 (Thr34) as measured by Western blot (López-Cruz et al. 2018). In contrast, the SERT inhibitor fluoxetine failed to reverse the effect of TBZ on selection of RW activity (Carratalá-Ros et al. 2021). This line of work highlights two theoretically important aspects of research on effort-based choice. First, it makes explicit what is evident in other studies of EBDM using lever pressing or barrier climbing as instrumental behaviors; the effects of low doses of DA antagonists or DA depletion are not dependent upon actions on primary or unconditioned food motivation or preference. Rather, the effects of these manipulations depend upon the specific physical activity requirements of the instrumental action, be they lever pressing, barrier climbing, or wheel-running. Second, in the context of the choice situation presented in the RW studies, haloperidol and TBZ decreased time spent running in the wheel, but actually increased time spent consuming sucrose. This is theoretically important because according to the classic behavioral literature, time engaged in an activity is an important index of preference, relative reinforcement value, and response choice (Baum and Rachlin 1969). Thus, if anything, haloperidol and TBZ were actually *increasing the relative value* of sucrose reinforcement, not decreasing it. This emphasizes that haloperidol and TBZ are not suppressing lever pressing because of a reduction in the primary or unconditioned value of a reinforcer such as sucrose per se.

The behavioral tests described above involve exertion of physical effort, but another important aspect of motivation involves cognitive effort. Winstanley and colleagues (Cocker et al. 2012) developed an attentional task for assessing cognitive effort choice in rats, in which animals have the option of performing either an easy trial, in which the attentional demand is low but the potential reinforcement is small, or a difficult trial that is more attentionally demanding but can lead to twice the magnitude of reward. The effects of amphetamine on choice depended upon baseline performance; amphetamine enhanced selection of high-effort trials in rats with low baseline choice of those trials ("slackers"), but reduced selection of high-effort trials in animals with high baseline performance (Cocker et al. 2012). Inactivation of prefrontal cortex in rats decreased selection of high-effort trials (Hosking et al. 2015). In one study that compared the effects of DA D1 and D2 antagonists on both physical and cognitive effort choice, DA antagonism reduced exertion of physical, but not cognitive effort (Hosking et al. 2015). These findings demonstrate that decision-making involving physical and cognitive effort is supported by partially overlapping but nevertheless distinct neural circuits (Winstanley and Floresco 2016).

3 Translation to Humans

This rodent literature has exhibited remarkable translational parity in human models, though some divergence emerges as one begins to consider cognitive vs. physical manifestations of effort, as well as some of the higher-order forms of abstract valuation and long-term foraging strategies (e.g., investing in a PhD) in which humans frequently engage. In this section, we first review some of the work paralleling the role of striatal DA in human EBDM, as well as the expanded role for dorsomedial prefrontal areas in effortful forging.

3.1 The Task of the Translator: Considerations for Translating Rodent EBDM Studies to Humans

One immediate challenge faced by translational researchers seeking to assess substrates of motivational impairment in humans is the need to create sufficiently salient stimuli that can approximate the intensity of a rodent's drive for food while on a calorie-restricted diet. Clinical researchers face the dual constraints of ethical limits on experimental controls in humans as well as their participants vastly expanded cognitive capacity for representing abstract rewards. Indeed, in the absence of acute physiological need (e.g., extreme hunger), the most common motivators that drive human effort are abstract, intangible, social constructs (love, friendship, prestige, accomplishment, etc.) (Maslow 1943). Consequently, most human EBDM paradigms in the literature rely on secondary reinforcers (money, points, or course credit), rather than the primary food rewards used in animal models (Treadway et al. 2009; Bonnelle et al. 2015; Hershenberg et al. 2016; Klein-Flügge et al. 2016; Schmidt et al. 2012). That said, a few studies have examined effort for food or drink rewards after some period of intake restriction (e.g., Rzepa et al. 2017) and have found similar patterns of behavior and circuit engagement. Consequently, it is unlikely that secondary reinforcers used in human EBDM paradigms represent a marked difference from food reward in animal paradigms.

A more subtle challenge is the impact of prior expectations or beliefs. The vast majority of participants in human EBDM studies come from industrialized, market-based economies and are likely to have strong pre-conceived beliefs about principles of labor exchange for reward. This can lead to strong biases in terms of the choices one "should" make, which may engage different circuits than those involved in basic cost/benefit computation. For example, recent work suggests that social influence can alter representations of value signals during choice paradigms in humans (Crockett et al. 2017; Zaki et al. 2011), and even a participant's own prior choice history can alter value-signaling and subsequent choice behaviors, as participants may often seek to impose a degree of consistency in their preferences (Ariely and Norton 2008). In clinical populations associated with high degrees of self-criticism, such as certain presentations of major depression, some preliminary evidence

suggests that feeling that one "should" try harder can influence performance on effort-based tasks. In one such EBDM study, Hershenberg and colleagues found that while depressed patients exerted less effort than healthy controls on average, individuals with higher feelings of worthlessness, guilt, and low self-esteem were associated with *more* effortful choices (Hershenberg et al. 2016). This potentially suggests that for some patients, self-critical beliefs may over-ride symptoms of fatigue or low motivation as assessed by EBDM tasks. Future studies will be needed to determine the extent to which abstract expectations and beliefs may guide behavior on human EBDM tasks above and beyond basic cost/benefit analysis.

3.2 Dopaminergic Drive in Human EBDM

As reviewed in the prior section, substantial evidence has suggested that EBDM paradigms are useful tools for isolating brain networks and neurotransmitters involved in cost/benefit analyses that determine the likelihood of investing effort in the pursuit of rewards (Salamone and Correa 2012; Salamone et al. 2001; Berke 2018; Hamid et al. 2016). A key region in this process has been the DA-rich striatum and its role in the function of distinct cortico-striatal "loops" (Haber and Knutson 2010). As in animal models, human studies have found clear evidence for the role of DA in modulating an individual's preferences to exchange work for effort. Potentiation of DA transmission via drugs such as L-Dopa (Zénon et al. 2016) or d-amphetamine (Wardle et al. 2011; Soder et al. 2021) has been shown to increase effortful behavior in humans, though with some subtle distinctions. In early studies using the EEfRT, a human effort-based decision task inspired by concurrent-choice effort tasks in animals, we observed that enhancing DA via amphetamine increased an individual's willingness to exert effort as a function of enhanced risk (i.e., low probability of receiving reward in exchange for effort) (Wardle et al. 2011). A subsequent study in a larger sample found that amphetamine primarily influenced effort aversion in the absence of clear effects on probability (Soder et al. 2021). In a separate paradigm, Zenon and colleagues found that L-Dopa did not increase the frequency of effortful choices, but did enhance the vigor with which effort was deployed (Zénon et al. 2016). Whether this discrepancy is due to more to the differential impact of amphetamine or L-Dopa as opposed to differences in experimental design remains unclear. In support of the former, it is plausible that the significant DA-releasing effects of amphetamine may incite more reward focused behavior resulting in lower sensitivity to effort costs, while the putatively activity-dependent actions of L-Dopa on striatal DA may result in less overt effects at the time of choice.

One notable divergence between humans and rodents in terms of DAergic effects on effort-based choice has been the apparent functional localization of DAergic and putatively DAergic (e.g., BOLD fMRI) signals. While concurrent-choice paradigms have primarily found that DAergic effects on effort-based choice were specific to the ventral striatum/nucleus accumbens, human studies have increasingly observed

distinct – and potentially oppositional – roles for antero-ventral and dorsomedial aspects of the ventral striatum (Suzuki et al. 2021). For example, one recent study by our group found that while an anterior-ventral region of striatum responded to rewards that were received following effort, a neighboring dorsomedial aspect of ventral striatum was engaged by effort initiation (as compared to simple, non-effortful movements). We further observed that these subregions exhibited markedly distinct patterns of fronto-striatal resting-state connectivity, further suggesting their participation in distinct circuits. Finally, a recent large sample PET study observed a significant association between methylphenidate induced DA release in dorsomedial caudate and willingness to expend cognitive effort for rewards (Westbrook et al. 2020). Whether this apparently expanded role for dorsomedial striatum represents a distinction between rodent and human striatal organization or reflects differences in behavioral paradigms is unclear. Perhaps suggesting the latter, recent animal work highlighted that substantia nigra DA neurons fire immediately before the onset of vigorous action (da Silva et al. 2018) and putatively "reward" encoding DA neurons also respond strongly to movement and effort variables (Engelhard et al. 2019). Additionally, a recent study of two-photon DA imaging in dorsomedial striatum found clear evidence for distinct "waves" of striatal dopamine release as a function of passive or active reward receipt (Hamid et al. 2021). Future studies will be required to better understand the effects of regional variation in DA disruption on effort- based choice.

3.3 Hierarchical Circuits for Effort Allocation

A second major brain area that has been implicated in effort-based choice in both humans and animals is the dorsal anterior cingulate (dACC) often extending into surrounding dorsomedial prefrontal cortex and preSMA (dACC/dmPFC). Early animal work suggested that lesions to the rodent homologue of the dACC, CG1, were associated with a consistent decline in the willingness to expend effort (Walton et al. 2002, 2003; Rudebeck et al. 2006). Using electrophysiology and fMRI in non-human primates and humans, respectively, researchers have consistently found that this area is uniquely associated with encoding a diverse array reward and cost signals, including signals apparently related to effort costs (Kennerley et al. 2006, 2009, 2011; Arulpragasam et al. 2018; Klein-Flügge et al. 2016; Bonnelle et al. 2015). More recently, however, it has been suggested that these associations may be driven by a shift in strategy (Heilbronner and Hayden 2016; Hayden 2019) – and perhaps a switch in value-based control (see below) than effort cost encoding per se.

It has been generally accepted that parallel, hierarchical, value-based decision-making systems exist in the brain, ranging from Pavlovian responses to detailed abstract reasoning (Rangel et al. 2008; Hunt and Hayden 2017; Hayden 2019). Further, it has been widely demonstrated that these systems vary substantially in their strengths and weakness related to bioenergetics and cognitive flexibility (Shenhav et al. 2017; Gershman 2021). A key substrate for adjudicating between

these possible decision-making systems is the dorsal aspect of anterior cingulate and surrounding dorsomedial prefrontal cortex (dACC/dmPFC) (Vincent et al. 2008). The dACC/dmPFC in particular may act as a critical nexus for updating value-based decisions with the richer, model-based representations maintained in lateral prefrontal cortex (Shenhav et al. 2013; Medalla and Barbas 2009; Hayden 2019). This is consistent with substantial data across species and imaging modalities showing that dACC/dmPFC becomes active following an error (suggesting the need to alter an existing strategy) (Kolling et al. 2012; Walton et al. 2009; Heilbronner and Hayden 2016; Bryden et al. 2019) as well as when choosing between two nearly equivalent options (high "choice difficulty") (Shenhav et al. 2013, 2014). Consequently, this region may play a critical role in motivated behavior that is somewhat distinct from striatal DA. That is, rather than driving action toward a given stimulus, it may be involved in prompting a more granular assessment of a given stimulus within a broader evaluation of an organism's current state, needs, and strategy.

4 Implications in Psychopathology and Treatment

A key challenge for the translation of these preclinical and human cognitive neuroscience literatures to clinical research continues to be the lack of symptom measures that adequately dissociate among different aspects of impairment, such as low motivation or impaired decision-making. There is a wide range of clinical evidence suggesting that patients with a common diagnosis of depression may experience anhedonia in distinct ways. While early instruments for anhedonia assessment such as the Chapman anhedonia scales (Chapman et al. 1976) and the Snaith-Hamilton Pleasure Scale (SHAPS (Snaith et al. 1995)) emphasized a capacity for "hedonic experience," more recent instruments such as the Temporal Experience of Pleasure scale (TEPS Gard et al. 2007), Apathy Motivation Index (AMI Ang et al. 2017), and Dimensional Anhedonia Rating Scale (DARS (Rizvi et al. 2015)) have found evidence for multiple domains of impairments, including motivation, anticipation, and sociality, and have found clear evidence for severe reported impairment across all domains (Rizvi et al. 2015; Olino et al. 2018; Ang et al. 2017). The presence of motivational and consummatory subdomains has also been supported by structured interviews, for which the Clinical Assessment Interview for Negative Symptoms (CAINS) is likely the gold-standard (Watson et al. 2020; Kring et al. 2013), and historical analysis of clinical phenomenology in depression (Kendler 2016).

While some improvements have been made in terms of assessing motivational and consummatory aspects of psychopathology (for a review, see Wang et al. 2022), there are likely limitations to the extent to which individuals can report on these subtle distinctions with high accuracy. This is almost certainly true in terms of decisional deficits related to the (often subconscious) competition between multiple value-based control systems. Though less well-studied than motivational or consummatory deficits, evidence for decisional deficits has been observed using structured interview methods (e.g., the DSM V A8. "impaired concentration" criterion for

depression (American Psychiatric Association 2013)) as well as evidence from a wide range of decision-making tasks. Individual studies (Mukherjee et al. 2020) and meta-analyses (Halahakoon et al. 2020) of multiple decision-making tasks have all found evidence for generalized sub-optimal performance in patients with depression and schizophrenia relative to controls, consistent with a broad deficit in the integration of relevant information to guide behavioral choices. One explanation for this general decision-making deficit is that some patients may experience selective difficulty in adjudicating between these different value-control systems, which may manifest in over-reliance on Pavlovian or habit-based systems and a subjective experience of "indecision" or "poor concentration".

Such decision-making deficits are important to understand, as they may superficially appear indistinguishable from basic effort aversion. As an example, one recent paper from our group (Cooper et al. 2019) applied a series of computational models to choice behavior during the EEfRT (Treadway et al. 2009). Unlike standard analyses of effort-based tasks that focus on *what* choices individuals make, this modeling approach permits inferences regarding *how* individuals make choices using a two-step analysis. In step 1, we compared the fit of a Subjective Value model to a very simple Bias model to identify participants who do not use reward, effort, and probability information systematically when making effort choices. The Subjective Value model uses the reward, probability of receipt, and required effort of each option to estimate subjective values that are used to guide choice, while the Bias model does not utilize any trial-wise information and represents unsystematic effort allocation. In step 2, individual parameters reflecting devaluation of reward (e.g., k discounting parameter) were compared across individuals who systematically allocated effort. In two independent samples of patients with schizophrenia (total $n = 153$), we found differences in model fit (Bayesian information criteria; BIC) were associated with measures of cognition, while a parameter for effort discounting (k) was associated with negative symptoms of low motivation. Interestingly, the association between k and measures of motivational impairments was significantly greater than the association between k and items associated with deficits in consummatory pleasure (Cooper et al. 2019).

It is also worth noting that while anhedonia subdomains may lead to different "sub-groups" of individuals in some cases, most data suggest that it may be more common for individuals to exhibit co-morbidity across anhedonia subdomains. For example, the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project published a series of papers exploring the psychometric aspects of DSM criteria as compared to alternative assessment criteria for depression using a structured interview in a sample of 1,523 subjects (McGlinchey et al. 2006). Overall, endorsements of anhedonia subdomains were high, with 731/829 (88%) of individuals meeting criteria for MDD endorsing diminished drive (MA), 81.7% endorsing impaired concentration, 80% endorsing the commonly used hybrid of "diminished interest or pleasure", and 21.5% endorsing a lack of reactivity to positive events (Mitchell et al. 2009). These data suggest that anhedonia subdomains as assessed by self-report may frequently overlap within individuals, while also being partially independent constructs. Similar results have been observed with self-report

measures such as the TEPS and DARS for which a high degree of covariance has been observed among anhedonia subdomains, despite factor-analytic evidence suggesting that the use of multi-factorial approaches yield superior model fits over single-factor models (Hallford and Austin 2020; Rizvi et al. 2015). Finally, we note that these subdomains likely exhibit a degree of dynamic interaction. For example, prior studies suggest that initial choices may shape subsequent preferences (Ariely and Norton 2008), and that receipt of larger-than-expected rewards may alter the perception of effort (Pooresmaeili et al. 2015).

Despite these measurement challenges, precision treatment strategies may depend on the appropriate isolation of patient-specific circuit deficits. Growing efforts should be made to develop behavioral measures and/or passive data collection methods that can isolate behavioral signatures of deficits that can be separably mapped onto distinct circuits.

4.1 Treatment Development: Animal Models

Tests of effort-related decision-making also have been used to model motivational symptoms seen in a variety of psychopathologies. In contrast to the effects of local accumbens overexpression of DA D2 receptors in adult animals, overexpression of D2 receptors in striatal medium spiny neurons throughout development produces the opposite effect, reducing behavioral activation and exertion of effort (Ward et al. 2012). Mice that overexpress D2 receptors show reductions in progressive ratio responding (Drew et al. 2007; Simpson et al. 2011), and a low-effort bias in tests of effort-based choice (Ward et al. 2012). However, these animals do not show blunting of the hedonic reactivity to food rewards, or changes in appetite or food preference. Filla et al. (2018) showed that D2 overexpression impaired effort-based, but not value-based decision-making. These motivational impairments in D2 receptor overexpressing mice could be useful for modeling some of the negative symptoms of schizophrenia (Simpson et al. 2012; Filla et al. 2018).

TBZ is used to treat Huntington's disease and can produce depressive symptoms including anergia and fatigue in humans (Frank 2009, 2010; Guay 2010; Chen et al. 2012). Formal animal models of effort-related motivational dysfunction have been developed using TBZ to impair effort-related aspects of motivation, which are particularly suited for preclinical exploration of drug treatment strategies. While the low-effort bias induced by TBZ in rats was not reversed by SERT or NET inhibitors (Yohn et al. 2016a, b), it was reversed by a wide array of drugs that block DAT (Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2015a, b2016a, b, c; Salamone et al. 2016a, b). Drugs that inhibit DAT, including the antidepressant bupropion, can also enhance selection of high-effort PROG responding on EBDM tasks (Sommer et al. 2014; Randall et al. 2015; Yohn et al. 2016d). These findings are consistent with the well characterized role of DA in EBDM (see section above), and also with clinical studies showing that motivational functions in depressed people can be improved by the catecholamine transport inhibitor bupropion

(Papakostas et al. 2006; Pae et al. 2007) and DAT blockers such as amphetamines or methylphenidate (e.g., Stotz et al. 1999; Bahji and Mesbah-Oskui 2021).

While cocaine is viewed as a "classical" DAT inhibitor, there is an emerging interest in novel "atypical" DAT blockers, such as analogs of GBR12909, benztropine, and modafinil (Schmitt and Reith 2011; Cao et al. 2016; Kalaba et al. 2020; Newman et al. 2021). These novel compounds can differ from cocaine in terms of their binding site on the DAT protein, binding kinetics, functional interaction with DAT, and the magnitude and duration of the elevation of extracellular DA (Desai et al. 2005a, b; Tanda et al. 2013a, b; Schmitt et al. 2008; Kohut et al. 2014), which may offer advantages in terms of clinical utility. Recent papers have assessed the effort-related effects of the novel atypical DAT inhibitors *(S)*-CE-123, (S,S)-CE-158, and CT-005404. All three compounds reversed the low-effort bias induced by TBZ, and also increased selection of high-effort PROG lever pressing while decreasing chow intake (Rotolo et al. 2019, 2020, 2021). These compounds also produced modest but significant increases in extracellular DA in nucleus accumbens core, with CT-005404 having a particularly long-lasting effect. Moreover, CT-005404 also reversed the suppression of lever pressing induced by the pro-inflammatory cytokine IL-1β (Rotolo et al. 2021). Along with adenosine A2A antagonists such as istradefylline and preladenant (Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2015a; Salamone et al. 2018), and D1 agonists (Yohn et al. 2015b), atypical DAT inhibitors offer promise as potential treatments for effort-related motivational symptoms.

4.2 Effects of Dopaminergic Manipulations in Animal Models: Anhedonia or Avolition/Anergia?

One tendency that is common in the literature would be to label any impairment in instrumental behavior induced by interference with DA transmission as an effect on "reward," or "anhedonia." However, a detailed examination of the specific findings from EBDM studies clearly demonstrates that such descriptors do not provide an accurate explanation of the research results. The shift from lever pressing to chow intake after DA depletion or low doses of DA antagonists and TBZ is not occurring because of a shift in food preference in rats (Salamone et al. 1991; Nunes et al. 2013) or mice (Yang et al. 2020b). Also, the low-effort biases produced by interference with DA transmission in rats and mice tested on the effort-based choice tasks do not resemble the effects of conditions that blunt primary food motivation, such as appetite suppressant drugs (Salamone et al. 2002; Sink et al. 2008; Randall et al. 2012, 2014), or reinforcer devaluation by pre-feeding (Randall et al. 2012, 2014; Correa et al. 2016; Yang et al. 2020a, b). In fact, appetite suppressants and reinforcer devaluation by removal of food restriction yield insights into what manipulations that blunt primary food reinforcement actually do; they suppress both food intake and food-reinforced behavior.

With versions of the operant choice task that use different concentrations of sucrose as the reinforcer options, or with the RW/sucrose choice tasks, DA antagonists and TBZ reduced lever pressing and wheel-running, but actually increased intake of the alternative choice (a lower concentration of sucrose, or sucrose pellets; Pardo et al. 2015; Correa et al. 2016; Carratalá-Ros et al. 2020). Nevertheless, these drugs did not alter sucrose intake or preference in two-bottle tests, and TBZ did not alter appetitive (i.e., hedonic) taste reactivity for sucrose. TBZ also did not reduce binge-like eating of chocolate in non-restricted rats (Salamone et al. 2022). In the T-maze barrier choice studies, DA antagonism or depletion reduced selection of the arm with the barrier when the other arm contained a lower reinforcement density. However, these conditions did not alter choice when the other arm contained no food, or when both arms had a barrier (Salamone et al. 1994; Cousins and Salamone 1994; Pardo et al. 2012; Yohn et al. 2015a), indicating that control of choice behavior by reinforcement magnitude was still intact, and also that animals were still capable of climbing the barrier. Trifilieff et al. (2013) found that enhanced D2 receptor expression in the accumbens during adulthood increased exertion of effort for food reward without altering consummatory behavior, or the representation of the value of the reinforcer. Vancraeyenest et al. (2020) used a double-infection viral vector technique to inactivate the DA pathway projecting from VTA to the accumbens in monkeys, and observed that the monkeys were less likely to select high-effort cues in a choice task, but reinforcement learning was not affected. Bailey et al. (2020) developed instrumental tasks for isolating the separate impacts of effort and value manipulations on cost-benefit decision-making. In one task, mice could choose between exerting two distinct types of effort, while in the other task, mice made the same type of response to earn rewards with different intrinsic values. Haloperidol altered effort-based, but not value-based decision-making.

In summary, the effects of low doses of DA antagonists administered systemically or into nucleus accumbens, as well as neurotoxic or pharmacological depletion of accumbens DA, interact powerfully with the physical effort requirements of the instrumental response, but depend very little upon changes in primary food motivation. This also is true of studies involving conventional FR schedules with varying ratio requirements. While total lever pressing on an FR1 schedule was unaffected by accumbens DA depletion, performance on FR16 and FR64 schedules was severely impaired, an effect known as *ratio strain* (Aberman and Salamone 1999). But the pattern of effects on the same FR schedules produced by reinforcer devaluation via pre-feeding was completely different, with FR1 responding showing great sensitivity to this manipulation. A behavioral economic interpretation of these findings would be to state that these DAergic manipulations are not exerting their effects on instrumental behavior by reducing the value of food per se. Rather, they are affecting selection of the instrumental response by altering elasticity of demand, and reducing the willingness to pay the costs necessary for overcoming the response constraints, in a manner analogous to a loss of buying power (i.e., diminished behavioral resources available for allocation, see Salamone et al. 2017, 2018).

Thus, it seems misleading to use the term anhedonia to describe situations in which animals show reduced selection of vigorous instrumental actions, but

low-effort instrumental responses, food intake, food or sucrose preference, binge-like eating of palatable foods, and appetitive taste reactivity are relatively intact (see also extensive work from Berridge (2007) and Berridge and Robinson (2003) on *wantin*g vs. *liking*). Terms such as fatigue, anergia (lack of energy), and avolition, which are widely used in the clinical literature, seem much more appropriate (see also Simpson et al. 2012). In fact, the clinical literature focusing on negative symptoms of schizophrenia emphasizes that anhedonia (reduced experience of pleasure) and avolition (reduced goal-directed activity due to decreased motivation) are psychometrically distinct (Correll and Schooler 2020). Human studies in healthy volunteers have reported that haloperidol induces avolition (Mas et al. 2013), and it is possible that DA antagonists can worsen avolition as a secondary effect in some schizophrenic patients. In a factor-analytic study of assessment results from depressed patients, Gullion and Rush (1998) identified a "*lack of energy*" factor that was related to problems such as low energy/increased fatigability, inability to work, and psychomotor retardation. This factor was the one that loaded most strongly onto a second-order factor for general depression. In order to understand how animal research on effort-based choice translates to human clinical studies, it is important to realize that relatively specific manipulations such as DA antagonists and TBZ are not mimicking human disorders in a broad sense, but rather, are producing effects that correspond to specific symptoms. This view is consistent with the NIMH Research Domain Criteria (RDoC) approach.

5 Conclusions

The goals of this chapter have been to summarize our current understanding of the molecular and circuit mechanisms that support effort-expenditure and effort-based decision-making. We have also sought to highlight the application of this knowledge toward the understanding of transdiagnostic pathophysiology related to motivational impairments, and their potential treatment. Future work will be needed to further refine these intervention targets so as to maximize the translational impact of this work.

Acknowledgments/Disclosures This work was supported by grants from the NIMH. In the past 2 years, MTT has served as a consultant for Blackthorn Therapeutics and Boehringer-Ingelheim. Additionally, MTT is a co-inventor of the EEfRT, which was discussed in this chapter. Emory University and Vanderbilt University licensed this software to BlackThorn Therapeutics. Under the IP Policies of both universities, Dr. Treadway receives licensing fees and royalties from BlackThorn Therapeutics, and JDS has received grants from Blackthorn, Psychogenics, Noema, Chronos, Lundbeck, and Acadia.

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Probabilistic Reinforcement Learning and Anhedonia

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Contents

Abstract Despite the prominence of anhedonic symptoms associated with diverse neuropsychiatric conditions, there are currently no approved therapeutics designed to attenuate the loss of responsivity to previously rewarding stimuli. However, the search for improved treatment options for anhedonia has been reinvigorated by a recent reconceptualization of the very construct of anhedonia, including within the Research Domain Criteria (RDoC) initiative. This chapter will focus on the RDoC Positive Valence Systems construct of reward learning generally and sub-construct of probabilistic reinforcement learning specifically. The general framework emphasizes objective measurement of a subject's responsivity to reward via reinforcement

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Curr Topics Behav Neurosci (2022) 58: 355–378
https://doi.org/10.1007/7854_2022_349
Published Online: 19 April 2022

learning under asymmetrical probabilistic contingencies as a means to quantify reward learning. Indeed, blunted reward responsiveness and reward learning are central features of anhedonia and have been repeatedly described in major depression. Moreover, these probabilistic reinforcement techniques can also reveal neurobiological mechanisms to aid development of innovative treatment approaches. In this chapter, we describe how investigating reward learning can improve our understanding of anhedonia via the four RDoC-recommended tasks that have been used to probe sensitivity to probabilistic reinforcement contingencies and how such task performance is disrupted in various neuropsychiatric conditions. We also illustrate how reverse translational approaches of probabilistic reinforcement assays in laboratory animals can inform understanding of pharmacological and physiological mechanisms. Next, we briefly summarize the neurobiology of probabilistic reinforcement learning, with a focus on the prefrontal cortex, anterior cingulate cortex, striatum, and amygdala. Finally, we discuss treatment implications and future directions in this burgeoning area.

Keywords Anhedonia · Animal models · Medications development · Probabilistic reinforcement schedules · Reverse translation · Reward learning

1 Introduction

1.1 Anhedonia: Definition and Statement of Problem

Anhedonia is traditionally defined as the loss of pleasure or lack of reactivity to previously rewarding stimuli. Although often associated with major depressive disorder (MDD; American Psychiatric Association 2013), its transdiagnostic relevance has emerged across neuropsychiatric conditions, including schizophrenia (Moran et al. 2022), bipolar disorder (Whitton and Pizzagalli 2022), post-traumatic stress disorder (Vinograd et al. 2022), anxiety disorder (Taylor et al. 2022), substance use disorders (Koob 2022; Gilbert and Stone 2022), eating disorders (Murray et al. 2022), neurodevelopmental disorders (Dichter and Rodriguez-Romaguera 2022), and neurodegenerative disorders (Turner and Husain 2022). Unfortunately, there are no approved treatments for anhedonia and first-line antidepressants such as selective serotonin reuptake inhibitors (SSRI) are typically ineffective at increasing hedonic tone in MDD (Calabrese et al. 2014). Therefore, a critical need for effective therapeutics to treat anhedonic conditions has inspired coordinated bi-directional research efforts between clinical investigations and animal models designed to optimize assays of relevant phenotypes (Der-Avakian et al. 2016; Silverman et al. 2020).

1.2 Using Probabilistic Contingencies to Examine Anhedonia

The search for improved treatment options for anhedonic individuals has been catalyzed by an important reconceptualization of the very construct of anhedonia in the latest revision (National Institute of Mental Health 2016) of the Research Domain Criteria (RDoC; Insel et al. 2010). This chapter will focus on the Positive Valence Systems construct of *reward learning* generally and sub-construct of *probabilistic reinforcement learning* specifically. Blunted reward responsiveness is a hallmark feature of anhedonia and examining a subject's responsivity to reward via reinforcement learning under asymmetrical probabilistic contingencies yields an objective probe to quantify reward learning. Indeed, a recent meta-analysis found that blunted reward bias was the metric most consistently associated with MDD (Halahakoon et al. 2020). In turn, these techniques can reveal neurobiological mechanisms and inform novel approaches to treat MDD and other neuropsychiatric conditions prominently characterized by anhedonic phenotypes and reductions in reward learning. In this review, we first explain how investigating reward learning can improve our understanding of anhedonia. To this end, we describe the four recommended tasks chosen for the reward learning subdomain of the Positive Valence Systems in the latest revision of the RDoC (NIMH 2016). These paradigms are used to probe sensitivity to probabilistic contingencies and their influence on choice behavior, and how such behavior is disrupted in various neuropsychiatric conditions. We then discuss promising examples of reverse translation of probabilistic assays in laboratory animals and the mechanistic understanding they have uncovered. Next, we summarize the neurobiology of probabilistic reinforcement learning, with a focus on the prefrontal cortex (PFC), anterior cingulate cortex (ACC), striatum, and amygdala. We end by discussing treatment implications and future directions in this burgeoning area.

2 How Probabilistic Contingencies Inform the Study of Anhedonia and Its Symptoms

This section highlights findings from the four RDoC-recommended behavioral tasks that have been designed to probe the reward learning subdomain across clinical populations. It should be noted that these empirical efforts are a significant departure from traditional clinical assessments and diagnostic tools that primarily rely on self-report questionnaires (Wang et al. 2022). Importantly, although the tactics vary among the tasks highlighted below, the approaches share a common strategy that emphasizes probabilistic reinforcement contingencies as an objective means to quantify responsivity to reward and participants' ability to learn from consequences, as well as investigate these processes across neuropsychiatric disorders.

2.1 Probabilistic Reward Task

The Probabilistic Reward Task (PRT) developed by Pizzagalli et al. (2005; modified after Tripp and Alsop 1999; see also Henriques et al. 1994) is a laboratory procedure designed to provide a quantitative measure of reward learning (i.e., ability to modulate behavior as a function of reinforcement history). The PRT uses probabilistic discrimination methodology to quantify responsiveness to changes in reinforcer frequency. In the prototypical computerized task, human participants are instructed to discriminate between two briefly presented mouths that vary minimally in length on a cartoon face. Unbeknownst to the participants, probabilistic contingencies are arranged so that correct responses on one alternative are rewarded 3 times more often (e.g., long line: rich alternative) than correct responses on the other alternative (e.g., short line: lean alternative). As predicted by signal detection theory (Luc et al. 2021; McCarthy and Davison 1979), healthy control participants consistently develop a response bias in favor of the rich alternative and do so without disruption in overall task discriminability (i.e., performance accuracy; Pizzagalli et al. 2005, 2008b).

During the last 17 years, the PRT has been widely used across laboratories and is one of the most common probabilistic reinforcement learning tasks used to study clinical populations (>85 empirical publications). Among others, selected studies have shown that response bias toward the more frequently rewarded stimulus: (a) is inversely related to current anhedonic symptoms in unselected adults (e.g., Pizzagalli et al. 2005), relatives of patients with MDD (Liu et al. 2016), and in a transdiagnostic sample with depression and anxiety disorders (Reilly et al. 2020); (b) predicts self-reported anhedonic symptoms 38 days later (Pizzagalli et al. 2005) and a diagnosis of MDD 8 weeks later (Vrieze et al. 2013); (c) is blunted in individuals with increased depressive symptoms (Pizzagalli et al. 2005), current MDD (e.g., Pizzagalli et al. 2008c; Vrieze et al. 2013, Liu et al. 2011; but see Reilly et al. 2020), and past MDD (e.g., Liu et al. 2011, 2016; Pechtel et al. 2013; but see Audrain-McGovern et al. 2014), particularly those with elevated anhedonic symptoms (Vrieze et al. 2013) or melancholic depression (Fletcher et al. 2015); (d) is blunted in youth reporting anhedonia across various DSM diagnoses (Morris et al. 2015) and individuals with PTSD and elevated anhedonia (Eskelund et al. 2018) but not schizophrenia (e.g., Barch et al. 2017); (e) is linked to functional, electrophysiological, and molecular markers within mesolimbic pathways (e.g., Bogdan et al. 2011; Santesso et al. 2009; Kaiser et al. 2018); (f) is potentiated by pharmacological challenges hypothesized to increase dopaminergic signaling (e.g., nicotine, amphetamine, k-opioid receptor antagonism) in both humans and rats (e.g., Barr et al. 2008; Der-Avakian et al. 2013; Kangas et al. 2020; Krystal et al. 2020; Lamontagne et al. 2018); (g) is reduced by pharmacological challenges hypothesized to decrease dopaminergic signaling in both humans and rats (e.g., Der-Avakian et al. 2013; Grob et al. 2012; Lamontagne et al. 2018; Pizzagalli et al. 2008a); and (h) is amenable to computational modeling that allows to parse reward sensitivity and learning rate (e.g., Huys et al. 2013).

2.2 *Probabilistic Stimulus Selection Task*

The Probabilistic Stimulus Selection Task (PSST) developed by Frank et al. (2004) is also a computerized task using visual discrimination methodology and probabilistic conditions. This laboratory protocol consists of two phases. First, in the *acquisition phase*, subjects are presented with three different stimulus pairs across trials that have varied asymmetric probabilistic contingencies arranged (A:B, 80%:20%; C:D, 70%:30%; E:F, 60%:40%). Following discrimination mastery, subjects are then exposed to a *transfer test phase* in which they are presented with the same stimuli, but in novel arrangements and without feedback, to enable examination of whether response biases that emerge are a function of *choosing* the more frequently rewarded (rich) stimulus or *avoiding* the less frequently rewarded (lean) stimulus. This task was originally designed to characterize reward learning via positive vs. negative feedback in patients with Parkinson's disease while either unmedicated or medicated with L-dopa. These initial studies verified the expected findings in reward responsiveness (i.e., the inability to learn from trial and error); however, this task was also able to reveal selectivity in the effects of positive vs. negative feedback. Specifically, impairment in learning under probabilistic contingencies was driven by insensitivity to positive feedback when unmedicated relative to their performance under medicated conditions and, also, sensitivity to negative feedback under unmedicated conditions that was greater than when medicated (Frank et al. 2004). These observations of functional segregation between responses to positive and negative outcomes, in turn, were examined further using computational models to mechanistically interrogate the so-called "Go" and "NoGo" dopaminergic signaling pathways, primarily in the basal ganglia which has well-known dopamine depletion in Parkinson's disease patients (Frank 2005).

The value of this experimental framework was extended in patients with schizophrenia (Waltz et al. 2007), a clinical population also known to have dopamine dysfunction in the basal ganglia and, often more critically, in the prefrontal cortex (Weinberger 1987; Weinberger and Berman 1988). These system deficits have been long associated with poor reinforcement learning rates, anhedonic phenotypes, and negative symptoms of schizophrenia (Kirkpatrick and Buchanan 1990). Pronounced deficits in prefrontal cortex function were indeed corroborated by an inability of most patients with schizophrenia to successfully learn to discriminate between the standard PSST stimuli (Hiragana characters) used in the studies with Parkinson's patients highlighted above. However, patients with schizophrenia were able to successfully engage with a task variant that used more familiar clip art images as stimuli (which could, however, introduce working memory requirements that could make result interpretations challenging). In addition, the modified task confirmed reduced reward learning in patients with schizophrenia. Specifically, reduced learning from positive, but not negative, outcomes were observed and have since been replicated (Dowd et al. 2016; see also Strauss et al. 2014 for a review on the role of reward learning in the motivational impairment of schizophrenic disorders).

The PSST has also been used to examine reward responsiveness in MDD participants. For example, Admon et al. (2017) conducted a randomized controlled trial in unmedicated depressed patients and healthy control participants receiving either placebo or a single, low dose of the D_2/D_3 receptor antagonist amisulpride (thought to increase dopamine signaling through presynaptic autoreceptor blockade). As hypothesized, depressed patients showed a reduced probability of selecting previously rewarding stimuli. However, despite the ability of amisulpride to potentiate corticostriatal functional connectivity (examined with fMRI) in response to monetary rewards in the same study, drug treatment did not modulate behavioral performance. Similarly reduced reward learning in PSST performance was also observed in a sample of women with remitted MDD and a history of childhood sexual abuse (Pechtel and Pizzagalli 2013), which included concurrent electrophysiological measurement; source-localized electroencephalographic (EEG) activity revealed blunted differentiation between correct and incorrect responses (feedback-related negativity and error-related negativity) and increased activation in the subgenual anterior cingulate cortex in the clinical sample. Cavanagh et al. (2019) extended our understanding of PSST performance in MDD participants by associating selective features of EEG responses to probabilistic reward and punishment by examining positive prediction errors (when the outcome is better than expected) and negative prediction errors (when the outcome is worse than expected). By teasing apart depressive and anxious dimensional aspects of MDD, the authors were able to document elevated anxiety as reliably associated with avoidance learning due to a tighter coupling of negative prediction error signaling (i.e., the mismatch between reward expectancy and actual reward omission) with punishment-specific EEG features (i.e., ERPs related to punishment stimuli and associated theta-band dynamics). Conversely, depressive symptoms were reliably associated with smaller reward-related EEG signature (i.e., smaller reward-specific ERPs and associated delta-band dynamics). These dissociations between diverse dimensions of MDD support further an RDoC view of multifaceted neuropsychiatric disorders.

More recently, Brown et al. (2021) examined in participants with MDD the ability of cognitive behavioral therapy (CBT) to improve probabilistic reward (and loss) learning during fMRI imaging of prediction error and value signaling in the striatum. Among the participants with MDD, expected reductions in reward learning rates, associations between prediction error and expected value in ventral striatum, and anhedonia were observed relative to healthy controls. Following CBT, participants with MDD exhibited expected reductions of anhedonic and negative affect symptoms and, as well, significantly higher reward learning rates and ventral striatum signaling to prediction error and expected value. Moreover, a correlation was observed between reported symptom change and task-related behavioral and neural responses, thus demonstrating that this nonpharmacological treatment strategy can have desirable effects on reinforcement learning processes. Importantly, however, inconsistent findings have been observed when examining behavioral and neural responses to probabilistic reinforcement conditions in participants with MDD. For example, Rutledge et al. (2017) found no evidence of reward learning reduction

using fMRI, computational modeling, and smartphone-based metrics between depressed participants and healthy controls in monetary earnings, choice accuracy, and reaction times, nor were differences observed in reward prediction errors in BOLD responses in the reward-relevant regions of interest in the ventral striatum.

Interestingly, healthy subjects also display blunted reward responsivity in the PSST following acute exposure to stressful conditions, which are known etiological factors in MDD (Hammen 2005). For example, Berghorst et al. (2013) examined the effects of threat-of-shock experimental protocols in healthy female subjects on self-report measures, cortisol, and PSST performance. Although not all subjects had expected elevations in self-reported stress or elevations in cortisol, those who were sensitive to the laboratory stressor were characterized by blunted learning from reward, but not punishment, as assayed by the PSST.

2.3 Probabilistic Pavlovian Conditioning Task

Examination of Pavlovian conditioning can provide insight into additional aspects of fundamental adaptive behavior that, unlike operant conditioning, allows for assessments of reward learning during passive stimulus-response exposure rather than through volitional behavioral responses determined by programmed response-reinforcement contingencies. Although there are numerous ways to arrange classical conditioning paradigms (Bouton 2016; Pavlov 1927), in keeping with the theme of this chapter, O'Doherty et al. (2004) promulgated a probabilistic variant of a Pavlovian conditioning task which has been subsequently refined for use in clinical studies of anhedonic phenotypes. The task was initially developed to serve as a control condition for a probabilistic operant task designed to examine the extent to which the ventral and dorsal striatum contributes to instrumental conditioning. In the operant task, subjects are exposed to two trial types: either reward trials or neutral trials. During reward trial types, one of two stimuli is presented that was either associated with a relatively high (60%) or a relatively low (30%) probability of obtaining a palatable juice reward. During neutral trial types, subjects are presented with two different stimuli that are also associated with either a relatively high (60%) or a relatively low (30%) probability of obtaining a neutral tasteless solution. In the probabilistic Pavlovian conditioning task, subjects are exposed to the same conditions, but in a passive manner with the computer making the selection that exposed the subject to what would become conditioned stimuli immediately preceding either palatable or neutral stimuli. Because the ventral striatum has been long associated with reward learning and motivation (Cardinal et al. 2002), whereas the dorsal striatum is implicated in learning stimulus-response associations (Packard and Knowlton 2002), the active (operant) and passive (Pavlovian) tasks were conducted under fMRI conditions to examine reward learning, during both variants of conditioning, in the striatum. And, indeed, behavioral and neuroimaging outcomes largely supported these dissociable roles.

The general approach of including assessments of Pavlovian mechanisms in the behavioral and neural study of anhedonia was subsequently advanced by Kumar et al. (2008). Dopaminergic function has been long known to encode highly specific and brief phasic reward learning signals to unconditioned reinforcers and, as well, track behavioral measures of classical conditioning until the conditioned response produces dopamine release following the conditioned stimulus alone (Montague et al. 1996; Schultz 2002; Schultz and Dickinson 2000; McClure et al. 2003; Tobler et al. 2006). These mechanisms have been repeatedly documented to be blunted in MDD populations (Gershon et al. 2007; Gradin et al. 2011). Therefore, dysfunction in phasic reward learning signals was interrogated by Kumar et al. (2008) in medicated but SSRI treatment-resistant MDD patients and in healthy control subjects following acute treatment with the antidepressant citalopram. Computer-based photographic stimuli served as conditioned stimuli (A and B), which were presented prior to small volume water deliveries in fluid-deprived subjects. Probabilistic schedules associated with the conditioned stimuli and water delivery were systematically varied across five 20-trial blocks (e.g., A:B, 80%:0%; A:B, 50%:20%; A:B, 0%:90%; A:B, 20%:20%; A:B, 80%: 0%) to allow for repeated measures of conditioning and re-conditioning of differing response strength during fMRI recording. Findings showed that patients with MDD had expected blunting in reward learning signals in the ventral striatum, rostral and dorsal anterior cingulate, retrosplenial cortex, midbrain and hippocampus, with a magnitude that correlated with anhedonic severity. In addition, they observed that acute administration of citalopram in healthy control subjects blunted reward learning and its associated neurophysiological activity, which is consistent with evidence that typical antidepressants initially suppress dopamine function before enhancing it following chronic treatment as illustrated by their well-known delayed onset of action (Taylor et al. 2006).

This probabilistic Pavlovian conditioning task was subsequently used in conjunction with fMRI to examine putative dopaminergic function associated with reward learning in the ventral striatum and ventral tegmental area. Computational modeling techniques revealed that in medication-free patients with remitted recurrent depression and a high risk of recurrence, greater anhedonia was significantly associated with lower prediction error-related activation of the ventral tegmental area, whereas greater anhedonia in healthy controls was associated with higher prediction error-related activation of the ventral tegmental area (Geugies et al. 2019). These findings are consistent with assumptions regarding the dissociation of MDD and anhedonia and the latter's resistance to frontline antidepressant treatment even when it successfully reduced depressive symptoms and led to remission (Admon and Pizzagalli 2015; Calabrese et al. 2014). In other studies that paired the probabilistic Pavlovian conditioning task with fMRI to assess reward value encoding and event-related connectivity, Rupprechter et al. (2021) observed in unmedicated participants with MDD both blunted striatal activation following presentation of reward and negative encoding of reward value in the hippocampus and rostral anterior cingulate cortex, thus, suggesting an impaired communication between these areas as a possible culprit in the subjective valuation of rewards in MDD. Finally, probabilistic Pavlovian conditioning tasks have also been modified to examine both appetitive and

aversive outcomes under fMRI conditions and using computational modeling. For example, in studies designed to investigate how the habenula encodes negative value of stimuli associated with punishment contingencies, healthy participants (Lawson et al. 2014) and unmedicated patients with current MDD (Lawson et al. 2017) were exposed to abstract computerized images that were followed by probabilistically high (75%) or low (25%) positive (e.g., win money), negative (e.g., lose money, painful electric shock), or 100% neutral outcomes. Findings showed that habenula activation increased in response to conditioned stimuli more strongly predictive of negative outcomes, especially electric shock; however, the opposite was observed in participants with MDD (i.e., habenula activation decreased in the presence of conditioned stimuli more strongly predictive of shock). Moreover, habenula volume was negatively correlated with self-reported anhedonic symptoms in participants with MDD, leading the authors to speculate that habenula dysfunction may contribute to a poorer ability to avoid aversive stimuli, thereby, exacerbating MDD symptomology.

2.4 Drifting Double Bandit Task

The Drifting Double Bandit task (also known as the Two-step task) was developed by Daw et al. (2011) and designed to examine another aspect of reward learning, namely, a subject's reliance on goal-directed behavior versus habit-based behavior (e.g., inflexible responding based on previously experienced contingencies). This task consists of two stages. In the first stage, the subject is presented with two visual stimuli (A and B). A fixed probability is programmed for the stimulus pair such that a response to stimulus A results in a second stimulus pair (C and D) 70% of the time or another stimulus pair (E and F) 30% of the time, whereas a response to stimulus B results in a second stimulus pair (C and D) 30% of the time or (E and F) 70% of the time. In this second stage, responses to C and D *or* E and F are rewarded with monetary outcomes that are programmed with variable probabilistic schedules that change slowly and independently throughout the session. This arrangement is designed to examine the extent to which subjects are relatively habit-based and make choices based on the fixed probabilities arranged during the first stage stimulus pair or relatively goal-directed and remain flexible in response allocation as the probabilities change during the second stage stimulus pairs. This task also lends itself well to computational modeling strategies that can be used to define a subject's response style to determine reward learning processes. Although the ability of this task to probe reward learning processes as they relate to anhedonic phenotypes in this subdomain is highly probable, there have yet to be any published reports using the Drifting Double Bandit expressly for this pursuit, despite it being a recommended task in the most recent RDoC revision (NIMH 2016).

3 Reverse Translation of Probabilistic Assays in Laboratory Animals

Given the correspondence between behavioral outcomes under probabilistic contingencies and anhedonic phenotypes across diverse clinical populations, there have been increasing efforts to reverse translate these tasks for use in laboratory animals. As reviewed above, although task performance in human participants has revealed critical information regarding neurophysiological mechanisms which, in turn, have allowed an ability to appraise novel behavioral and pharmacological treatment strategies, there is considerable value in the ability to conduct similar studies in animals while healthy and following conditions designed to produce anhedonic-like phenotypes. Functional similarities in task outcome are the primary objective; however, recent advances in apparatus technologies have also afforded the ability to maintain certain formalistic features of various computerized cognitive tasks. More generally, the expectation is that this coordinated bi-directional approach will help bridge the preclinical gap between therapeutic discovery and treatment (Der-Avakian and Pizzagalli 2018).

One prominent example of this approach has been the reverse translation of the PRT into rats and nonhuman primates. The first variant of this task designed for laboratory animals established a protocol using tone duration discriminations in rats which, after acquisition, were programmed with a 3:1 rich:lean probabilistic contingency modeled after the human task detailed above (Der-Avakian et al. 2013). Expected task outcomes were observed, including a reliable response bias toward the more richly rewarded stimulus alternative and a pharmacological blunting of the response bias following administration of low doses of pramipexole (thought to decrease dopaminergic signaling via presynaptic autoreceptor activation) as seen previously in humans (Pizzagalli et al. 2008a). Subsequent independent studies advanced this approach by documenting task sensitivity to chronic stress, with rats exposed to social defeat exhibiting a blunted response bias relative to non-stressed controls (Der-Avakian et al. 2017) and highlighted the role of dopamine and glucocorticoid systems in reward responsiveness (Lamontagne et al. 2018).

Subsequent efforts to reverse translate the PRT capitalized on recent advances in touchscreen technology (Kangas and Bergman 2017) to develop a task variant using visual line-length discriminations under probabilistic contingencies designed for rats (Kangas et al. 2020) and nonhuman primates (Wooldridge et al. 2021). In addition to enhanced formal similarity of the touchscreen-based animal task variant to the computerized human task, expected response biases were observed in both species that closely approximated values observed in humans. Subsequent drug studies using these reverse-translated PRT variants in laboratory animals have confirmed the ability of putative antidepressants and pro-hedonics, such as amphetamine, scopolamine, and ketamine, to dose-dependently enhance reward learning. These findings confirm and extend their therapeutic promise previously documented in clinical populations using traditional metrics (Jaffe et al. 2013; Kim et al. 2019; McIntyre et al. 2017). Most recently, studies in rats have confirmed the ability of the

touchscreen PRT to characterize enduring deficits in reward responsiveness during adulthood long after exposure to a rodent model of early-life adversity and simulated poverty (Kangas et al. 2022).

Reverse translation of the other probabilistic tasks highlighted in this chapter has either yet to be developed for use to examine anhedonic phenotypes or has yet to be subjected to extensive pharmacological and neurophysiological analysis in healthy and chronically stressed animals. Some tasks (e.g., the probabilistic Pavlovian conditioning task) should be relatively straightforward to adapt for laboratory animals with aims to study anhedonic phenotypes, whereas other tasks (e.g., the PSST) will likely require creative modifications given the well-documented difficulty in reliably establishing transfer of function in laboratory animals (Lionello-DeNolf 2009; Zentall et al. 2014). Nevertheless, as illustrated above, coordinated translational efforts studying clinical populations and animal subjects can yield complementary approaches and mutually beneficial advances from clinical observations and laboratory discoveries.

4 Neurobiological Mechanisms of Probabilistic Reinforcement Learning

Several studies in both humans and laboratory animals have implicated corticolimbic circuits, modulated primarily by dopamine, norepinephrine, and serotonin in probabilistic reinforcement learning. In this section, we will provide a brief overview of neurobiological mechanisms that underlie probabilistic reinforcement learning.

4.1 Prefrontal Cortex and Probabilistic Learning

Two areas of the prefrontal cortex (PFC) that are heavily implicated in decision-making processes associated with probabilistic reinforcement include the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). The OFC encodes reward value and responds to reward expectancy (Gottfried et al. 2003; Schoenbaum and Roesch 2005). Thus, the OFC is sensitive to both the magnitude and probability of future rewards, and lesions or pharmacological impairment of this area generally results in an inability to select optimal outcomes in the face of uncertainty, which may occur when the probability of obtaining a reward is relatively low (Mobini et al. 2002; Rogers et al. 1999a). For example, electrophysiological activity in the OFC is correlated with reward valence and expectancy (Hikosaka and Watanabe 2000; Schoenbaum and Roesch 2005; Kennerley et al. 2011). Similarly, in nonhuman primates, the magnitude of a reward modulates activity of OFC neurons, which can be modulated by reward expectancy and history (Saez et al. 2017). Moreover, cerebral blood flow is increased in the OFC in humans making a choice between

small rewards with a relatively high outcome probability and large rewards with a relatively low outcome probability (Rogers et al. 1999b). Lesioning the OFC in rats has been shown to increase risky decision-making and preference for uncertain rewards, whereby animals become more likely to respond for rewards that are large but have a relatively low probability (Stopper et al. 2014). Evidence suggests that this change in choice preference can be partially, but not exclusively, explained by deficits in reward valuation that are accompanied by OFC lesions (Stalnaker et al. 2015). That is, the OFC is important for coding reward expectancy under probabilistic conditions.

The ACC has also been implicated in signaling reward expectancy. In particular, the ACC is thought to code reward prediction errors, whereby a mismatch occurs between expected and actual reward outcomes (Hyman et al. 2017). Evidence in humans and nonhuman primates also suggests that the ACC codes for reward valuation as well (Amiez et al. 2006; Kolling et al. 2016). As with the OFC, inactivation of the prelimibic cortex (PrL) in rats, which is thought to approximate human ACC area 32/25, also increased risky decision-making, but only when the probability of reward decreased over time (St Onge and Floresco 2010). Interestingly, inactivation of this region decreased risky decision-making when reward probability increased over time, suggesting that the ACC plays an important role in updating reward probabilities based on outcome to help guide future decision-making. Thus, like the OFC, reward expectancy signals in the ACC may contribute to the coding of rewards of a particular magnitude and probability of outcome.

It is unlikely, however, that two distinct PFC regions play functionally identical roles with regard to reward expectancy. Differences between these two PFC areas may emerge in the rate at which they track reward probability, and thus expectancy, over time. Soltani and Izquierdo (2019) recently suggested that while the ACC may be responsible for rapid updating of reward probabilities based on immediate computation of unexpected events, the OFC may provide slower, longer-term updates on changes in reward valuation and expectancy. Alternatively, Winstanley and Floresco (2016) have suggested that the OFC plays a role in risky decision-making when one of the options includes an aversive stimulus, thereby promoting the value of the appetitive option. On the other hand, the ACC may help guide choices of two or more uncertain rewards to ensure maximal possible outcomes. Given that these two areas maintain reciprocal connections, it is important to also consider that discrete functional processes specific to one area are likely communicated to the other area to help guide decision-making during probabilistic reinforcement learning.

Both norepinephrine and serotonin appear to play neuromodulatory roles in the PFC with regard to reward expectancy signaling. Norepinephrine is thought to regulate the balance between exploitation and exploratory behavior as animals navigate different actions with varying probabilities of reward outcomes (Aston-Jones and Cohen 2005). The firing rates of noradrenergic cells originating from the locus coeruleus change with alternating reward contingencies. When reward outcomes are uncertain, tonic firing of noradrenergic cells facilitates alternating behavior from current actions that may be suboptimal to new actions that may produce

more certain outcomes (i.e., exploration; Aston-Jones et al. 1999). On the other hand, when reward outcomes become more certain, phasic firing of noradrenergic cells promotes optimized task performance (i.e., exploitation; Aston-Jones and Cohen 2005). Additionally, noradrenergic signaling in the orbitofrontal cortex may facilitate the learning of current or prior associative states (Sadacca et al. 2017). That is, the ability to recognize and adapt to changes in reward probabilities and expectations may require an understanding of different task states whereby different actions yield different outcomes depending on the task state. Maximizing reward outcomes requires actions to be implemented that are appropriate for a given state. The OFC is believed to mediate learning of these task states and may promote rapid learning under conditions of changing and unexpected reward contingencies.

Serotonin originating from the midbrain dorsal raphe nucleus (DRN) is also involved in reward expectancy and probabilistic learning and may regulate the timescale of reward predictions (Miyazaki et al. 2020). Whereas midbrain dopamine activity encodes prediction error signals, serotonin is believed to modulate the degree to which these prediction error signals for uncertain outcomes are integrated into action. Given the dense reciprocal connections between the dorsal raphe nucleus and OFC, it is possible that this serotonergic modulation of prediction error signaling is at least partially mediated by the OFC.

4.2 Striatum and Probabilistic Learning

Both ventral and dorsal striatum, which form corticostriatal loops with the PFC areas described above, appear to be involved in probabilistic reinforcement learning. In humans, parts of the midbrain that send dopaminergic projections to the NAc respond to stimulus uncertainty, and activity of these dopaminergic cells correlates with reward probability (Dreher et al. 2006). Moreover, increasing reward probability is associated with increased blood flow in the striatum in humans (Abler et al. 2006). Consistent with these findings in humans, lesions of the NAc in rats promote risk-aversive behavior by biasing choices away from large rewards with a low probability of occurrence and toward small rewards with a high probability of occurrence, while discrimination of the reward value of different choices remains largely intact (Cardinal and Howes 2005). Interestingly, despite the role of the shell subregion of the NAc in processing the hedonic value of rewards, the suppression of risky behavior described above was specific to the core subregion of the NAc, as NAc shell lesions had no effect on choice behavior based on reward probability. In both nonhuman primates (Costa et al. 2016) and rodents (St Onge et al. 2012), lesions of the dorsal striatum also impaired learning during probabilistic, but not deterministic, reward schedules. Much of the role of the striatum in signaling reward expectancy has focused on the neurotransmitter dopamine. Midbrain dopamine neuronal activity encodes the mismatch between expected and actual reward error signals (Schultz et al. 1997). That is, during positive prediction errors, the firing of

midbrain dopamine neurons is increased, whereas during negative prediction errors, firing of midbrain dopamine neurons is reduced. Thus, either too much or too little dopamine signaling may disrupt prediction error processing, thereby impairing learning during activities with unexpected or probabilistic reward schedules.

4.3 Basolateral Amygdala (BLA) and Probabilistic Learning

Evidence suggests that the BLA represents expected reward valuation and learning from changes in the expected value of rewards (Stolyarova and Izquierdo 2017). As described above, the OFC is also involved in coding the valuation of rewards, and it may do so via reciprocal connections with the BLA. Inactivation of the BLA in rats results in a shift toward risky decision-making, although this effect may not just rely on the value of positive outcomes. For example, if a particular choice leads to negative or aversive events, the BLA is thought to bias choice away from the aversive event. Further evidence supports the role of the BLA in rapidly detecting unexpected changes (positive or negative) to reward outcomes (Wassum and Izquierdo 2015). This rapid signaling of changes to expected reward outcomes could be mediated via reciprocal connections with the ACC, OFC, and insula. For example, amygdala connectivity with these cortical regions shifts preference toward smaller, certain rewards compared to larger, uncertain rewards (Ghods-Sharifi et al. 2009).

4.4 Overlapping Neural Circuits Underlying Probabilistic Learning and Anhedonia

The brain regions and neurotransmitters described above that support probabilistic reinforcement learning are strongly implicated in the symptom of anhedonia and several psychiatric disorders characterized by anhedonia. Activation of the OFC, and in particular the medial OFC that signals the value of rewards, is suppressed in MDD, impairing reward-related processes that likely contribute to the symptom of anhedonia. In contrast, the lateral OFC, which is responsible for signaling non-reward or aversive outcomes, is overactive in depression (e.g., Rolls 2019). Thus, suppression and potentiation of OFC subregions responsible for computing the value of rewarding and aversive outcomes, respectively, are thought to bias an individual with depression away from pleasant experiences and toward negative states. Indeed, the acute administration of the rapid-acting antidepressant ketamine in patients with treatment-resistant depression suppressed lateral OFC activity, and this suppression correlated with the alleviation of anhedonia (Lally et al. 2015). Activity of the ACC, and functional connectivity with surrounding cortical and

limbic areas, is also suppressed in patients with depression (Pizzagalli and Roberts 2022). Given the role of the ACC in encoding differences between expected and actual reward outcomes (i.e., prediction errors), the value of chosen rewards, and the integration of prior behavioral actions and subsequent reward outcomes, suppression of this region would be expected to impair reward-guided behavior. The striatum is involved in many aspects of reward-related behavior that are also impaired in patients with anhedonia. Suppression of activity in this region can negatively impact reward valuation, anticipation/expectancy, and motivation, each of which would hinder reward-guided behavior and manifest as anhedonia.

In summary, the neural computations of probabilistic learning when engaged in choices about different rewards (or aversive events) involves a diverse set of cortical and subcortical structures that are tightly interconnected, each of which computes different variables related to reward probability. The connections from cortical areas involved in reward valuation and uncertainty to subcortical areas are also widely involved in the pathophysiology of depression and other psychiatric disorders characterized by anhedonia. Thus, the different reward-related deficits observed in patients with anhedonia are likely reflected by disruptions in one or several corticolimbic structures that normally process reward valuation and expectancy signals.

5 Conclusions and Future Directions

The ability to learn from reward and adjust behavior accordingly is fundamental to survival across the animal kingdom. Here, we reviewed and integrated convergent preclinical and clinical findings highlighting the centrality of abnormalities in probabilistic reinforcement learning across neuropsychiatric disorders. Several important conclusions can be extracted from this burgeoning area. First, psychiatric conditions reporting similar levels of anhedonia, such as MDD and schizophrenia, are characterized by divergent patterns of reward learning abnormalities. For example, whereas MDD has been linked to blunted reward learning in implicit reinforcement tasks (such as the PRT), schizophrenia has been linked to (surprisingly) preserved implicit reward learning but blunted explicit reward learning (Barch et al. 2017; for an extended discussion, see Moran et al. 2022). This dissociation points to partially non-overlapping neurobiological abnormalities in the manifestation of anhedonia (i.e., MDD: more striatal-based vs. schizophrenia: more PFC-based), which implies that different therapeutic strategies might be needed to address anhedonia in these conditions. Second, by focusing on objective behavioral metrics that can be precisely quantified across species (e.g., rodents, nonhuman primates, humans) using functionally identical tasks, the field has an unprecedented opportunity to accelerate translational discoveries toward the development of novel treatments for anhedonia. In this context, it is noteworthy that, in both rats (Kangas et al. 2022) and humans (Pechtel and Pizzagalli 2013), early adversity has been

linked to blunted reward learning abilities in adulthood. Owing to such parallel findings, promising (and safe) compounds with efficacy to restore reward learning abilities in preclinical models could be useful for anhedonic individuals with a history of early-life adversity. Along similar lines, recent neuroimaging and behavioral findings – which were inspired by robust preclinical data highlighting kappa opioid blockade as a promising target for anhedonia – indicate that a kappa opioid receptor antagonist increased reward-related activation in the nucleus accumbens, boosted reward learning, and reduced self-reported anhedonia in a transdiagnostic sample (Krystal et al. 2020; Pizzagalli et al. 2020). In light of this evidence of "target engagement," clinical studies evaluating kappa opioid receptor antagonists to reverse anhedonic phenotypes are warranted. Third, as recently demonstrated by Ang and colleagues, parsing the heterogeneity of MDD using objective measures of reward learning abilities might provide a means to guide treatment selection, and thus speed up recovery (Ang et al. 2020). Specifically, in that study, reward learning rates that more closely approximated those observed in healthy control participants predicted response to the atypical antidepressant bupropion after failing 8 weeks of treatment with an SSRI. Finally, although we highlighted several possible pharmacological targets, it is important to emphasize that other treatment modalities are currently under intense investigation to tackle anhedonic phenotypes, including psychological treatments inspired by the RDoC (Sandman and Craske 2022) and neurostimulation (Siddiqi et al. 2022). With respect to the latter strategy, it is interesting to note that, among healthy controls, reward learning (as assessed by the PRT) could be potentiated by high-frequency rapid TMS (Ahn et al. 2013) or intermittent theta burst stimulation (Duprat et al. 2016) over the left dorsolateral PFC. Such findings raise the possibility that psychiatric conditions characterized by reward learning dysfunction might benefit from similar types of neurostimulation.

In spite of significant progress in this area, there are important outstanding questions for future studies. First and foremost, although reward learning abnormalities have emerged across tasks in specific psychiatric disorders (e.g., MDD), the causal status of blunted reward learning in anhedonia needs to be directly evaluated. Specifically, do improvements in anhedonia drive reward learning or does the resolution of anhedonia require normalization of reward learning? Dense sampling (e.g., within the context of a randomized clinical trial) of both constructs would be needed to clarify the temporal (and putatively, causal) relationship between them (e.g., early improvements in reward learning in week 1 predicts reduction in self-reported anhedonia in week 2). Second, reward learning abnormalities have often emerged using tasks (e.g., PRT) that include only adjusting behavior as a function of rewards. Thus, in such studies, it is unclear whether the documented abnormalities are specific to reward or might reflect more global (non-specific) learning deficits.

Ultimately, and as reviewed in detail in other chapters within this volume, we believe that parsing anhedonia into subdomains that are biologically more homogenous, can be probed in similar ways across species, and are subserved by distinct neurobiological pathways will give us the best chance at developing more efficacious and much needed treatments for anhedonia and reward learning deficits.

Acknowledgments BDK was partially supported by grant R01 DA047575 from the National Institute on Drug Abuse. AD was partially supported by grants R01 MH121352 and UH3 MH109334 from the National Institute of Mental Health and R01 AA026560 from the National Institute on Alcohol Abuse and Alcoholism. DAP was partially supported by grants R01 MH095809, P50 MH119467, R01 MH108602, R37 MH068376, and UH3 MH109334 from the National Institute of Mental Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

Disclosures Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Concert Pharmaceuticals, Engrail Therapeutics, Neumora Therapeutics (former BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; honoraria from the Psychonomic Society (for editorial work), one honorarium from Alkermes, and research funding from National Institute of Mental Health, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics, Compass Pathways and Neuroscience Software. Dr. Pizzagalli has a financial interest in Neumora Therapeutics (former BlackThorn Therapeutics), which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Massachusetts General Brigham in accordance with their conflict-of-interest policies. Dr. Der-Avakian holds equity ownership in PAASP US. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. Dr. Kangas reports no financial relationships with commercial interest.

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Part IV
Special Topics

The Transdiagnostic Nature of Social Anhedonia: Historical and Current Perspectives

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Contents

Abstract In this chapter, we trace the historical roots of the social anhedonia (SoA) construct to current conceptualizations. We first describe the aspects of SoA that distinguish it from anhedonia in general. We summarize evidence that SoA is a transdiagnostic symptom and risk factor. Although several forms of psychopathology are associated with elevated rates of self-reported SoA, one unresolved issue is whether the processes and mechanisms underlying SoA in one disorder are the same as the processes and mechanisms underlying SoA seen in another disorder. We assert that there may be different causal factors underlying SoA across disorders. Considering both the principles of equifinality and multifinality, we offer an integrative model for social reward processing. This conceptualization considers roles for the following: attention; social cognition, including, but not limited to, social skills; reward learning and valuation; working memory; anticipation, prediction, and remembering; and motivation and effort. We conclude that SoA may be caused by

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Curr Topics Behav Neurosci (2022) 58: 381–396
https://doi.org/10.1007/7854_2021_301
Published Online: 14 February 2022

multiple underlying impairments, all of which may serve as targets for intervention. This conceptualization is provided as an impetus for further research in the area.

Keywords Interpersonal pleasure · Model · Reward processing · Social cognition · Working memory

1 Anhedonia, the Broader Construct

The origin of the word "hedonic" is from Ancient Greek (ἡδονικός, hēdonikós, "pleasant"). The term "anhedonia," which originated with the French psychoanalyst Ribot (1896), is translated to mean "without pleasure." Kraepelin (1919) described anhedonia as one of the main characteristics of dementia praecox. The earliest theoretical models of anhedonia can be traced back to Rado (1953, 1962) and Meehl (1962, 1989). These models conceptualized anhedonia as a diminished or reduced ability to experience pleasure from typically pleasurable situations and/or stimuli. Here, one does not assume that the individual ever found the stimuli pleasurable or had experience with them. In contrast, other models of anhedonia regard anhedonia as a decrease in hedonic experience from previously pleasurable activities (Ho and Sommers 2013). Typically, investigators who are more interested in the state-related nature of anhedonia focus on the latter conceptualization.

Anhedonia was included in the Feighner et al. (1972) criteria for Major Depressive Disorder (MDD). The third edition of the Diagnostic and Statistical Manual (DSM) included the term "anhedonia" (American Psychiatric Association 1980) for the first time. Anhedonia assumed a more central role in the DSM-IV-TR (APA 2000), when it appeared as a major symptom of depression. The DSM 5 (APA 2013) considers anhedonia one of the two main symptoms for the diagnosis of major depression.

Andreasen (1982, 1983) brought further attention to the construct of anhedonia-asociality with the construction of her interview-based measure, the Schedule for Assessment of Negative Symptoms (SANS). The DSM-IV (APA 2000) included anhedonia as one of the negative symptoms of schizophrenia, though it is not given as much diagnostic significance as the more florid positive symptoms. The DSM 5 (APA 2013) defines asociality as a lack of interest in social interactions, though it suggests that it may be secondary to avolition. The DSM-5 consideration of asociality as secondary to avolition contrasts with Meehl (1962) who regarded anhedonia as a primary deficit. The DSM-5 conceptualization also contrasts with Andreasen (1982, 1983) who made clear delineations between the constructs of avolition and asociality; the latter was grouped with anhedonia. As such, we assert

that asociality and anhedonia are better captured by one construct, namely, social anhedonia (SoA).[1]

Descriptions of anhedonia have evolved over time. Anhedonia can be described in terms of the domains affected, such as social/interpersonal and nonsocial (i.e., physical/sensory or personal value-driven, e.g., money). It has also been described in terms of the temporal unfolding of the affective experience. Klein (1987) was the first to distinguish between consummatory and appetitive pleasure. Berridge and Kringelbach (2011) distinguish the experiential/affective aspects of pleasure into three major reward processes, namely, wanting, liking, and learning. According to their model, wanting is associated with incentive salience, while liking is associated with a reward's hedonic impact. Reward learning encompasses a range of processes including "...associations, representations, and predictions about future rewards based on past experiences" (p. 4). Therefore, anticipatory anhedonia refers to impairment of hedonic experience or function relating to expectation of a reward (i.e., "wanting"). Consummatory anhedonia refers to impairment in and/or loss of enjoyment of a reward (i.e., "liking"). Reward responsiveness is a component of consummatory pleasure. While some emphasized the temporal distinction, others emphasized anhedonia in terms of impairment in reward learning, i.e., disruptions in subjective valuation of a reward, or impaired prediction about future rewards (Gold et al. 2008).[2]

Anhedonia has also been parsed in terms of its cognitive characteristics, namely, motivational anhedonia, reduced incentive to pursue rewarding stimuli, and decisional anhedonia, diminished decision-making in the context of rewards (Treadway and Zald 2011). According to their view, decisional anhedonia may be the result of motivational anhedonia or consummatory anhedonia. Advances in neuroscience indicate that anhedonia is a multifaceted construct, one that implicates the neural circuitry of reward (Rizvi et al. 2016). In summary, anhedonia is operationally defined as a reduction or deficit in pleasure in one or more domains.

2 The Unique Nature of Social Anhedonia

Beginning at birth, human beings are inclined to be social animals. In typically developing individuals, social interactions are inherently rewarding. Social anhedonia (SoA) can be defined as a deficit in pleasure from social contact, reduced experience of reward from social stimuli, and/or reduced motivation and disinterest

[1] Henceforth, social anhedonia is abbreviated as "SoA" until the concluding paragraph. Social Anhedonia is not abbreviated in chapter headings.

[2] We note that a recent meta-analysis (Visser et al. 2020) revealed no statistically significant difference between self-reported anticipatory and consummatory pleasure in schizophrenia-spectrum participants, suggesting only modest support for the temporal distinction of affective experience in humans.

in pursuing relationships. The current construct of SoA is more broadly construed than its historical conceptualization.

There is ample empirical evidence, both psychometrically and experimentally, that SoA is associated with, but distinct from, nonsocial anhedonia (c.f. Chapman et al. 1976; Gooding and Pflum 2014a, b). A person may experience anhedonia in one domain yet remain hedonic in other domains, e.g., enjoy sensory pleasures, and/or ideological pleasures related to product meanings and personal values, yet receive little or no joy from interpersonal and group relationships, or experience little to no reward from engaging in a social activity that was previously emotionally and cognitively valuable (Alba and Williams 2013). Individuals with SoA display comparable responses to monetary rewards as typically hedonic controls, but reduced anticipatory and consummatory experience in response to positive social rewards (Xie et al. 2014). Research findings also support a clear distinction between SoA and other trait constructs, such as social anxiety (Alden and Auyeung 2014; Kwapil et al. 2014; Gooding et al. 2015; Cicero et al. 2016), shyness (Alden and Auyeung 2014; Gooding et al. 2015; Cicero et al. 2016), and introversion (Martin et al. 2016).

3 The Transdiagnostic Nature of Social Anhedonia

Most of the research on SoA has been focused on the schizophrenia spectrum. SoA is reported by outpatients (Blanchard et al. 1998; Tremeau et al. 2014; Waltz et al. 2015; Fortunati et al. 2015; Park et al. 2015; Umesh et al. 2018; Liang et al. 2020) and inpatients with schizophrenia (Tremeau et al. 2014; Wang et al. 2014; Ritsner et al. 2018), as well as first-episode patients (FEP; Lee et al. 2015; Zou et al. 2018) and recent-onset patients (Jhung et al. 2016). Longitudinal studies of birth cohorts (Miettunen et al. 2011), army conscripts (Davidson et al. 1999), and college undergraduates (Kwapil 1998; Gooding et al. 2005, 2007) indicate that elevated levels of SoA predict the later development of schizophrenia and schizophrenia-spectrum disorders (SSD). Individuals at ultra-high risk (UHR) for psychosis or being in the prodromal stages of psychosis also display significantly higher levels of self-reported SoA (Velthorst et al. 2009; Lee et al. 2015; Jhung et al. 2016; Park et al. 2018; Seo et al. 2018; Pelizza et al. 2020a, b). A recent meta-analysis of the association between schizophrenia risk and SoA (Pflum 2019) revealed that across all studies, the experimental group had higher SoA scores, regardless of the self-report measure used. The overall effect size was very large, $g = 1.14$, suggesting that SoA is a core aspect of a schizophrenia diathesis.

Patients with major depressive disorder (MDD; Blanchard et al. 2001; Pelizza and Ferrari 2009; Ho and Sommers 2013; Olsen et al. 2015; Atherton et al. 2015) report elevated SoA. Although SoA appears to be state-related in major depressive disorder (Blanchard et al. 2001), it remains an important target for intervention. Elevated SoA has also been observed in youths, adolescents, and adults with autism spectrum disorder (ASD; Chevallier et al. 2012a; Berthoz et al. 2013; Han et al. 2019; Gadow

and Garman 2020). There is growing evidence of SoA among individuals with post-traumatic stress disorder (PTSD) (Wechsler-Zimring and Kearney 2011; Frewen et al. 2012: Nawjin et al. 2015; Olson et al. 2021). A small but growing literature also implicates SoA in eating disorders (Tchanturia et al. 2012; Mason et al. 2021, substance use disorders (Gooding et al. 2013), and obsessive-compulsive disorder (Xia et al. 2019).

According to the principle of multifinality, the same risk or trait may have heterogeneous outcomes (Cicchetti and Rogosch 1996). SoA in adolescence may be an indicator of incipient psychopathology, whether in depression or a schizophrenia-spectrum disorder. For individuals with a diathesis for an SSD, SoA serves as a specific risk factor. For individuals with ASD, the presence of SoA may be a risk factor for major depression (Han et al. 2019). For individuals with mood disorders, particularly MDD, social anhedonia may serve as an indicator of greater symptom severity and suicide risk.

4 An Integrative, Transdiagnostic Conceptualization of Social Anhedonia

According to equifinality, multiple etiological pathways can result in phenotypically similar outcomes (Cicchetti and Rogosch 1996). Thus, two patients with very different underlying pathophysiological processes may both experience and report SoA (the outcome) due to different social reward impairments. We propose a model (Fig. 1) to account for SoA. Our model encompasses reward subdomains of previously presented models (Kring and Barch 2014; Rizvi et al. 2016), such as interest, anticipatory pleasure, effort computation, approach motivation, action plan computation, approach behavior, consummatory behavior, and integrating and updating valuation. However, our adaptation accounts for the unique aspects of SoA. First, social cognition is a requisite component in our model. Second, we do not make as a clear-cut distinction between the temporal ordering of anticipatory and consummatory social pleasure. We note that the distinction between anticipatory and consummatory pleasure was based upon animal models, which while providing a compelling analogue are limited in approximating the complexity of social experience of humans. Social pleasure often involves an amalgam of anticipatory and consummatory aspects. Other factors such as cognitive biases and level of social skills are explicitly incorporated into the model. Finally, in contrast to previous models which account for general reward impairments in SSD (Kring and Barch 2014) or MDD (Rizvi et al. 2016), our model is intended to be a transdiagnostic account of social reward processing.

As illustrated in Fig. 1, the hedonic experience of social/interpersonal stimuli involves various processes, any one (or more) of which may be disrupted and result in SoA. Depending upon the form of psychopathology and the individual's history, cognitions, and skill levels, different subprocesses may be impaired or disrupted.

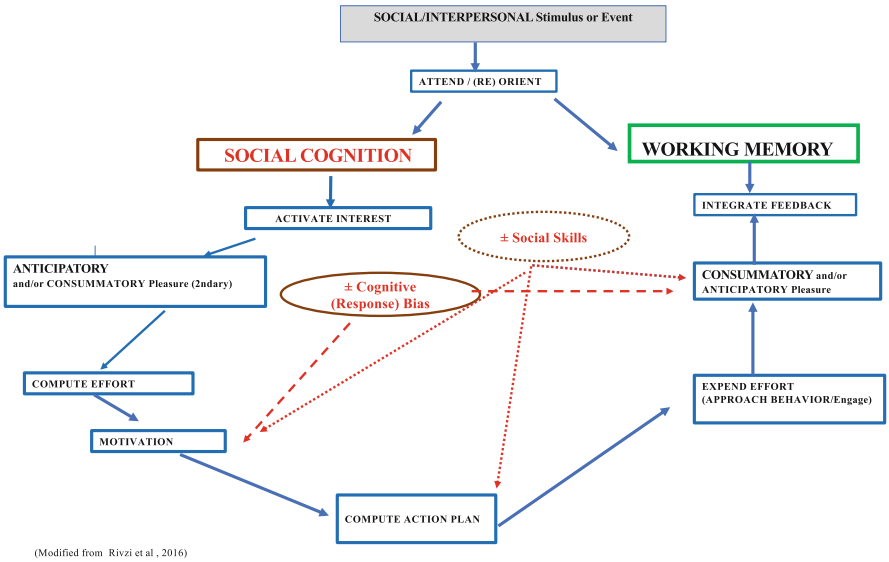

Fig. 1 A schematic modified from prior models (Kring and Barch 2014; Rizvi et al. 2016) displays the processes involved in the reward processing of social/interpersonal stimuli or events. Attentional capacity, social cognitive processes, social skills, working memory, and cognitive response biases are all thought to play significant roles in the reward processing of social/interpersonal stimuli. This model can also be considered a heuristic for social anhedonia because impairments in attention, social cognition, working memory, or any combination of these, may lead to disruptions in any of the processes involved in reward processing

Not all the processes that contribute to SoA reflect a primary pleasure deficit. Nonetheless, by mapping out the possible points during affective processing of social stimuli something might go awry, we intend to identify viable targets for more personalized intervention. Finally, as others (Lambert et al. 2018) have noted, several aspects of reward processing may occur in parallel rather than sequentially, i.e., social interest in itself may be a source of consummatory pleasure.

5 The Role of Attention in Social Pleasure

A social/interpersonal stimulus must be attended to before it can be deemed rewarding. When presented with a social stimulus, the person must be able to direct their selective attention to the features of the social stimulus, such as the facial features of the person speaking for nonverbal cues. In a social situation, the person must be able to discern the salient features and orient to them. Findings linking the association between high SoA and high social impairment (Tully et al. 2014), along with compelling evidence of attentional impairments among individuals in the schizophrenia spectrum (Erlenmeyer-Kimling and Cornblatt 1992; Erlenmeyer-Kimling

et al. 1993; Cohen et al. 2006; Gooding et al. 2006) suggest that attentional control may underlie SoA in individuals at risk for or affected by SSD. Similarly, social interest is a prerequisite for social/interpersonal pleasure.[3] Findings also indicate that individuals diagnosed with MDD display attentional bias to negative social information (Gotlib et al. 2004a). This attentional bias may reduce interest in engaging in social interactions.

6 The Role of Social Cognition in Social Pleasure

Social cognition is defined as information processing about social interactions, such as perceiving, interpreting, and generating responses to the intentions, feelings, and behaviors of others (Green and Horan 2010). Individuals may not find social interactions rewarding due to their social cognitive impairments. Theory of Mind, or attributing a mental state to others on the basis of immediately perceptual information, e.g. their actions, or body, voice and/or facial expressions (Tager-Flusberg and Sullivan 2000) is very important in social interactions. Social cognitive impairments are well documented in people with SSD (Green et al. 2015) and in people with ASD (Tager-Flusberg 2007). If a person does not have Theory of Mind, they are less likely to be interested in engaging with another person. In this way, social cognitive deficits may at least partly account for the SoA reported by people with SSD and ASD, i.e., an inability to appreciate humor and/or interpret nuanced meanings would diminish the rewarding nature of social interaction (Krach et al. 2010).

7 The Role of Reward Learning and Reward Valuation

Reward learning, reward valuation, and the maintenance of emotion all play important roles in determining whether an individual will find social stimuli interesting. One's history with a social stimulus (reward learning) will affect reward valuation as well as hedonic experience. Typically, interaction with a person with whom one has a history is accompanied by a mixed emotion of pleasure, partly based on the recall of past encounters (consummatory) as well as a feeling of anticipation. However, a history of abuse or insecure attachment may adversely impact social reward learning and/or reduce the value one places on social interactions. A history of trauma in the form of sexual abuse may account for the social anhedonia reported by some people with PTSD.

[3] We make the distinction between low social interest (i.e., relative to other individuals), which may be regarded as a preference, and reduced interest (i.e., relative to one's baseline or a clinical norm), which may be less adaptive.

8 The Role of Working Memory in Social Pleasure

SoA may be secondary to a working memory impairment. Working memory processes include encoding, forming mental representations (maintenance), and manipulation of information. There is ample evidence that working memory impairment is an endophenotypic marker of a schizophrenia diathesis (Park and Gooding 2014). SSD patients display affective working memory deficits (Gooding and Tallent 2004) as well as deficits in the ability to represent the value of response options to guide decision-making (Gold et al. 2008).

Once the individual decides to engage with the social stimulus, the next step would be to generate goal-directed behavior. To successfully perform goal-directed social behavior, such as have a conversation, accompany someone to a restaurant, a person needs to exert a sufficient effort, e.g., respond to the person speaking, use nonverbal cues, and persist. Intact working memory would be necessary to assist in formulating an action plan. Similarly, the person would need to be able to inhibit other responses to execute the plan. Working memory functioning and inhibition of responses are compromised in several psychiatric disorders.

9 The Cognitive-Affective Interface: Anticipation, Prediction, and Remembering

The interplay of cognitive and affective factors is particularly salient in the domain of social pleasure. Social reward may differ from physical reward in terms of its salience and the discriminability of its temporal aspects. Anticipatory pleasure, positive affect associated with looking forward to or wanting something, involves reward prediction as well as affective forecasting, the ability to forecast future pleasure correctly (Zhang et al. 2020). At times, it may be difficult to differentiate social anticipatory pleasure from social consummatory pleasure; even the process of looking forward to a social/interpersonal encounter can be pleasant and invoke consummatory pleasure. A negative attributional bias that is internal, stable, and global could also contribute to perceptions of SoA. For example, a person with social anxiety disorder may have felt so self-conscious and anxious during a social encounter that they did not enjoy it. However afterwards they might think "I did not like that social event because I must not enjoy doing social things."

Furthermore, reward prediction, reward responsivity, and remembering reward can be influenced by one's cognitive bias. Research indicates a negative response bias in individuals with MDD and in social anxiety disorder, whereby they are more likely to remember negative information (Gotlib et al. 2004a). Individuals' expectation of social reward may be based on past events, learned stimulus-reward associations, or on available probability information. Patients' cognitive biases can distort recognition or acceptance of information indicating the probability of a positive outcome occur. A person with a distorted response bias may expect negative

events and/or a decreased likelihood of positive events. This may result in reinforcing their social isolation, and belief that they do not enjoy social interaction. After all, one may think, "why put myself out there if I'll end up being rejected?" Accordingly, an individual with MDD may be more likely to recall examples of negative social encounters more readily than encounters with more positive outcomes.

10 The Role of Social Skills in Social Pleasure

A person's level of social skills may contribute to their experience of social pleasure. Interacting with others involves a great deal of social cognition, i.e., cognitions about the thoughts, feelings, and behaviors of others. Impairments in social cognition render social interactions more difficult and less enjoyable. Lack of access to a social network and/or perceived insufficient support network may also lead an individual to believe that social interactions are not associated with pleasant feelings. If an individual lacked the opportunity to develop certain social skills, e.g., dining in a restaurant, this might lead them to respond less positively when asked to predict how much enjoyment they'd have in that social situation with friends or in a group setting. Given some patient groups' deficits in their ability to imitate gestures, particularly facial gestures (Park et al. 2008), social interactions may be perceived as onerous or taxing, in the absence of social skills training. In this way, although these factors are not primary hedonic deficits, they contribute to overall sense of SoA.

11 The Role of Motivation and Effort in Social Anhedonia

Individuals differ in terms of their levels of approach motivation, which may lead to two different aspects of SoA, namely, motivational anhedonia and decisional anhedonia. When faced with a social stimulus, the person computes the effort before deciding whether to engage. Part of the process of evaluating the "effort" or work involved requires reward calculation. The other facet of approach motivation, decisional anhedonia, is the process by which the person makes a cost/benefit analysis regarding their decision. "How rewarding will the social encounter be?" "How risky will engaging with this person/social situation be?" Factors that may influence the cost/benefit analysis may include reward learning and memory, such as the person's past history with the social group. Factors that might influence an individual to inconsistently applying the rules of the cost/benefit analysis include negative response bias, tendency to remember negative information, and hypersensitivity to punishment (Gotlib et al. 2004a, b; Treadway and Zald 2011). Such a bias would dampen one's motivation. Cost/effort computation deficits are seen in both SSD and MDD. It is unclear whether the SSD patients' cost/effort impairments

reflect a working memory impairment, cognitive bias, or both. Conversely, the depression literature suggests that the depressive group's cost computations are likely secondary to their cognitive distortions (see Treadway and Zald 2011).

Another group hypothesized to have social motivation deficits are people with ASD. According to Chevallier et al. (2012a), early-onset deficits in social attention contribute to developmental processes that disrupt social learning, social cognition, and the development of social skills. These social cognitive deficits reflect the reduced reward value that social stimuli hold for individuals with ASD. Thus, according to the social motivation theory of autism (Chevallier et al. 2012b) deficits in social motivational mechanisms contribute to the social deficits experienced by individuals with ASD. If a person does not find social interactions rewarding, then they are less motivated in pursuing those interactions. In this sense, social anhedonia in ASD may reflect motivational anhedonia as much as consummatory anhedonia.

SoA may also reflect impairments in approach behavior. A related process here includes affective forecasting, the ability to predict one's emotional responses to future events (Zhang et al. 2020). Expectations of good outcome in a social situation would encourage an individual to socially engage. Impairments in positive affective forecasting would contribute to a higher likelihood of SoA. Preliminary evidence based on nonclinical samples supports this hypothesis; SoA is correlated with low-pleasure beliefs and inversely correlated with prediction for future pleasant events (Hu et al. 2018). After the social engagement, the person is likely to experience an amalgam of consummatory and anticipatory pleasure. If an individual had a negative social experience, the feedback could affect future views regarding social engagement. A depressed patient may have an experience with one specific person or a specific type of social interaction, yet due to the cognitive distortion of overgeneralization, they attribute their discomfort to social engagement in general.

Individuals with schizophrenia may encounter difficulties learning stimulus-reward associations, which would render encoding positive social experiences and using them to guide later behaviors and judgments regarding social preferences more unlikely; thus, as we and others (Strauss et al. 2011) have postulated, at least some of SSD patients' SoA may reflect working memory impairments. The processing of pleasure also involves integration of feedback and updating reward valuation. Despite a positive social experience, an individual may still report not enjoying that social stimulus if there is a failure to encode their positive social experience. If there's a working memory impairment, the social information may not be properly encoded, and the social stimulus value will not be updated. A related construct, satiation, i.e., the ability to increase pleasure through the conscious consideration of past consumption (Alba and Williams 2013), is similarly relevant. Satiation may be used to modify beliefs about feelings and social valuation over time. Individuals who are unable to distinguish between sated and unsated conditions will have less access to remember pleasure. Waltz et al. (2015) demonstrated that patients with schizophrenia may be unable to use satiation information effectively; this inability to update stimulus value representations and use the information to guide goal-directed behavior (i.e., working memory) is likely to underlie some of the SoA reported by patients. Due to aberrant salience processing – the faulty inappropriate

generalization of one stimulus (i.e., a particular social interaction) to stimuli (other social experiences) more broadly (i.e., other social interactions) – the individual with schizophrenia may conclude that they do not enjoy social interactions. Despite being able to experience social pleasure in the moment, some people may report SoA because of an inability to integrate that feedback into their ongoing internal representation and valuation of social stimuli. Critically, although we presented these possible contributors to SoA as discrete processes, it is possible that one person may experience more than one of these challenges.

12 Future Research Directions

As a construct, SoA has considerable significance in terms of understanding risk, course, and treatment response across various forms of psychopathology (Olino et al. 2016). Our understanding of SoA will be enhanced if we incorporate the developmental principles of multifinality and equifinality into our conceptualization of this transdiagnostic symptom. As we investigate possible differences in the etiological pathways underlying social anhedonia across the different forms of psychiatric illness using a mechanistic perspective, it will be important to consider how working memory performance, social cognitive functioning, and social skills contribute to reward processing. Identifying the underlying contributory factors would help guide the development of prevention as well as treatment efforts. As we strive towards personalized medicine, we must go consider all the subprocesses inherent in social pleasure (and its impairment) in our assessments.

In conclusion, social anhedonia is distinct from nonsocial anhedonia and appears to be a transdiagnostic symptom and risk factor. As such, it warrants further study as it pertains to psychopathology risk, treatment, and outcome of various forms of psychopathology. Guided by both principles of multifinality and equifinality, we presented a model to help guide future considerations of the construct. Although individuals with different forms of psychopathology report social anhedonia, it is likely that there are differing aberrant processes underlying it. Even within one nosological category, or one individual, social anhedonia may be caused by multiple underlying impairments – not all of them primarily hedonic in nature – which are targets for intervention.

Acknowledgments First and foremost, we thank the individuals with lived experience of mental illness and community participants who have contributed to our research. Ms. Malory Schultz kindly prepared the manuscript. We are appreciative of our collaborators, especially Raymond R.C. Chan, Eduardo Fonseca-Pedrero, Jeffrey S. Bedwell, Daniel N. Klein, and H. Hill Goldsmith for invigorating discussions and reminders of the joys of scientific inquiry.

No conflicts to disclose.

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Inflammation as a Pathophysiologic Pathway to Anhedonia: Mechanisms and Therapeutic Implications

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Curr Topics Behav Neurosci (2022) 58: 397–420
https://doi.org/10.1007/7854_2021_294
Published Online: 1 January 2022

Abstract Anhedonia, characterized by a lack of motivation, interest, or ability to experience pleasure, is a prominent symptom of depression and other psychiatric disorders and has been associated with poor response to standard therapies. One pathophysiologic pathway receiving increased attention for its potential role in anhedonia is inflammation and its effects on the brain. Exogenous administration of inflammatory stimuli to humans and laboratory animals has reliably been found to affect neurotransmitters and neurocircuits involved in reward processing, including the ventral striatum and ventromedial prefrontal cortex, in association with reduced motivation. Moreover, a rich literature including meta-analyses describes increased inflammation in a significant proportion of patients with depression and other psychiatric illnesses involving anhedonia, as evident by elevated inflammatory cytokines, acute phase proteins, chemokines, and adhesion molecules in both the periphery and central nervous system. This endogenous inflammation may arise from numerous sources including stress, obesity or metabolic dysfunction, genetics, and lifestyle factors, many of which are also risk factors for psychiatric illness. Consistent with laboratory studies involving exogenous administration of peripheral inflammatory stimuli, neuroimaging studies have further confirmed that increased endogenous inflammation in depression is associated with decreased activation of and reduced functional connectivity within reward circuits involving ventral striatum and ventromedial prefrontal cortex in association with anhedonia. Here, we review recent evidence of relationships between inflammation and anhedonia, while highlighting translational and mechanistic work describing the impact of inflammation on synthesis, release, and reuptake of neurotransmitters like dopamine and glutamate that affects circuits to drive motivational deficits. We will then present insight into novel pharmacological strategies that target either inflammation or its downstream effects on the brain and behavior. The meaningful translation of these concepts through appropriately designed trials targeting therapies for psychiatric patients with high inflammation and transdiagnostic symptoms of anhedonia is also discussed.

Keywords Anhedonia · Cytokines · Depression · Dopamine · Glutamate · Inflammation · Motivation · Neuroimaging

1 Introduction and Overview

Converging evidence from clinical and laboratory animal studies consistently indicates that innate immune activation and the release of inflammatory cytokines affects neurotransmitters and circuits relevant to reduced motivation and symptoms of

anhedonia (Felger and Treadway 2017). A significant proportion of otherwise medically healthy patients with major depressive disorder (MDD) and other psychiatric disorders exhibit evidence of increased peripheral inflammation, including inflammatory cytokines and acute phase reactants like C-reactive protein (CRP), which are elevated in relation to symptoms of anhedonia (Felger et al. 2020; Swardfager et al. 2016). Interestingly, both inflammation and anhedonia have been independently associated with resistance to standard antidepressant therapies (McMakin et al. 2012; Raison et al. 2013a; Uher et al. 2012). Moreover, several recent studies demonstrate that blocking inflammation with anti-cytokine therapies specifically reduces symptoms of anhedonia in depressed patients (Lee et al. 2020; Raison et al. 2013b; Salvadore et al. 2018). Given these cause and effect relationships indicating that anhedonia can be both induced by inflammatory stimuli and reversed by cytokine blockade, motivational deficits and anhedonia have received attention as potential treatment targets for therapies to block inflammation or its effects on the brain in patients with high inflammation (Miller et al. 2017).

The current review will briefly summarize the rich literature highlighting elevated peripheral biomarkers of inflammation in patients with MDD and other psychiatric disorders, including mention of the sources of increased inflammation in otherwise medically healthy individuals, many of which are also risk factors for psychiatric illness. Emerging evidence that increased inflammation in psychiatric illness may uniquely contribute to symptoms of anhedonia will then be presented in the light of treatment implications. Supporting clinical and basic science studies involving exogenous administration of inflammatory stimuli have demonstrated the impact of inflammation on reward-sensitive brain regions, while addressing the specific constructs of anhedonia affected by inflammation within the context of this multifaceted symptom domain. Our current understanding of the underlying neurobiological and neurotransmitter mechanisms has additionally revealed potential for new therapies. Finally, we discuss how these concepts can be meaningfully translated by appropriately designed, biomarker-driven trials targeting specific therapies for patients with high inflammation and the transdiagnostic symptom of anhedonia.

2 Inflammation and Anhedonia in Psychiatric Disease

2.1 Inflammation in Depression and Other Psychiatric Disorders: Causes and Consequences

Numerous studies including meta-analyses have reported increased peripheral and central inflammatory markers like CRP and the inflammatory cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) in MDD (Dowlati et al. 2010; Felger et al. 2020; Howren et al. 2009; Raison et al. 2013b). Similar increases in inflammatory markers have been described in other psychiatric disorders where anhedonia is a prominent symptom, ranging from anxiety disorders such as post-traumatic

stress disorder (PTSD) (Costello et al. 2019; Passos et al. 2015) to bipolar disorder and schizophrenia (Goldsmith et al. 2016; Munkholm et al. 2013). Increased circulating inflammatory markers may be in part due to genetics given that single-nucleotide polymorphisms within genes encoding immune and inflammatory mediators (cytokines, chemokines, major histocompatibility complex molecules) have been linked to depression and schizophrenia (Barnes et al. 2017; Pouget 2018). Additionally, associations between variants in the CRP gene, elevated circulating CRP levels, and PTSD are found among trauma-exposed individuals (Michopoulos et al. 2015; Miller et al. 2018). In psychiatric patients who are otherwise medically healthy, genetic predisposition may interact with a range of environmental and lifestyle factors that activate the innate immune system and contribute to low-grade systemic inflammation including stress, early life trauma, disturbed sleep, physical inactivity, obesity and metabolic disturbances, Western diet, aging, and smoking (Berk et al. 2013). Many of these causes of inflammation are risk factors for both major medical and psychiatric illnesses, suggesting shared pathophysiologic processes that may explain notable comorbidity between psychiatric disorders and cardiovascular disease, diabetes, and cancer (Furman et al. 2019). Whereas not every patient with MDD has increased inflammation, recent studies find that depending on the sample ~25–40% of MDD patients have evidence of increased inflammation, most commonly defined as CRP >3 mg/L (per the CDC/AHA definition of high risk for developing cardiovascular disease) (Felger et al. 2020; Raison et al. 2013b; Rapaport et al. 2016; Uher et al. 2014), with higher concentrations observed in patients with evidence of treatment resistance (Chamberlain et al. 2019; Haroon et al. 2018b). Not only are treatment-resistant patients more likely to have increased inflammation but increased inflammatory markers prior to treatment are also associated with reduced response to conventional therapies (Cattaneo et al. 2013; Jha et al. 2017; Lanquillon et al. 2000; Uher et al. 2014). Finally, longitudinal work has found that increased inflammatory markers can often predict subsequent depression symptoms above and beyond baseline depression severity (Bondy et al. 2021).

2.2 *Relationships Between Inflammation and Symptoms of Anhedonia Across Diagnoses*

Increased cytokines and CRP have been associated with the severity of anhedonia across diagnoses. For example, we recently identified clusters of cerebrospinal fluid (CSF) cytokines and their soluble receptors that were associated with high plasma CRP (>3 mg/L) in otherwise medically stable MDD patients (Felger et al. 2020). These CSF markers were in turn associated with symptom severity with the strongest relationships identified between CSF TNF and reduced motivation per a subscale from the multidimensional fatigue inventory (MFI), and CSF IL-6 soluble receptor and anhedonia per a subscale from the Inventory of Depressive Symptomatology

Self-Report (IDS-SR) that correlates with the both the self and clinician-administered Snaith-Hamilton pleasure scale (SHAPS) (Ameli et al. 2014; Felger et al. 2016). These results were confirmed and extended by another study demonstrating that both T and non-T cell cytokines were associated with anhedonia severity per the IDS-SR subscale (Jha et al. 2018). Furthermore, longitudinal relationships between cytokines and anhedonia have been reported in depression where higher baseline plasma TNF predicted greater severity of anhedonia both at baseline and at a four-month follow-up (Rengasamy et al. 2021). In schizophrenia, many studies have found associations between negative symptoms – which include motivational deficits, blunted affect, and social withdrawal among others – and various inflammatory markers (Goldsmith and Rapaport 2020). Moreover, concentrations of plasma TNF and IL-6 predicted severity of negative symptoms over a year of follow-up in patients at chronic high risk for psychosis (Goldsmith et al. 2018). Together, these studies provide a clinical framework for the role of inflammation in anhedonia and are supported by mechanistic studies using administration of inflammatory stimuli to understand the effects of inflammation on the brain (Sects. 3 and 4).

2.3 Inhibition of Inflammation Reduces Anhedonia Symptoms

Numerous studies treating psychiatric patients with rather non-specific anti-inflammatory agents having multiple off-target effects, e.g., nonsteroidal anti-inflammatory drugs and minocycline (Eyre et al. 2015; Husain et al. 2020; Rosenblat and McIntyre 2018), were not targeted to patients with increased inflammation and yield mixed results. Although having limited viability as antidepressants for a myriad of reasons (Dreyer et al. 2016; Miller et al. 2017), more specific anti-cytokine therapies have shown efficacy for reducing depressive symptoms, particularly anhedonia, in depressed or medically ill patients with high inflammation. For example, treatment of patients with autoimmune or inflammatory disorders with anti-cytokine therapies reduces depression symptom severity (Kappelmann et al. 2018). The TNF antagonist infliximab reduced depression severity with respect to placebo in treatment-resistant MDD patients with higher concentrations of plasma CRP, and anhedonia (*work and activities*) was the most improved symptom (Raison et al. 2013b). Anti-TNF or IL-6 therapies in unipolar or bipolar depressed patients with evidence of increased inflammation were primarily effective in reducing symptoms of anhedonia as measured by SHAPS (Lee et al. 2020; Raison et al. 2013b; Salvadore et al. 2018). These data reinforce specificity for the effects of inflammation on motivational pathways that contribute to anhedonia, as discussed below.

3 Impact of Inflammation on Reward Pathways and Anhedonia: Clinical Evidence

Neuroimaging studies have consistently found that a variety of inflammatory stimuli, including cytokines and cytokine inducers (e.g., endotoxin or vaccination), preferentially target the basal ganglia and prefrontal cortex in association with symptoms relevant to anhedonia (Fig. 1) (Felger and Treadway 2017). Causal evidence for the effects of inflammation on neural circuits and neurotransmitters relevant to reduced motivation and anhedonia were initially revealed by studying patients administered the antiviral and antiproliferative cytokine interferon (IFN)-α, which caused clinical depression in up to half and depressive symptoms in nearly all patients over weeks to months of treatment for infectious diseases or cancer (Capuron et al. 2002; Capuron et al. 2012). Like IFN-α, endotoxin and vaccination induce depressive symptoms and release of classic inflammatory cytokines IL-6, IL-1, and TNF, and are commonly used in lab settings to understand their acute effects on the brain (Eisenberger et al. 2010; Harrison et al. 2016), as reviewed below.

3.1 Cytokine-Induced Depression: Mechanisms and Relevance to Anhedonia

Early positron emission tomography (PET) studies investigating broad effects of chronic exogenously administered cytokines on the brain consistently found that resting glucose metabolism was increased in basal ganglia and decreased in frontal cortex (Capuron et al. 2007; Juengling et al. 2000), whereby increased metabolism in the left putamen and left nucleus accumbens correlated with IFN-α-induced anergia and fatigue (Capuron et al. 2007). This pattern of increased glucose metabolism in basal ganglia nuclei is similar to that seen in patients with Parkinson's disease (PD) (Mentis et al. 2002) and thought to indicate increased oscillatory burst activity secondary to loss of inhibitory dopamine input (Wichmann and DeLong 2003). Accordingly, functional magnetic resonance imaging (fMRI) was used to reveal decreased ventral striatal (VS) neural activation to win versus loss in a gambling task after IFN-α, which correlated with self-reported reduced motivation (Capuron et al. 2012). Complementary PET using radio-labeled dopamine precursor, [^{18}F] fluorodopa, in IFN-α-treated patients showed both increased uptake and decreased turnover of FDOPA, reflecting decreased availability of dopamine/precursor and impaired packaging or release of newly synthesized dopamine, in caudate, putamen, and VS (Capuron et al. 2012). Magnetic resonance spectroscopy (MRS) also showed increased glutamate in left basal ganglia and dorsal anterior cingulate cortex in patients treated with IFN-α (Haroon et al. 2014), which correlated with reduced motivation and was modified by age (Haroon et al. 2015). Thus, chronic peripheral inflammation causes selective changes in brain regions relevant to reduced motivation and involving dopamine and glutamate.

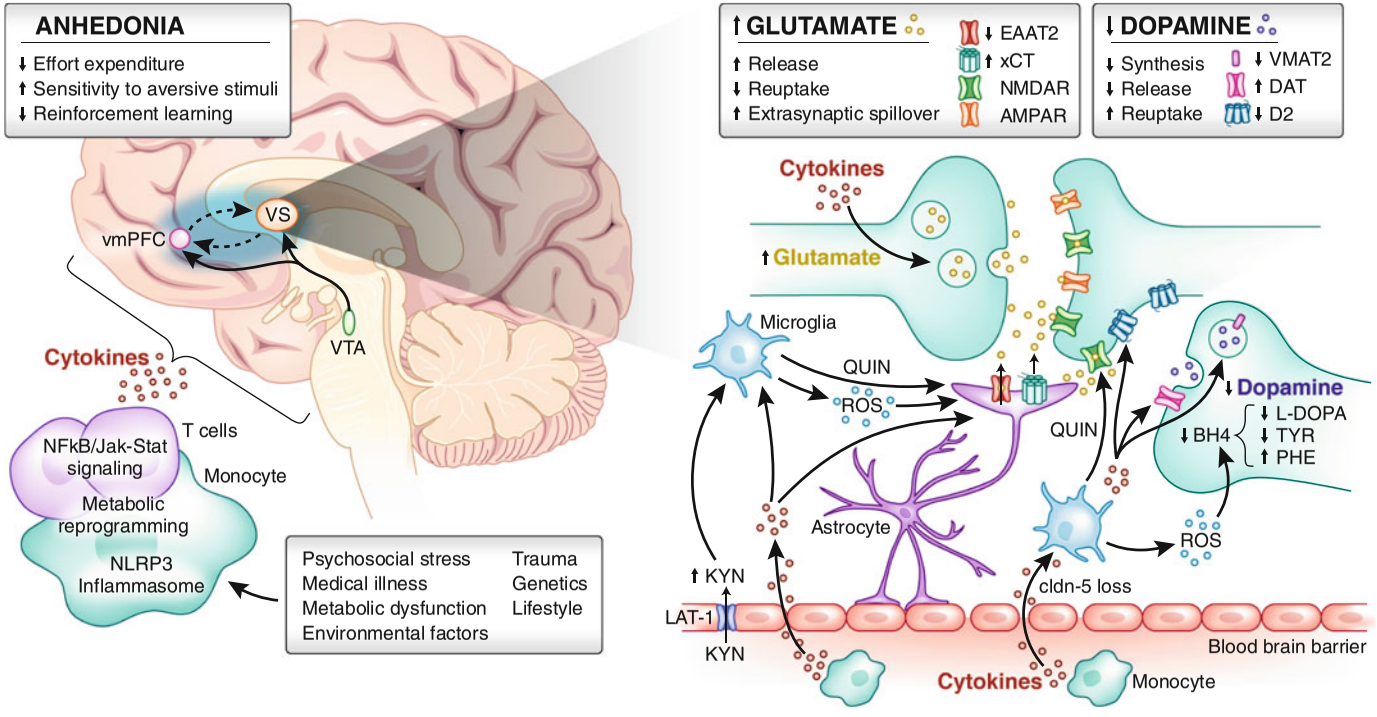

Fig. 1 Inflammation affects dopamine and glutamate transmission and corticostriatal reward circuitry to contribute to symptoms of anhedonia. A host of medical, environmental, and lifestyle factors contribute to innate immune activation in patients with depression and other psychiatric disorders. Peripheral immune cells like monocytes and T cells activate inflammatory signaling pathways and undergo a metabolic reprograming that facilitates cellular effector function, thus leading to release of cytokines and trafficking to the brain. Inflammatory cytokines can impact functional connectivity within reward-related brain regions including ventral striatum and ventromedial prefrontal cortex in association with symptoms of anhedonia. Inflammation-related anhedonia is characterized by deficits in reward processing and motivation involving reduced effort expenditure and reward learning and heightened sensitivity to aversive stimuli. Neurotransmitter mechanisms of inflammation effects on reward circuitry involves decreased dopamine synthesis and release along with increased reuptake and/or receptor signaling, resulting in low dopamine signaling. Inflammation also promotes glutamate release and extrasynaptic spillover, impaired

3.2 Acute Inflammatory Challenge and Reward Processing

Supporting a preferential impact of inflammation on key basal ganglia regions, acute challenge with IFN-α caused rapid (4 h) changes in striatal microstructure that predicted subsequent development of fatigue symptoms during therapy (Dowell et al. 2019; Dowell et al. 2016). Studies in healthy controls using vaccination and subfebrile doses of endotoxin have also assessed acute effects of inflammation on reward processing (Lasselin et al. 2021). Reduced activation of VS to reward-predicting cues during a monetary incentive delay task (MIDT) was associated with increased self-reported depressed mood (Eisenberger et al. 2010), and with cytokine responses in women but not men hours after endotoxin (Moieni et al. 2015). In a probabilistic instrumental learning task combined with fMRI, typhoid vaccine compared to saline control reduced behavioral attractiveness of rewards while making punishments more aversive, in association with opposing change in VS responses that were decreased to positive feedback but increased to negative feedback (Harrison et al. 2016). This corresponds with a study showing that greater inflammatory responses to laboratory stress correlated with decreased VS sensitivity to positive feedback (Treadway et al. 2017). Most studies administering endotoxin or vaccination to healthy subjects to further understand the effects of inflammation on effort expenditure versus aspects of reward processing reported that motivation for high-effort reward was more significantly reduced than reward sensitivity (Boyle et al. 2019; Draper et al. 2018). Finally, acute administration of IFN-α or typhoid vaccination has been shown to acutely decrease functional connectivity (FC) within motivation-relevant brain regions including nuclei in the ventromedial prefrontal cortex (vmPFC) and VS (Dipasquale et al. 2016; Harrison et al. 2009).

3.3 Endogenous Inflammation in Psychiatric Disorders and Reward Circuitry

In light of converging evidence of the impact of exogenously induced inflammation on motivation-related circuits and symptoms (as described above), recent studies

Fig. 1 (continued) removal via reuptake, and increased receptor signaling through kynurenine pathway metabolites. *Key*: *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *BH4* tetrahydrobiopterin, *DAT* dopamine transporter, *EAAT2* excitatory amino-acid transporter 2, *NFκB* nuclear factor kappa B, *Jak-Stat* Janus kinase-Signal transducer and activator of transcription, *KYN* kynurenine, *L-DOPA* L-3,4-dihydroxyphenylalanine, *NLRP3* NOD-, LRR-, and pyrin domain-containing protein, *NMDAR* N-methyl-D-aspartate receptors, *PHE* phenylalanine, *QUIN* quinolinic acid, *ROS* reactive oxygen species, *TYR* tyrosine, *VMAT* vesicular monoamine transporter 2, *vmPFC* ventromedial prefrontal cortex, VS ventral striatum, *VTA* ventral tegmental area, *xCT* cystine-glutamate exchanger

have examined a potential role for increased endogenous inflammation in motivational deficits and alterations in relevant corticostriatal circuits that are frequently observed in patients with psychiatric disorders involving anhedonia (Kaiser et al. 2015; Whitton et al. 2015). In medically stable, unmedicated MDD patients, endogenous inflammation as measured by plasma CRP and inflammatory cytokines was associated with lower VS to vmPFC (VS-vmPFC) FC, which in turn correlated with anhedonia symptom severity as measured by the IDS-SR subscale (Felger et al. 2016). These findings in MDD were corroborated by parcellation-based network analysis revealing vmPFC and VS (a region parcellated as anterior ventral caudate) as the two most significant hubs, respectively, in a widely distributed network of low FC within 63 features in relation to CRP, 16 of which were highly predictive of anhedonia (Yin et al. 2019). Similar relationships between inflammation and low VS-vmPFC FC were identified among trauma-exposed women in association with a measure of anhedonia based on a Beck Depression Inventory subscale (Mehta et al. 2020). Relationships between inflammation and functional changes in reward circuitry are further evidenced by findings that MDD patients with high CRP (>3 mg/L) exhibited low neural activation in dorsal caudate in the MIDT that was significantly different compared to both controls and MDD with low CRP during anticipation of low value rewards (Burrows et al. 2021). While the above findings generally indicate a role for reduced dopamine signaling, increased inflammation in MDD has also been associated with higher MRS glutamate concentrations in left basal ganglia that correlated with anhedonia (Haroon et al. 2016). Patients with combined elevations in CRP and glutamate displayed both high anhedonia and low regional homogeneity in left basal ganglia, indicating disrupted local coherence of activity that may be driven by increased glutamate (Haroon et al. 2018a).

Like patients with mood disorders, individuals with schizophrenia also exhibit a pattern of increased inflammation, dopamine disruption, and motivational deficits. However, isolating relationships among inflammation, brain circuits, and specific symptoms like anhedonia in schizophrenia has been complicated by antipsychotic medications, frequent medical comorbidities, cyclic nature of symptoms, and particularly cognitive deficits that can affect symptom reporting and task performance (Eisenberg et al. 2017; Hennekens et al. 2005; Strauss and Gold 2012). Recent computational work has suggested that the appearance of motivational deficits in schizophrenia may emerge equifinality from distinct deficits. For example, in laboratory effort-based decision-making tasks, a reliable subset of patients exhibit a pattern of inconsistent, "irrational" choices that suggest a primary cognitive deficit related to using information about potential rewards and effort costs to guide choices, while a separate subgroup has shown a stronger aversion to effort (Cooper et al. 2019; Whitton et al. 2020). Interestingly, human amphetamine challenge studies suggest that modulation of dopamine is most strongly associated with reducing aversion to effort, but not altering effortful allocation strategies during effort-based choice (Soder et al. 2021). Moreover, subgroups of schizophrenia patients with treatment-resistance and/or persistent negative symptoms, both of which have been associated with increased inflammation (Goldsmith and Rapaport 2020; Mondelli et al. 2015; Noto et al. 2015), have been shown to exhibit evidence

of hypodopaminergic states in striatal subregions including ventral striatum (Avram et al. 2019; Demjaha et al. 2012; Kim et al. 2017). Therefore, it is possible that inflammation exerts a primary impact on corticostriatal circuitry through bottom-up influence on dopamine, yet these effects may be partially occluded by cognitive deficits that appear to contribute to altered behavior in patients with schizophrenia. That said, it is also possible that direct effects of inflammation on cortical regions like vmPFC (Harrison et al. 2009; Yin et al. 2019) might contribute to decreased motivation through top-down influence, especially considering that treatment-resistant schizophrenia has also been associated with increased cortical glutamate (Mouchlianitis et al. 2016). Additional work in this area is required to determine whether increased inflammation in a subset of patients with schizophrenia may exert similar effects on dopamine and glutamate in corticostriatal circuits as those shown to contribute to reduced motivation in the mechanistic clinical and translational studies described below.

4 Neurobiological and Neurotransmitter Mechanisms: Basic and Translational Studies

A number of environmental and lifestyle factors activate the innate immune system to drive behavioral change even in the absence of pathogens. Indeed, "sterile inflammatory" signals like stress can produce danger associated molecular patterns that activate the NLRP3 inflammasome complex to promote release of IL-1β and production of other cytokines (Iwata et al. 2013). Translational models of stress and/or inflammation-induced depressive and anxiety behavior show that circulating cytokines produced by peripheral blood immune cells can access specific brain regions via disruption of the blood brain barrier (BBB), including notably the nucleus accumbens in VS (Menard et al. 2017). Interestingly, this involves decreased claudin-5, a key protein that regulates BBB integrity, which was also observed in the VS of postmortem brain samples from MDD patients (Menard et al. 2017). Activated circulating immune cells that traffic to perivascular and parenchyma spaces of specific brain regions are required for the full expression of stress-induced behavioral changes (D'Mello et al. 2009; Weber et al. 2017). These peripheral immune cells, cytokines, and other inflammatory mediators that access the brain in turn activate local microglia (DiSabato et al. 2016) and affect neurobiological and neurotransmitter substrates like dopamine and glutamate that are abundant in subcortical regions including VS (Fig. 1). The striatum may be additionally sensitive to peripheral inflammatory signals due to the vulnerability of select populations of midbrain dopaminergic neurons to oxidative damage (Wang and Michaelis 2010), which promotes further inflammation. The molecular mechanisms via which inflammation impacts striatal dopamine and glutamate neurotransmission that are crucial for motivated behaviors have been best studied via immune challenge paradigms in rodent and non-human primate models.

4.1 *Laboratory Animal Models of Inflammation Effects on Motivation*

Earlier animal studies assessing the role of inflammation in anhedonic behavior used the sucrose preference test to probe reward sensitivity. To gain information about inflammation effects on motivation for reward and reward learning that cannot be obtained from sucrose preference alone, effort-based models in which animals perform tasks to obtain highly palatable sucrose pellets have been employed. In harmony with the data mentioned above in humans, using a choice paradigm where mice were concurrently presented with low effort/low value and high effort/high value rewards, systemic endotoxin (a.k.a., LPS) led to a decrease in effort to obtain reward while maintaining sensitivity to high value reward (Vichaya et al. 2014). Similarly, systemic administration of IL-1β in rats decreased effortful responding to food despite intact the preference for highly palatable food over chow (Nunes et al. 2014). Interestingly, inflammation-induced motivational deficits have been shown to be reversed by dopamine-modulating agents such as lisdexamfetamine (Yohn et al. 2016b). In addition to these systemic inflammation-driven changes in reward behavior, a recent study showed that selective activation of striatal microglia is sufficient to reduce sucrose consumption and conditioned place aversion, the latter of which critically depended on IL-6 and prostaglandin signaling in microglia (Klawonn et al. 2021). Consistent with findings in both mice and humans, chronic administration of systemic IFN-α causes peripheral and central immune activation and behavioral changes including reduced exploration and huddling, a depression-like index in non-human primates (Felger et al. 2007). Chronic IFN-α exposure also led to reductions in sucrose consumption when effort was required to obtain sucrose pellets from a puzzle task, but not when they were freely available (Felger et al. 2013b). Together, these findings from effort-based animal models recapitulate that inflammation preferentially impairs reward motivation (rather than sensitivity) and provide a context to study how inflammation impacts neurotransmitter systems.

4.2 *Neurotransmitter Mechanisms: Dopamine Synthesis, Release, and Reuptake*

Studies in rodents administered acute or sub-chronic IFN-α reported either increased or decreased dopamine and/or its metabolites in concert with inconsistent behavioral changes varying with regard to dose, length of exposure, and lack of use of species-specific IFN-α (Felger and Lotrich 2013). Conversely, monkeys given chronic IFN-α exhibited depressive-like huddling at a similar rate as depression in IFN-α-treated humans (~50% of animals) in relation with reduced CSF concentrations of dopamine metabolites (Felger et al. 2007; Felger and Miller 2012). To determine whether inflammation reduces release of striatal dopamine, in vivo microdialysis and PET neuroimaging with [^{11}C]raclopride displacement following

amphetamine (AMPH) challenge were conducted and indicated that stimulated dopamine release was decreased in the striatum (including nucleus accumbens) after chronic IFN-α in monkeys (Felger et al. 2013b). Decreased dopamine release as measured by in vivo microdialysis correlated with reduced effort-based sucrose consumption (Felger et al. 2013b). These results were corroborated in rodents that exhibit decreased extracellular dopamine in nucleus accumbens after acute systemic IL-6 in association with reduced motivation (Yohn et al. 2016a).

These above translational data established decreased dopamine release as a neurobiological substrate of inflammation effects on motivation and, combined with results in IFN-α-treated patients (Capuron et al. 2012), suggested dopamine synthesis and availability as a mechanism. Accordingly, IFN-α-induced decreases in striatal dopamine release were reversed by the dopamine precursor levodopa (L-DOPA) administered via reverse in vivo microdialysis (Felger et al. 2015). Inflammation and cytokines may decrease dopamine availability and release by decreasing tetrahydrobiopterin (BH4), an enzyme co-factor required for the enzymatic conversion of phenylalanine (Phe) to tyrosine (Tyr) and Tyr to L-DOPA. We and others observed increased plasma Phe/Tyr ratio, which goes up when BH4 is low (Felger et al. 2013a; Zoller et al. 2012), in IFN-α-treated patients. Evidence of reduced CSF BH4 activity correlated with increased CSF IL-6, and plasma Phe/Tyr correlated with depressive symptoms and decreased CSF dopamine and its metabolites (Felger et al. 2013a). Similar relationships were found in healthy, elderly persons with low-grade inflammation where increased blood Phe/Tyr correlated with behavioral symptoms including anhedonia and altered sleep (Capuron et al. 2011). Gene expression signatures enriched in peripheral blood immune cells from medically healthy MDD patients with both high CRP and anhedonia also reflected reduced Tyr metabolic pathways (Bekhbat et al. 2020). Additional mechanisms by which inflammation may impact dopamine transmission include dopamine packaging, release, and reuptake mechanisms (Felger and Treadway 2017). Both IL-1 and TNF have been shown to decrease vesicular monoamine transporter 2 (VMAT2) expression in rat cell lines (Kazumori et al. 2004). Stimulation of the inflammatory signaling molecule mitogen activated protein kinase (MAPK) in a human cell line increased DA transporter (DAT) activity, and inhibition of MAPK was associated with decreased DAT transport capacity in striatal synaptosomes (Moron et al. 2003). Neither in vitro activation of MAPK nor in vivo administration of IFN-α to monkeys was associated with reduced DAT expression (Felger et al. 2013b; Moron et al. 2003), but reduced dopamine 2 receptor (D2) binding by PET after IFN-α suggests they may also contribute to inflammation effects on dopamine signaling.

4.3 *Neurotransmitter Mechanisms: Glutamate Release, Reuptake, and Modulation by Kynurenines*

Inflammatory cytokines can affect glutamate transmission in several ways that increase extracellular glutamate and may contribute to anhedonia (Haroon et al. 2017). A rich literature has shown that cytokines can decrease astrocytic expression of the excitatory amino-acid transporter 2 that removes glutamate from the synapse and increase release of glutamate from activated microglia (Dantzer and Walker 2014). Of note, glutamate released from glia may have preferential access to extrasynaptic n-methyl-d-aspartate (NMDA) receptors, leading to reduced production of trophic factors and excitotoxicity (Haydon and Carmignoto 2006). These effects may be further compounded by inflammation-induced activation of indoleamine 2,3 dioxygenase (IDO) and downstream kynurenine pathway (KP) metabolites on glutamate signaling (Savitz 2020). Immune-mediated activation of IDO catabolizes tryptophan to kynurenine which, when produced in or taken up into the brain by large neutral amino-acid transporters, is further catabolized in microglia into the neurotoxic metabolite quinolinic acid (QUIN). QUIN was increased in the plasma and CSF of IFN-α-treated patients and correlated with depressive symptoms (Raison et al. 2010). In addition to increasing oxidative stress, QUIN also activates NMDA receptors contributing to excitotoxicity (Santamaria et al. 2003; Tavares et al. 2002). Higher symptoms of anhedonia were observed in MDD patients with evidence of both increased inflammation (plasma TNF) and KP activity (Haroon et al. 2020), and increased evidence of serum QUIN and KP activity correlated with volume loss in the striatum (Savitz et al. 2015).

5 Therapeutic Targets to Reverse the Impact of Inflammation on the Brain

5.1 *Neurotransmitter Targets*

Antidepressant medications that affect dopamine and norepinephrine systems such as bupropion and nortriptyline have exhibited improved efficacy compared to those selectively targeting serotonin in MDD patients with increased inflammation (Arteaga-Henríquez et al. 2019; Jha et al. 2017; Uher et al. 2014). Considering strong evidence above that inflammation inhibits dopamine synthesis, strategies to increase dopamine or its signaling may improve inflammation-related anhedonia (Escalona and Fawcett 2017; Felger and Treadway 2017). Support comes from a recent study showing antidepressant effects of L-DOPA and improved psychomotor speed in aged MDD patients (who are likely to have high inflammation) in relation to reduced [^{11}C]raclopride binding reflecting increased synaptic dopamine (Rutherford et al. 2019). A number of compounds are also available that boost BH4 activity and promote dopamine synthesis, e.g., BH4 itself, folic acid, L-methylfolate, or S-

adenosyl-methionine (SAMe), all of which have shown efficacy as adjuvants to antidepressants (Felger and Miller 2012). Biomarkers of inflammation or metabolic disturbance also predicted greater symptom improvement after adjuvant therapy with L-methylfolate (Shelton et al. 2015). Similarly, glutamatergic modulation may exert antidepressant efficacy for patients with high inflammation. Administration of glutamate receptor antagonists like the NMDA antagonist ketamine have potent antidepressant effects, especially in treatment-resistant patients, and future work should further examine links between increased inflammation and treatment response (Arteaga-Henríquez et al. 2019; Yang et al. 2015).

5.2 Anti-Inflammatory and Immunomodulatory Strategies

While results from many trials in psychiatry using anti-inflammatory therapies are mixed at best (Eyre et al. 2015), only a handful of studies have enriched for patients with evidence of increased inflammation and used specific anti-cytokine drugs with little off-target effects. Interesting, all three of these studies found that anhedonia was the symptom most improved (Lee et al. 2020; Raison et al. 2013b; Salvadore et al. 2018). While existing cytokine-antagonists may not be viable antidepressants (Dreyer et al. 2016; Miller et al. 2017), immunotherapies are evolving with even more specificity for immune cell subpopulations or intracellular signaling pathways (Iwakura and Ishigame 2006). Despite considerable interest in the role of the immune system in psychiatric disorders and therapeutic implications, little information exists regarding the specific immunologic mechanisms required to design better therapies. A recent study suggests that high inflammation in MDD involves both monocytes and T cells, and evidence of the metabolic and energetic reprograming immune cells use to sustain inflammatory activation was seen only in cells from medically stable MDD patients who had both high CRP and significant anhedonia (Bekhbat et al. 2020; Lynall et al. 2020). Immunometabolic pathways in specific cell types are being targeted for new therapies in autoimmune and inflammatory disorders (O'Neill et al. 2016), and align with recent data that rapamycin, an inhibitor of mTORC1 signaling involved in such processes, enhanced the antidepressant benefit of ketamine therapy (Abdallah et al. 2020). While interventions (e.g., exercise, meditation, yoga, dietary changes, omega-3 fatty acid supplements) to modify environmental and lifestyle factors that drive inflammation and related symptoms like anhedonia can reduce inflammation and have been successful in research studies particularly in non-psychiatric patients with high inflammation (i.e., cancer patients) (Bower and Irwin 2016), their effects are not specific to immune processes and may be difficult to implement in psychiatric populations with anhedonia.

6 Translational Challenges and Future Directions

In this chapter, we present extensive clinical and translational evidence supporting increased inflammation and its effects on the brain as one pathophysiologic pathway to reduced motivation and symptoms of anhedonia. Decreased dopamine availability and excessive glutamate may serve as mechanisms of inflammation's impact on reward motivation, as well as potential therapeutic targets for anhedonia and related symptoms in psychiatric patients with elevated biomarkers of inflammation. Moreover, studies employing anti-cytokine therapies in depression have consistently found anhedonia to be the symptom most improved. Despite consistent findings of associations between inflammation and alterations in neurotransmitters and neurocircuits involved in reward processing and reduced motivation, several challenges and considerations exist. While current anti-cytokine therapies may reduce anhedonia or related symptoms in patients with high but not low inflammation, translation of these therapies is limited by efficacy in only one symptom domain, concern for blockade of potentially beneficial effects of innate immune signaling on other neurobiological pathways, and risk for misclassification of patients. Development of more specific immune-targeted therapies is on the horizon, and approaches targeting neurotransmitters impacted by inflammation with existing therapies may serve as more proximal means for translating these concepts into patients. Crucial in this regard is intelligent trial design. Biomarker-driven approaches should target specific therapies to patients with evidence of high inflammation (i.e., using CRP) and/or relevant symptoms like anhedonia, and assess not only response and remission but also target engagement of relevant circuits and symptoms. Given the relationships between inflammation, anhedonia, and treatment resistance, inflammation should also be considered in trials developing new therapies for psychiatric patients with anhedonia. Finally, despite consistent findings of increased inflammation in schizophrenia and relationships with negative symptoms including reduced motivation, future work is needed to better understand the role of inflammation in the brain in these patients and how it relates to treatment response. In sum, an emerging understanding of the mechanisms by which peripheral inflammation can affect corticostriatal circuits and relevant neurotransmitters to impact motivation and contribute to anhedonia has provided a framework for development of novel therapies. Further identification of a platform of neuroimaging, behavioral, and peripheral biomarkers that can be used to test these therapies lends potential for future personalization of treatments targeted to biologically based subgroups of patients with transdiagnostic presentation of symptoms like anhedonia.

Acknowledgements This study was supported by grants R01MH109637, R61MH121625, and R21MH121891 (Felger); R01MH108605 and R21MH119622 (Treadway); and F32MH119750 (Bekhbat) from the National Institute of Mental Health.

Financial Disclosure Dr. Treadway, co-inventor of an effort-based learning task, has served as a paid consultant to Blackthorn Therapeutics. Emory University and Vanderbilt University licensed this software to BlackThorn Therapeutics. Under the IP Policies of both universities, Dr. Treadway receives licensing fees and royalties from BlackThorn Therapeutics. Additionally, Dr. Treadway has a paid consulting relationship with BlackThorn. The terms of these arrangements have been reviewed and approved by Emory University in accordance with its conflict of interest policies. Dr. Felger has previously consulted for Otsuka on a topic unrelated to this work. No funding from these entities was used to support the current work and all views expressed are solely those of the authors. Dr. Bekhbat has no financial disclosures.

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A Computational View on the Nature of Reward and Value in Anhedonia

Quentin J. M. Huys and Michael Browning

Contents

Abstract Anhedonia – a common feature of depression and other neuropsychiatric disorders – encompasses a reduction in the subjective experience and anticipation of rewarding events, and a reduction in the motivation to seek out such events. The presence of anhedonia often predicts or accompanies treatment resistance, and as such better interventions and treatments are important. Yet the mechanisms giving rise to anhedonia are not well understood. In this chapter, we briefly review existing computational conceptualisations of anhedonia. We argue that they are mostly descriptive and fail to provide an explanatory account of why anhedonia may occur. Working within the framework of reinforcement learning, we examine two

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Curr Topics Behav Neurosci (2022) 58: 421–442
https://doi.org/10.1007/7854_2021_290
Published Online: 22 December 2021

potential computational mechanisms that could give rise to anhedonic phenomena. First, we show how anhedonia can arise in multi-dimensional drive-reduction settings through a trade-off between different rewards or needs. We then generalise this in terms of model-based value inference and identify a key role for associational belief structure. We close with a brief discussion of treatment implications of both of these conceptualisations. In summary, computational accounts of anhedonia have provided a useful descriptive framework. Recent advances in reinforcement learning suggest promising avenues by which the mechanisms underlying anhedonia may be teased apart, potentially motivating novel approaches to treatment.

Keywords Anhedonia · Computational psychiatry · Homeostasis · Model-based · Reinforcement learning

1 Introduction

Anhedonia, broadly defined as a loss of interest or pleasure in rewarding activities (American Psychiatric Association 2013), is a common feature of many psychiatric presentations (Husain and Roiser 2018; Treadway and Zald 2011; Trøstheim et al. 2020). Its association with adverse outcomes generally (Spijker et al. 2001), and poor response to treatment specifically (Uher et al. 2012; McMakin et al. 2012), has motivated interest in the mechanistic processes that underlie it, with the ultimate aim of developing novel and more effective interventions.

While there have been many lines of enquiry investigating the mechanisms of anhedonia, a particularly popular approach has been to frame it as arising from abnormalities in reinforcement learning (RL) processes. Reinforcement learning considers how organisms use experiences of reward and punishment to motivate future actions and so has clear face validity when considering anhedonic experiences in which participants report reduced pleasure from, and a decreased motivation to complete, daily activities. Further, the development and characterisation of a set of formal models with demonstrable explanatory validity at a behavioural and neurobiological level suggests that RL is well placed to identify causally important targets for novel interventions.

In this chapter we will describe the clinical symptoms and experience of anhedonia and provide a basic overview of the logic of RL models and the processes they describe. We will then summarise the literature suggesting an association between abnormalities in RL processes and anhedonia, critically appraising what it does, and does not tell us about mechanism. To summarise our argument, we will suggest that previous work utilising an RL framework has provided consistent evidence that anhedonic patients behave 'as if' rewarding outcomes were less valuable, but have provided little evidence as to why this might have occurred. We argue that, in order to understand why this occurs, it will be necessary to move beyond the largely descriptive RL models employed to date and develop mechanistic models with

deeper explanatory ability. We then summarise recent work demonstrating that humans represent reward and derive value estimates in a more complex manner than suggested by the commonly used descriptive RL models. Lastly, we briefly consider some of the implications of this work on how anhedonia might be treated.

2 The Components of Anhedonia and Patient Experience

The diagnostic manuals provide a broad definition of anhedonia as diminished interest or pleasure in activities (American Psychiatric Association 2013; WHO 1992). As has been noted previously (Husain and Roiser 2018; Treadway and Zald 2011), this definition encompasses a number of distinct components:

1. The subjective experience of pleasurable events (e.g. how much I enjoy an experience at the time)
2. The anticipation of future pleasurable events (e.g. how much I look forward to an enjoyable experience)
3. The motivation to engage in pleasurable activity (e.g. whether I act and expend effort to increase the likelihood of experiencing enjoyable experiences)

While a number of instruments have been developed to measure these components individually (Rizvi et al. 2016), they are clearly not independent (e.g. your motivation to engage in an activity will be influenced by how pleasurable you find it), suggesting that similar anhedonic presentations may arise from distinct mechanisms. To illustrate this point and motivate the formal description of RL models, which can be used to link the components together, Table 1 describes a variety of different mechanisms that might lead to the same anhedonic behaviour– not attending a party.

Before introducing the RL framework used to investigate anhedonia, it is important to highlight that, belying the simple descriptions of the components provided above, patients' experience of anhedonia (and of pleasure generally) are often far from simple. For example, a qualitative study of adolescents with depression (Watson et al. 2020) who were asked to describe their experience of anhedonia identified general themes of reduced joy and motivation, but also of a loss of connection with others and a questioning of their self and their purpose. This indicates that the 'value' relevant to patients is often multi-faceted and future orientated, for example relating to an individual's social roles and their ultimate ability to fulfil these. As a consequence, any account of anhedonia that seeks to explain why patients treat potentially rewarding experiences as less valuable must be able to capture the influence of these complex valuation processes. We now provide a brief overview of the basics of RL models and how they have been applied to study mechanistic processes in anhedonia.

Table 1 Distinct causes of a single anhedonic behaviour

Mechanism	Mechanism in terms of RL model	Narrative
Reduced hedonic value	Smaller r_{reward}	A woman is invited to a party. She attends the party and does not enjoy it. She does not attend the next party she is invited to as she does not want to repeat an unenjoyable experience.
Increased effort sensitivity	More negative r_{effort}	A man is invited to a party. He attends the party and enjoys it, but finds the experience exhausting. He does not have the energy to attend the next party he is invited to.
Reduced learning from past experience	Smaller model-free learning rate α	A woman attends a party and, against her expectation, enjoys it. When asked if she wants to attend another party, she declines, still feeling she will not enjoy it.
Asymmetric reward function	$\frac{\partial r}{\partial \text{work}} > \frac{\partial r}{\partial \text{social}}$ See Sect. 4	A man is invited to a party. He thinks he may enjoy it but is worrying that he is not performing well at work at present. He declines the invitation, as it will not improve his work performance.
Reduced constructed value	Low $V(s)$ see Sect. 5	A woman is invited to a party. Although she likes the idea of a party, she thinks she will experience rejection and panic attacks if she attends and hence declines.

3 Existing Computational Research

The motivation to engage in an activity rests on the judgement that it is worth the effort in the longer run. This depends on the rewards produced by the activity, its costs in terms of effort or associated punishments, and what the long-term consequences of the activity are (e.g. will it lead to more or less reward in the future). The field of reinforcement learning (RL) is concerned with identifying optimal solutions to this difficult problem.

To be a little more precise, imagine that an individual starts in state, s, one of the sets of all possible states, S, each of which is associated with some reward r_s. The individual is able to perform one action, a, from those available in that state, A_s, with the action resulting in a change of the state to s' and the associated reward $r_{s'}$. RL algorithms approach the problem of what action, a, to take by estimating the value, $V(s)$, of the states – the long-term sum of future rewards that will be experienced if the state is visited (Sutton and Barto 2017).

One of the simplest algorithms (Rescorla and Wagner 1972) recursively estimates the value of states simply through experienced outcomes. A variant of this algorithm frequently used in studies of anhedonia is:

$$V_{t+1}(s) = V_t(s) + \alpha(\rho r_t - V_t(s)) \quad (1)$$

Here, value is updated by the reward prediction error, the difference between the experienced reward, r_t (NB, which may include a negative punishment/effort term as well as a positive reward term), and the estimated value, V_t. Two parameters influence the algorithm's behaviour and allow it to be fitted to participant data; a learning rate term, α, which controls how quickly the algorithm updates its value, and a reward sensitivity term, ρ, which changes the effective magnitude of the experienced rewards. The differential effects of these parameters on learning are apparent when the model is exposed to states with static reward associations – here the reward sensitivity parameter influences the final (asymptotic) estimated value difference between states, whereas the learning rate influences the speed with which the asymptotic estimate is reached. While this algorithm provides a straightforward account of reward learning that links experienced rewards to estimated values, it is important to note that it does not account for a number of important processes that are likely to influence human learning. In particular:

(a) The algorithm has no principled way of allowing the internal state of an individual to influence reward magnitude. For example, drinking water is generally more rewarding when one is thirsty than when one is not. The only way this can be accommodated in the algorithm is by engineering separate states for 'thirsty' and 'not thirsty' and simply telling the algorithm that the reward for drinking water is higher in the first state. In other words, the algorithm can describe how learning might proceed if the reward associated with drinking was reduced, but not explain how or why it occurs.
(b) The algorithm learns the association between immediate reward and a state, but ignores the values of all subsequent states. For example, as exercise is effortful it would find no reason to do it, even if it leads to the valuable future state of being healthy. As described above, the value of a state is defined as the long-term reward expected from visiting that state. This algorithm ignores all future reward.

The most common behavioural observation from empirical studies which have employed this class of algorithm in depressed and anhedonic individuals is a cross-sectional association between anhedonia and reduced reward sensitivity ρ or equivalently noisiness of exploratory choice (Steele et al. 2007; Chase et al. 2010; Kunisato et al. 2012; Blanco et al. 2013; Huys et al. 2013; Robinson and Chase 2017), with some evidence of increased punishment sensitivity (Beevers et al. 2013; Herzallah et al. 2013). An association between anhedonia and behavioural estimates of learning rate, α, has been reported (Chase et al. 2010), although much less commonly.

As the ρ parameter in Eq. 1 acts to scale the magnitude of experienced reward, one interpretation of this finding is that anhedonic individuals have a generalised reduced hedonic response to the sensory experience of rewarding events. If correct, this would predict that such individuals should provide a lower rating of the hedonic

value of all primary rewards in the absence of learning. This question has been addressed in a number of studies, most of which have utilised olfactory or gustatory stimuli. Overall, this literature consistently finds that symptoms of depression and anhedonia are associated with a decreased ability to discriminate between different sensory stimuli (Colle et al. 2020; Atanasova et al. 2010; Pause et al. 2001; Lombion-Pouthier et al. 2006; Kohli et al. 2016; Amsterdam et al. 1987; Berlin et al. 1998), but have not consistently found that the hedonic value of the stimuli is attenuated (Colle et al. 2020; Atanasova et al. 2010; Pause et al. 2001; Naudin et al. 2012; Amsterdam et al. 1987; Berlin et al. 1998; Clepce et al. 2010; Swiecicki et al. 2009; Dichter et al. 2010).

A related prediction is that anhedonic individuals should show a reduced neural response to the experience of rewarding stimuli, again in the absence of learning. Although this effect has been observed in depressed patients (Pizzagalli et al. 2009), the relationship is more frequently found with anticipation of stimuli, i.e. with the value or the prediction error (Kumar et al. 2008; Knutson et al. 2008; Geugies et al. 2019; Greenberg et al. 2015; Eckstrand et al. 2019; Rupprechter et al. 2020; Pizzagalli et al. 2020). However, one large study using a task with no learning did not find an effect of either prediction error or outcome on neural activity (Rutledge et al. 2017).

Overall, the work described above suggests that it is difficult to account for the lower ρ parameter observed in RL studies of anhedonic individuals simply as the result of a reduced hedonic response to outcomes. What then might be causing this effect? One possibility is that the radically simple RL model described in Eq. 1 is mis-specified (Nassar and Frank 2016), it ignores important processes that may alter the effective reward experienced by an individual and can only account for the effect of these processes in its ρ parameter. In other words, anhedonic individuals behave 'as if' rewarding events are of lower magnitude, but to understand why they behave this way we must consider in more detail how rewards are constructed and used to estimate value. Indeed, a more reliable reduction of the hedonic impact of both positive and negative items can be observed in response to more complex stimuli, such as visual images or films (Bylsma et al. 2008), where any 'reward' has to be constructed or inferred. In the next sections we discuss potential processes that may impact the reward experienced by individuals, illustrate how they may be incorporated into RL models and describe how their perturbations may account for anhedonic behaviour.

4 Reward as Distance

As we have seen above, a number of empirical studies have suggested that, when learning about the values of actions, people with anhedonia seem to treat rewarding outcomes as if they were of a smaller magnitude than people without anhedonia. When thinking about why this might occur, one important question is what

determines how rewarding an event actually is (or should be). In this section we consider the implications of two basic observations relevant to this question:

(a) The reward experienced following an event is influenced by your current state – drinking water is more rewarding if you are thirsty than if you are not.
(b) Distinct aspects of your current state can independently influence the reward associated with an event – if I am both hungry and thirsty, eating will reduce my hunger, and will also reduce how rewarding future food is, but will not influence how rewarding water is.

These observations underpin 'drive-reduction' theories of motivation (Fig. 1), which suggest that the reward experienced following an event is a function of the degree to which the event moves you towards a homeostatic 'set-point' (Hull 1943). While a number of distinct drive-reduction theories have been proposed (Berridge 2004; Bolles 1980; Juechems and Summerfield 2019; Keramati and Gutkin 2014; Berridge 2012), their common element is that a multi-dimensional 'drive space' can be defined with distinct dimensions representing different basic drives (e.g. hunger, thirst). An individual's current state is represented by a position in this space (i.e. with a thirst of 'x' and a hunger of 'y'). The space also includes a homeostatic set-point, the point at which all of the individual's drives are fulfilled. Different events (e.g. drinking water) move the individual from their current position to a new position in drive space, with the reward experienced by the individual following the event being equivalent to the reduction in distance between their location and the set-point. When first conceived, these drive-reduction theories were motivated by physiological homeostasis (i.e. regulating temperature, hydration etc.; Hull 1943), although more recent iterations have suggested that a similar approach might be applied to more abstract goals, such as maintaining social status, with clear relevance to subjective experiences such as anhedonia (Juechems and Summerfield 2019; Keramati and Gutkin 2014).

Formally (Keramati and Gutkin 2014), if an individual's current position at time t in an N dimensional drive space is defined as $H_{(t)} = (h_{1,t}, h_{2,t}, h_{3,t}, \ldots, h_{N,t})$ and the position of their set-point is defined as $H^* = \left(h_1^*, h_2^*, h_3^*, \ldots, h_N^*\right)$, then the distance from the current position can be described as:

$$D(H_t) = \left(\sum_{n=1}^{N} \left| h_n^* - h_{n,t} \right|^q \right)^{1/p} \tag{2}$$

The parameters p and q influence the geometry of the drive space, with $p = q = 2$ defining a Euclidean space (some implications of different values of these parameters are discussed below). If an event occurs to change the individual's position in drive space, the reward experienced as a result is defined as:

$$r_{t+1} = D(H_{t+1}) - D(H_t) \tag{3}$$

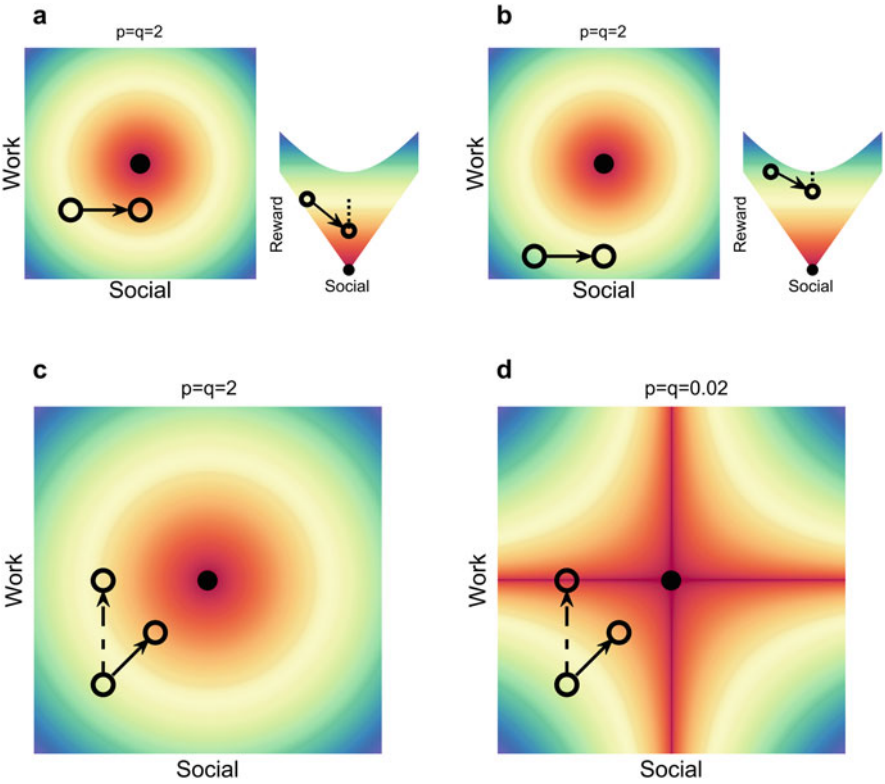

Fig. 1 Reward as a reduction in drive. Each panel illustrates a two-dimensional drive space, with social function being represented along the *x* axis, and work performance along the *y* axis. The black circle in the centre of each plot is the set-point at which all drives are satisfied. Distance from the set-point is represented by the colour of the plot and is determined by the geometry of the drive space (Eq. 2). Events experienced by an individual will change their position in drive space, for example the arrows connecting the two circles in panels (**a**, **b**) illustrate the effect of attending a party which specifically changes an individual's position on the social dimension. The reward associated with an event is defined as the reduction in distance to the set-point produced by a change in position (Keramati and Gutkin 2014). Two situations in which the reward experienced by attending a party may be reduced are illustrated. The first situation is shown in panels (**a**) and (**b**) which are identical other than the starting position of the points on the *y*-axis – in panel (**b**) the individual is less content with his work situation than in panel (**a**). This has the effect of reducing the reward experienced from attending a party (the insets of both panels show the same drive space rotated by 90° around the *x* axis so that the reward associated with attending the party is represented by the dotted line). The second situation is illustrated in panels (**c**, **d**). These panels illustrate the relative effect of an event that improves both work and social drive (solid lines, e.g. attending a work party, which moves +1 in both axes) and an event that only satisfies the work drive (dashed line, e.g. working longer, which moves +2 along the work dimension). Panel (**c**) illustrates the change when the drive space is Euclidean ($p = q = 2$) and the work party produces higher reward. In panel (**d**) the drive space is warped ($p = q = 0.02$) resulting in longer work producing more reward. In general as p and q increase, multi-dimensional reductions in drives produce increasingly greater rewards than uni-dimensional

The important property of this formulation for our argument is that, by providing an account of how reward is generated, it illustrates situations when r, the reward associated with an event, should be relatively higher or lower. In other words, it describes situations in which apparently anhedonic behaviour is expected and thus potentially provides insights into why individuals may exhibit this behaviour. We describe two specific examples below.

4.1 A General Effect of Unsatisfied Drives on Reward

It is more difficult to enjoy a party if you are constantly worrying about your job than if you are not. At first glance, this observation seems trivial, however if the party has nothing to do with your job, then why should work worry make it less enjoyable?

Figure 1a, b illustrates why this might occur (Keramati and Gutkin 2014). It shows an example drive space in which the x dimension encodes social satisfaction and the y dimension encodes work functioning. The filled black circle in the centre represents the set-point (the ideal level of both the work and social dimensions). The distance to this set-point is represented by the colour of the plot (for this example the space is Euclidean, with the parameters of Eq. 2 being $p = q = 2$). In this setting, attending a party with friends moves one along the x axis of drive space – it will make one feel less lonely, but would not improve work performance. The effect of attending a party for someone who is a bit lonely and not very worried about work is illustrated in Fig. 1a by the arrow moving the position to the right. The reward associated with attending the party is the reduction in distance to the set-point from the start to the end of the arrow and is illustrated by the change in colour (and by the dotted line in the inset). Figure 1b illustrates exactly the same situation for an individual who is more worried about their work (the points are lower on the y axis). As can be seen, even though this individual starts out just as lonely before the party, and the party has an identical effect of reducing this loneliness, the increased worry about work results in a smaller reward associated with attending the party, an effect that is present for all drive geometries that satisfy $p = q > 1$.

4.2 The Geometry of Drive Space Influences Preference for Multi-dimensional Rewards

In reality, a single event will often be associated with different types of reward (and/or cost), such as a work party that improves both your work functioning and social satisfaction (at least to some extent). Drive-reduction accounts of reward are able to capture this sort of multi-dimensional effect well (Juechems and Summerfield 2019) and to compare it to simpler effects which change just one dimension of drive.

Interestingly, the geometry of the drive space influences this comparison in a way that may be relevant to anhedonia.

Figure 1c, d illustrates the situation where an individual is equally far from their set-point on both the social and work axes. Imagine they have to decide whether to attend a work party (which will improve both dimensions by +1, illustrated by the solid arrow in both panels) or just stay at work longer (which will improve work by +2 but not influence social satisfaction, illustrated by the dashed arrows). The reward associated with these choices is, as per Eq. 3, the reduction of distance to the set-point. Figure 1c illustrates the case when the space is Euclidean, with $p = q = 2$. Here the multi-dimensional work party brings the individual closer to the set-point than the uni-dimensional effect of working longer, and thus results in a larger reward. However, as both the p and q parameters reduce, the relative advantage of the multi-dimensional option drops, with Fig. 1d illustrating an extreme case where $p = q = 0.02$ and staying at work is substantially more rewarding than attending the party. Overall, as p and q increase, a multi-dimensional 'bundle' of effects on different drives will increasingly produce larger rewards than uni-dimensional effects, with $p = q = 1$ being the indifference point at which the two effects produce equivalent reward.

Drive-reduction effects may be incorporated into RL accounts by substituting the experienced reward term, r, from algorithms such as that described by Eq. 1 with the function described by Eq. 3 (Keramati and Gutkin 2014; Juechems and Summerfield 2019; Zhang et al. 2009). However, as described above, a second process ignored by Eq. 1 is the value of future states. In the next section we consider a more general framework that incorporates the impact of estimated future states on experienced reward.

5 Rewards on Graphs

The geometrical view of rewards as distances is particularly useful for homeostatic situations. However, distances are harder to define in more general, abstract spaces, where the geometry is not necessarily predefined by physiologically existing imperatives. Furthermore, the criticism directed against the RescorlaWagner model, that it is largely descriptive rather than explanatory, is not completely resolved by simply replacing the r term with the output from a multi-dimensional drive space. For example, this output depends on the geometry of the drive space, but what determines this geometry? We now turn to RL on graphs as one way to define distances in more complex spaces and when considering more general goals. Briefly, RL provides a potentially general framework for thinking about how anhedonia may arise when important goals cannot be achieved by providing algorithms to measure progress towards goals that are sensitive to individuals' beliefs and priorities.

At the heart of these models is the value $V(s)$ of states. It is akin to the distance function in Eq. 2, and can be used to analogously quantify the progress towards a goal in terms of a change in value when going from one state to another:

$$\delta_v = V(s') - V(s) \tag{4}$$

We note that δ_V takes on a role similar to the reward r in Eq. 3. Readers familiar with RL may note that it is similar to the temporal difference prediction error δ, but is missing the r term. We omitted it here to emphasise that actions in most states do not lead to immediate primary rewards r, but instead lead to a change in state. Hence, the prediction errors are mostly driven by differences in value. We now examine whether the term δ_V may provide fruitful insights into the origins of anhedonia.

We first illustrate how $V(s)$ can capture effects akin to the distance in Eq. 2, and then discuss how it is more general and encompasses a broader set of findings. $V(s)$ is defined as the long-term reward expected from visiting the state. In the grid in Fig. 2a, the goal is the red circle, providing an actual reward r, whereas no actual reward is obtained anywhere else. In this case, the value $V(s)$ is related to how rapidly the goal will usually be reached from each state s to the goal state. A number of factors can influence this value, for example it will decrease when transitions are not fully controllable and hence occur least partially at random, or when only unidirectional moves along the axes are possible (black vs grey connections). In most situations, as in Fig. 1, moving along the social dimension results in a steeper increase in value (a higher δ_V) for the green path than the yellow path (Fig. 2b, c, e, bottom panels). Hence, assumptions about how feasible it is to move between states affect the perceived distance and hence value of each state. If hedonic experience is related to δ_V, this qualitatively replicates the examples illustrated in Fig. 1, whereby an event may be more or less 'rewarding' depending on the presence of other competing priorities or goals.

However, this formulation of values on a graph goes beyond the reward as distance view in two ways. First, it allows us to formalise complex relationships to goals. For instance, it may not always be possible to simply choose actions that bring us straight towards a goal. If certain moves in the grid are not allowed (Fig. 2f, g), a distance as in Eq. 2 may no longer be a good guide. RL allows us to measure distance in more complex graphs and to integrate constraints in how individuals believe they can move in this homeostatic or goal-related space.

Second, estimates of the long-term value $V(s)$ depend on two terms: the immediate reward experienced in the current state, and all future (discounted) rewards from subsequently visited states. The future component has to be estimated. Model-free algorithms estimate it from past experienced rewards, while model-based algorithms derive it from a type of internal simulation according to internally held beliefs about what might happen in the future (Daw et al. 2005; Sutton and Barto 2017). The latter, model-based process, allows individual beliefs to influence the value estimates. Equation 4 formally describes how beliefs about future events will impact the hedonic impact of current experience. An individual's belief structure can be viewed as a graph, with reward being obtained at the goal state. In this graph, beliefs about the links between future states are represented as the edges (connections). These edges control the long-term reward expected from, and hence the hedonic impact of visiting a state. We now illustrate this with two examples.

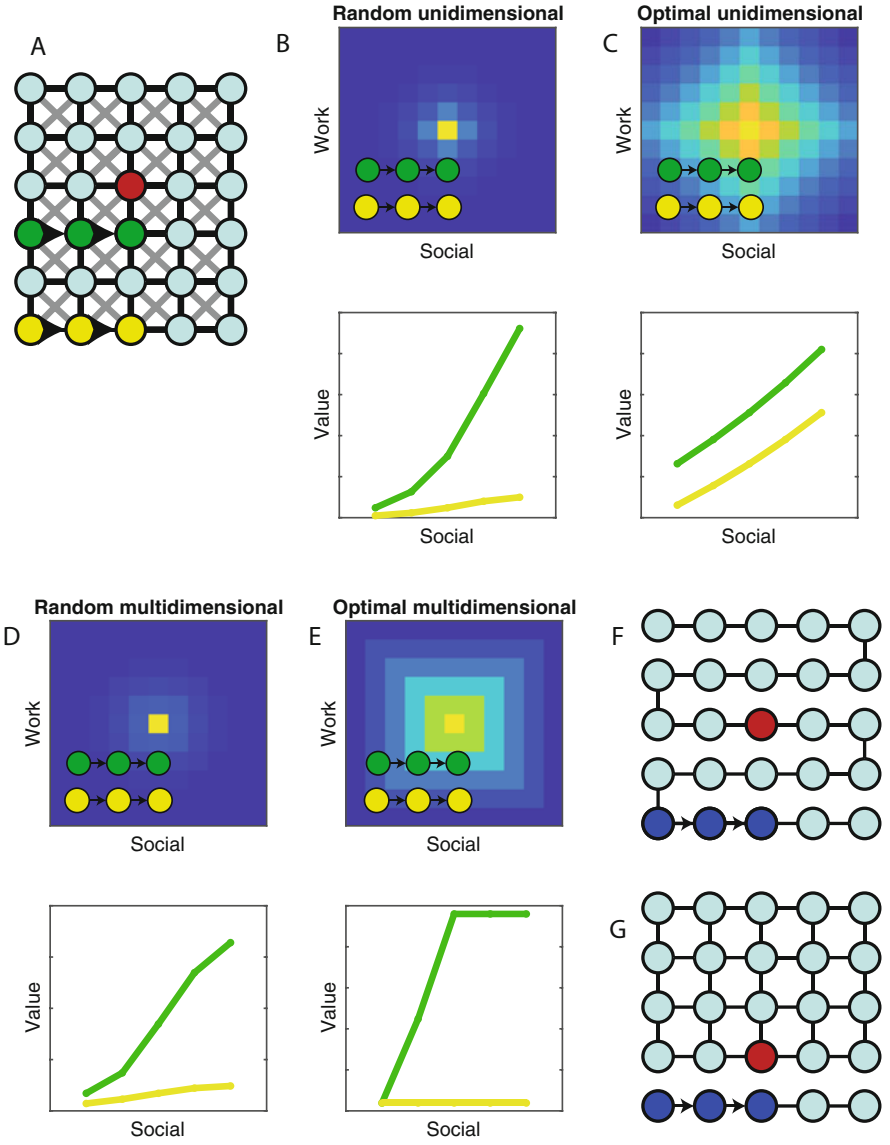

Fig. 2 Goal distance in RL. (**a**) A grid of states. The agent considers moving along the green or yellow path. The goal, or reward, can be retrieved in the red state. The green and yellow moves are equivalent to those in Fig. 1a, b. Note this does not define a Euclidian distance as in Fig. 1, but this can be approximated by setting the transition probabilities accordingly. (**b**–**e**) *top panels*: Heatmaps showing the value, the long-term expected reward, for being in each of the states as derived from the Bellman equation (Bellman 1957). The effects of different allowed transitions between states, i.e. when movement is only allowed along the axes ('uni-dimensional', dark transitions in (**a**)), or also diagonally ('multi-dimensional', grey transitions in (**a**)), and different action policies (i.e. 'random', in which the agent selects an action at random and 'optimal' in which the agent always selects the action that increases value the most) are shown. For illustration purposes, the space is more finely quantised than suggested in (**a**). (**b**–**e**), *bottom panels*: The value of states along the green and yellow trajectories. The value generally increases more rapidly for the green than for

5.1 How Cognitive Distortions Can Reduce Hedonic Experience

Hopelessness and helplessness theories of depression (Seligman and Maier 1967; Maier and Watkins 2005; Alloy et al. 1999) emphasise the importance of beliefs about the inachievability of important goals and a perceived lack of control. Such beliefs can be captured formally in terms of either graph structure, or the ability to navigate effectively within the graph structure (Huys and Dayan 2009). Consider first Fig. 2g. In this graph, the person believes that there is no path from their state (blue) to the goal (red). Here, engaging in a social activity would bring the individual 'closer' to the goal in a simple distance sense, but it would have zero hedonic impact because there is no path to the goal: none of the states the person believes they can visit are linked to the goal. A related effect is obtained if the individual doubts their own ability to select the best action, or in the effect of that action. In this case, the selection of an action will not reliably cause transition to a state closer to the goal, which effectively flattens out the value function, and thereby reduces the hedonic δ_V signal.

Hence, helpless or hopeless structures of an individual's belief graph can result in profound changes to the perceived hedonic impact δ_V of events.

5.2 How the Meaning of Events May Arise from Associational Graphs

Instruments that assess anhedonia require individuals to report how much pleasure or enjoyment they would have derived from certain events or activities, or how much they anticipate or engage in them. This requires individuals to internally instantiate or simulate the events, and then engage in a process that allows them to estimate the required quantities such as pleasure or anticipation.

We now consider this process in terms of reinforcement learning on a graph.

Graphs provide a way to formulate how individuals believe events are related. This in turn allows events to be valued in relationship to other valued events. Consider a question akin to those typically asked in an anhedonia questionnaire

Fig. 2 (continued) the yellow trajectory (shown in green and yellow, respectively). The experienced reward is the change in value, represented by the slope of the lines. As can be seen, the relative advantage of the green trajectory is influenced by the available transitions and the agent's policy (note that similar effects were produced by changes in the geometry of the drive space in Sect. 4). (**f**) If not all state transitions are believed to be available, a previously rewarding action may result in reduced value and thus be punishing. Here, for instance the lack of transitions means that improving social functioning by moving to the right actually takes the agent further from the goal and will result in reduced value (and thus punishment). (**g**) In the extreme case, where there is no path to the goal at all, the agent is helpless and no action will produce reward

'How much would you enjoy going to a party?'. When thinking about this, one person might imagine getting dressed, looking good, going to dance, enjoying the music, flirting, conversing and making friends. Going to a party is hence not only potentially appetitive in itself, but is also associated with positive events, and so the person might respond that they would quite enjoy going to the party. A different person might instead imagine the effort associated with going to a party, having panic attacks on the way there, feeling rejected, sweating and even ruining any existing relationships. Even if the actual experience of the party was enjoyable, this person might still respond that they would not enjoy the prospect of the party. Hence, as illustrated in Fig. 3, even if both individuals would enjoy the actual party equally when they were there, the different associations between the party and other events would result in different assessments of its hedonic value and different motivations to attend. In other words, how nice it is to go to a party is different for different individuals because it is related, in their minds, to other events. This may be one approach to capturing how the 'meaning' of events differs for individuals as a function of their beliefs (c.f. Jackson et al. 2019).

A few points about this are worth noting. First, the estimate of a value V(s) can be arrived at in different ways. The literature review above discussed prediction error learning from experience as one way to arrive at it. Alternatively, the conceptually simplest algorithm to estimate V(s) is to explicitly consider ('think through') all possible future consequences, weighing them by their probability, and computing the expectation. This requires access to an internal model of what is likely to happen. This is often very demanding because the future holds many possibilities (Daw et al. 2005). As a result, not all possible scenarios can be evaluated and thus the outcome of the evaluation is highly sensitive to the subset of scenarios selected for evaluation (Huys et al. 2012; Huys and Renz 2017). An approximation to an exhaustive evaluation can be arrived at by sampling from the network according to the transition probabilities, e.g. generating lots of sequences as in Fig. 3b, and then averaging over their values. There is substantial behavioural evidence that humans do engage in such sample-based evaluation, and that it is modulated by attentional processes (Krajbich 2019). A bias in the sampling process can hence effectively mimic an alteration in the underlying model samples are drawn from (Huys and Renz 2017), and even with high bad to bad transition probabilities, and low good to good transition probabilities, sometimes the sampled associations may be positive. Such an iterative sequential sampling process may be slow, whereas hedonic assessments can often be very rapid. An interesting possibility comes from Successor representations (Dayan 1993; Russek et al. 2017), where estimates of *what* is likely to happen, i.e. which states are likely to succeed which other states, are constructed and stored. Values can then be derived rapidly and without sampling by weighing these predictions about the future by how rewarding they are. Such successor representations could allow for very rapid evaluations without having to consider all options repeatedly or sampling.

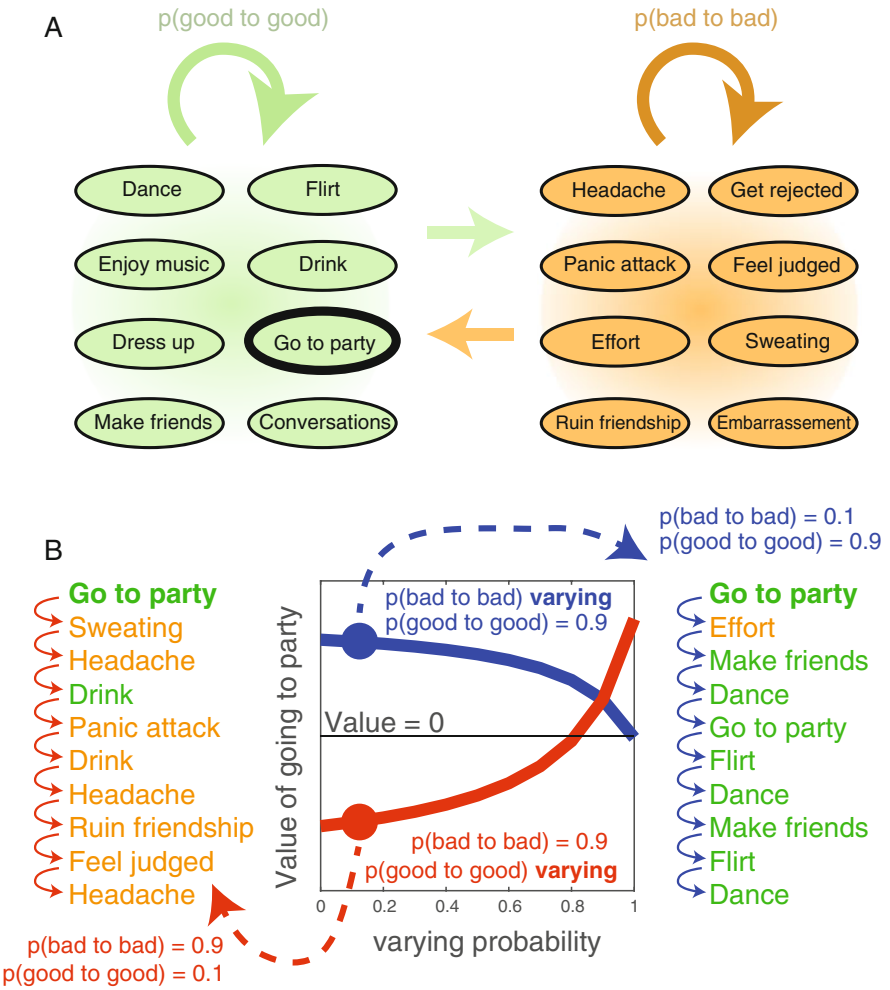

Fig. 3 Values in thought association space. (**a**) Grid of semantically associated states. One subset of states is roughly positive (green), the other is roughly negative (orange). We parametrise individual's internal belief models in terms of two parameters. The first parameter p(good to good) is the probability of going from one positive to another positive state, i.e. to sample a positive thought after having sampled a positive thought. The second parameter is the probability of sticking with bad thoughts (p(bad to bad)). The probability of transitioning from good to bad is simply $1 - p$(good to good), and $1 - p$(bad to bad) for bad to good. (**b**) The sequence of words shows two random sequences drawn from this associative model. For a high bad-to-bad transition probability and a low good-to-good transition probability, a sequence starting in the 'go to party' state rapidly transitions to the bad states and stays there most of the time. The converse is true for a high good-to-good and low bad-to-bad transition probability (sequence of words on the right). The graph in the middle shows the value assigned to the 'go to party' state as a function of varying transition probabilities. We assume that the rewards associated with the green and orange states are random positive and negative numbers, respectively. The value is then the average over sequences experienced when starting from the 'go to party' state. Critically, although the reward associated with the 'go to party' thought is always positive, its value can vary widely, from strongly positive to strongly negative, depending on the nodes it is associated with. The red line in the middle panel shows the value of 'go to party' for a high bad-to-bad probability. Here, the value is only positive if the good-

6 Discussion

We first argued that existing behavioural data suggest that anhedonia is associated with a reduction in reward sensitivity ρ. However, the simple RL models employed in this work can only accommodate changed reward sensitivities by postulating a change in the underlying state. In the absence of a cogent theory linking rewards to particular states, these models therefore provide a purely descriptive account of anhedonia. Second, we argued that the reduction of physiological drives is one area where there is a cogent theory that links specific states to reward changes. Indeed, this provides some interesting insights into how anhedonia-like phenomena may arise not from abnormalities in one reward system, but from a trade-off or balance between different types of rewards or needs. Finally, we argued that reinforcement learning on graphs provides a useful generalisation of the drive-reduction account to complex spaces. We argued that the underlying graph is related to individuals' belief structure which defines the distances between states, and thereby determines the estimated long-term value of visiting a state. We have briefly outlined how this may be related to hopelessness, future expectations and meaning.

These considerations have a number of implications regarding the treatment of anhedonia. The framing of reward as a drive-reduction process indicates that the belief (correct or otherwise) that one is doing particularly badly in one aspect of life will reduce the experienced reward from all other aspects. As a consequence, when attempting to treat anhedonia it may be important not just to focus on the particular activity an individual is not enjoying (e.g. going to a party), but rather on those aspects of life in general that they feel are least satisfactory (e.g. work). Similarly, the effect of the geometry of an individual's drive space on preference for multi-, relative to uni-, dimensional drive-reduction effects may lead certain individuals to forgo rewards that occur in multi-dimensional bundles. Identifying, and potentially modifying, such 'black and white' propensities during treatment may help patients alter maladaptive behavioural policies and increase the range of rewarding activities they engage with. More generally, it will be important to understand how existing pharmacological, psychological and social treatments influence the trade-off between rewards. Characterising the impact of these treatments on measures of choice preference for uni-relative to multi-dimensional rewards (Juechems et al. 2019) may be a useful initial step in this task. An understanding of hedonic experience as arising, at least in part, from expectations of future reward conditioned on belief about the associative structure of the world suggests that anhedonic symptoms may be seen as expected consequences of cognitive distortions, rather

Fig. 3 (continued) to-good probability is even higher. This would be a striking state, where positive and negative thoughts strongly cue each other, with little possibility of sampling a thought from the opposite valence. The blue line shows the value when the good-to-good probability is high. The value is reduced as the bad-to-bad probability increases. Note that the fact that it does not cross the zero value line here is due to random sampling of the rewards - on other simulations where the rewards were sampled less large the line did cross into negative territory

than as causes of those distortions. This highlights the importance of recent innovations in cognitive therapy to increase the focus on rewarding experience generally (Craske et al. 2019; Dunn et al. 2019; Geschwind et al. 2019) and the practice of drawing attention to richer facets of reward, such as feelings of mastery (Martell et al. 2010), rather than the simple hedonic experience.

A notable omission from our discussion is an explicit consideration of effort, which has been linked to response vigour in average reward RL models (Niv et al. 2007) and associated with symptoms of apathy (Nair et al. 2020). While space limitations prevent an extensive discussion we note that viewing effort as negative reward or cost (Table 1), suggests that it may be incorporated in the drive-reduction view as movement away from the set-point and, as we illustrate in Sect. 5, it may also affect event value through associational belief networks (Fig. 3).

In summary, we suggest that it is important to move beyond descriptive to explanatory models of anhedonia and have argued that reinforcement learning provides a framework for understanding how different types of reward might interact and how beliefs can determine individual hedonic experiences.

Acknowledgements QH is supported by the UCLH Biomedical Research Centre. MB is supported by the NIHR Oxford Health Biomedical Research Centre and the NIHR Oxford cognitive health Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.

Disclosures QH has received options and consultancy fees from Aya Health, and a research grant from Koa Health. MB has acted as a consultant for Janssen Research, P1vital Ltd. and CHDR, owns shares in P1vital Products Ltd. and was previously a paid employee of P1vital Ltd.

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Anhedonia and Suicide

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Contents

Abstract Suicide is a leading cause of death, and presently, there is no definitive clinical indicator of future suicide behaviors. Anhedonia, a transdiagnostic symptom reflecting diminished ability to experience pleasure, has recently emerged as a risk factor for suicidal thoughts and behaviors (STBs). This overview, therefore, has the

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Curr Topics Behav Neurosci (2022) 58: 443–464
https://doi.org/10.1007/7854_2022_358
Published Online: 19 April 2022

following aims. First, prior research relating anhedonia to STBs will be reviewed, with a particular focus on clarifying whether anhedonia is more closely associated with suicidal thoughts versus behaviors. Second, the National Institute of Mental Health's Research Domain Criteria Positive Valence Systems provide a useful heuristic to probe anhedonia across different units of analysis, including clinical symptoms, behaviors, neural mechanisms, and molecular targets. Accordingly, anhedonia-related constructs linked to STBs will be detailed as well as promising next steps for future research. Third, although anhedonia is not directly addressed in leading suicide theories, this review will provide potential inroads to explore anhedonia within diathesis-stress and interpersonal suicide frameworks. Last, novel approaches to treat anhedonia as a means of reducing STBs will be examined.

Keywords Anhedonia · Positive Valence Systems · Reward processing · Suicidal behavior · Suicidal ideation

1 Introduction

Suicide is a major public health concern and a leading cause of death (CDC 2019). Despite considerable global efforts to enhance access to prevention and intervention services (Mann et al. 2021), each year approximately 700,000 people die by suicide worldwide (WHO 2019). Given the clinical imperative to stem the rising prevalence of suicidal thoughts and behaviors (STBs), research has sought to clarify risk factors contributing to the emergence of suicidal thoughts as well as those that facilitate the transition from ideation to action. Although definitive clinical predictors of suicide remain unclear (Franklin et al. 2017), there is recent evidence supporting anhedonia – a transdiagnostic symptom reflecting diminished ability to experience pleasure – as a promising risk factor for STBs (Bonanni et al. 2019; Ducasse et al. 2018). Accordingly, the following aims will be addressed. *First*, we will summarize extant findings – with a particular focus on clarifying whether anhedonia is more closely associated with suicidal thoughts versus behaviors (e.g., aborted, interrupted, and actual attempts). *Second*, several anhedonia-related constructs within the National Institute of Mental Health's Research Domain Criteria (RDoC) Positive Valence Systems have been linked to STBs, and thus, we will detail promising findings as well as highlight potential inroads for future research. *Third*, we will outline the role of anhedonia within leading suicide theories, with a particular focus on diathesis-stress and interpersonal frameworks. *Last*, we will explore how leading treatment approaches target anhedonia in the service of reducing suicide risk.

2 Anhedonia as a Risk Factor for STBs

At present, research implicating anhedonia as a precursor to STBs is inconclusive. Core questions about the association between anhedonia and STBs remain regarding: (1) the specificity to suicidal thoughts versus behaviors, (2) developmental differences, and (3) the differential impact of state versus trait anhedonia. Within this body of research, there is substantial diagnostic heterogeneity (e.g., mood disorders, schizophrenia), which has important clinical implications, and critically, few studies focus on completed suicide. Recent meta-analyses have focused specifically on establishing the anhedonia-suicidal ideation relationship (e.g., (Ducasse et al. 2018)). Thus, this review emphasizes studies examining associations between anhedonia and suicide behavior, as nonfatal suicide attempts are markedly more related to future suicide deaths relative to suicide ideation (Nock et al. 2008).

2.1 Anhedonia and Suicidal Behaviors

A substantive body of research has found that anhedonia severity associates with suicidal ideation, above and beyond depression symptom severity (Ducasse et al. 2018). Less research has definitively linked anhedonia to suicide death or attempts. To the best of our knowledge, only two studies have demonstrated a link between anhedonia and suicide death. In a large sample of psychiatric patients, primarily diagnosed with mood disorders, anhedonia was predictive of suicide death within a year of initial assessment (Fawcett et al. 1990). Similarly, among patients diagnosed with schizophrenia, the presence of anhedonia (based on the Structured Clinical Interview for the DSM) was more common among those who died by suicide compared to those dying of other causes (Kelly et al. 2004).

Generally, research testing the impact of anhedonia on suicide attempts has used either a cross-sectional, retrospective case-control design – that is, examining whether anhedonia is more severe among attempters versus ideators – or has prospectively tested whether anhedonia severity contributed to an attempt. Results from case-control studies among adult patients also are equivocal. There is evidence that among patients diagnosed with major depressive disorder, but not schizophrenia, social anhedonia was more common among attempters relative to non-attempters (Sagud et al. 2021), suggesting that specific aspects of anhedonia (e.g., social versus physical) may confer increased vulnerability to suicidal behaviors. By contrast, Yaseen and Colleagues (2016) found no differences in anhedonia among inpatients, primarily diagnosed with mood disorders, with and without a suicide attempt history (Yaseen et al. 2016).

Longitudinal research is equivalently mixed, with findings generally relating anhedonia severity to suicidal behaviors (but see (Loas 2007)). For example, secondary data analyses of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial explored dynamic changes in anhedonia within patients

who attempted or died by suicide. In the 6-month follow-up, there was increased acuity of suicidal ideation and loss of interest prior to the occurrence of suicidal behaviors (Ballard et al. 2016). In a large sample of psychiatric outpatients diagnosed with mood disorders, baseline anhedonia severity was related to attempts over the subsequent 3 years, however, this effect was non-significant when accounting for sociodemographic and other clinical factors (Ducasse et al. 2021). There also is partial support for a model in which baseline anhedonia severity mediates the relationship between depression symptoms and STBs. However, this study did not differentiate between suicidal thoughts versus behaviors, and based on the design (Amazon Mechanical Turk) and self-report measure used (i.e., Suicide Behaviors Questionnaire-Revised (Osman et al. 2001)), findings most likely reflect a global measure of current and past ideation as opposed to behaviors (Zielinski et al. 2017). By contrast, among psychiatric outpatients anhedonia severity was cross-sectionally related to ideation severity but unrelated to attempt history, and at the 1-month follow-up assessment, anhedonia was not predictive of suicide attempts (Hawes et al. 2018). Collectively, although there is a consistent relationship between anhedonia and suicidal ideation (Bonanni et al. 2019; Ducasse et al. 2018; Loas 2014), cross-sectional and longitudinal research has yet to definitively link anhedonia severity to suicide behaviors. Studies also varied widely in their sample characteristics, measurement of suicide behaviors, and longitudinal time scale, all of which may affect this association. Thus, further research is needed to better understand whether there are specific types of anhedonia that may be more predictive of suicidal behaviors, particularly as this may differ as a function of clinical diagnosis.

2.2 Youth, Anhedonia, and STBs

Compared with research in adults, less research has investigated associations between anhedonia and STBs in youth. Earlier work in children reporting non-suicidal self-injury indicated that anhedonia severity differentiated patients with and without a suicide attempt history (Nock and Kazdin 2002). These findings were in line with our own work among psychiatrically hospitalized adolescents showing that anhedonia severity distinguished adolescents with a suicide attempt history from depressed adolescents with suicidal ideation – an effect that persisted when accounting for current depression, anxiety, and suicidal ideation severity (Auerbach et al. 2015). Interestingly, among psychiatric adolescent inpatients, lower positive affect scores – a proxy for anhedonia – predicted the occurrence of suicidal events (i.e., suicide attempt, psychiatric hospitalization, emergency department visit) within 6 months post-discharge (Yen et al. 2013). Though promising, these studies included relatively modest sample sizes (Stewart et al. 2019a), and cross-sectional findings did not replicate in larger samples (Stewart et al. 2017a, b, 2019b), underscoring the urgent need for more research within younger patient populations.

2.3 State Versus Trait Anhedonia and STBs

It is believed that anhedonia includes both state and trait characteristics. State-based anhedonia is more variable and often fluctuates with the intensity of a depressive state (Treadway and Zald 2011). By contrast, trait-based anhedonia is believed to be stable, perhaps reflecting a personality predisposition (Conway et al. 2019). Accordingly, suicide research has begun exploring the differential impact of state versus trait anhedonia on the emergence of STBs. Whereas acute increases in anhedonia severity (state) relate to increases in suicidal ideation, trait measures have demonstrated less consistent results as well as difficult to interpret effects whereby lower trait anhedonia related to greater ideation (e.g., (Yang et al. 2020a, b; Loas et al. 2019; Winer et al. 2016)).

Probing state versus trait anhedonia reflects a promising growth area for suicide research as this has been understudied in the context of suicidal behaviors. Prior research has primarily investigated this association in non-clinical settings using methodological approaches that may be ill-suited to capture dynamic changes in anhedonia (i.e., state-based questionnaires relying on retrospective recall over extended periods). Advances in smartphone technology, however, allow assessment of changes in affect (e.g., ecological momentary assessment) and behavior (e.g., accelerometer, geolocation data) that may reflect changes in *real-time* anhedonia acuity (Allen et al. 2019). These approaches are sensitive to subtle differences in psychomotor and behavioral disturbances that distinguish healthy from remitted depressed individuals (e.g., Auerbach et al. 2022a), and thus, hold enormous promise as a means of detecting clinically significant changes in state anhedonia that may precede suicide, which, ultimately, could facilitate the development of just-in-time interventions.

3 RDoC Positive Valence System (PVS) and Suicide

The NIMH RDoC initiative provides a framework for conceptualizing transdiagnostic neurocognitive mechanisms, across units of analysis (e.g., genes, molecules, brain systems, behavior), that can be used to characterize psychiatric disorders (Cuthbert 2014; Insel et al. 2010). This transdiagnostic approach is well suited for studying STBs, which occur across a range of disorders (Glenn et al. 2017, 2018; Stewart et al. 2019a). Further, rather than treating anhedonia as a monolithic entity (Treadway and Zald 2011; Der-Avakian and Markou 2012; Rizvi et al. 2016), RDoC *Positive Valence Systems* (PVS) (sub)constructs can be used to probe a wide range of dimensions and features that map onto anhedonia (e.g., deficits in reward anticipation [wanting] versus initial response to reward [liking] versus discounting of effort required to achieve reward). This RDoC approach, therefore, allows processes underlying anhedonia to be operationalized more concretely. For example, at the neural level, anhedonia is often characterized by alterations within reward

circuitry involving fronto-striatal regions (e.g., (Der-Avakian and Markou 2012; Auerbach et al. 2017, 2022b; Gabbay et al. 2013; Schlaepfer et al. 2008)), and prior research also has implicated structural and functional alterations in reward-related circuitry in relation to STBs (Schmaal et al. 2020). Neuroimaging studies of STBs in youth are limited (Auerbach et al. 2021), and the few studies that have examined the neurocognitive underpinnings of STBs, particularly in youth, have not been well integrated into the RDoC framework (Glenn et al. 2017; Stewart et al. 2019a). Consequently, although research exploring PVS-STB relationships is a promising area of research, it currently warrants additional attention.

3.1 PVS: Reward Responsiveness

The RDoC Reward Responsiveness construct consists of three proposed sub-constructs: initial response to reward, reward anticipation, and reward satiation. These characterize different phases of hedonic responding over time from the representation of potential future rewards (wanting), current experience of reward (liking), and updating the incentive value of a past reward as it is consumed or experienced. To the best of our knowledge, studies have not examined differences in reward satiation in relation to STBs.

Simple monetary guessing tasks (Levinson et al. 2017; Helfinstein et al. 2013; Luking et al. 2014; Delgado et al. 2000) are often used to study initial response to reward. Event-related potential (ERP) studies tend to probe the reward positivity (RewP) reflecting activity comparing reward versus loss feedback (or alternatively the feedback negativity (FN) indexing activity stemming from loss versus reward feedback), which has been linked to ventral striatal activation in the context of functional magnetic resonance imaging (fMRI) (Carlson et al. 2011). Of note, children of parents with a lifetime suicide attempt history exhibit a blunted ERP (smaller RewP/larger FN) in response to winning versus losing money, though this is potentially driven by loss trials (Tsypes et al. 2019). Other work, however, has found no significant difference in adolescent girls' RewP based on maternal STB history but did find that a blunted RewP moderated the association between maternal STB history and girls' depression outcomes (Burani et al. 2021). Beyond family history, a blunted RewP has been noted among children with a history of recent suicidal ideation, compared to those with no recent ideation (Tsypes et al. 2017). More broadly, the association between a blunted RewP and suicide ideation has been confirmed in meta-analytic work, but there does not seem to be a clear signal that relates to individuals reporting a history of suicide attempts (Gallyer et al. 2021). One neuroimaging study found higher activation in dorsal prefrontal cortex (PFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) to wins versus losses between depressed adults with an attempt history compared to those with a history of depression but no attempts ((Olie et al. 2015); c.f., (Jollant et al. 2010)). In another gambling task, depressed adults with an attempt history exhibited greater insula deactivation to subjective loss compared to depressed adults with no attempt

history and psychiatrically healthy adults (Baek et al. 2017), but, perhaps surprisingly, no clear differences emerged within striatal regions. Overall, findings on reward responsivity are somewhat mixed but suggest potential associations with ideation rather than attempts. Intriguingly, these findings tend to be driven by loss sensitivity.

Experimental designs such as the Monetary Incentive Delay Task (Knutson et al. 2000) allow for separation of the neural processes underlying reward anticipation from receipt of reward. In an ERP study, whereas adults with no suicide attempt history exhibited a stronger P3 ERP to incentive versus neutral cues – thought to reflect attentional allocation to reward-predicting stimuli – adults with an attempt history exhibited less differentiation of cue types (Tsypes et al. 2021). In a gambling task, depressed adults with an attempt history exhibited blunted subgenual ACC and amygdala response to potential gain compared to depressed adults with no attempt history and psychiatrically healthy adults (Baek et al. 2017). Neuroimaging research also suggests decreased activation to reward cues in the putamen, amygdala, and OFC among self-injuring adolescent girls (mix of non-suicidal self-injury and STBs), compared to girls with no history of self-injury (Sauder et al. 2016). Taken together, there seems to be preliminary evidence that individuals with a history of STBs are characterized by blunted response to reward-predicting cues; though this does not necessarily stem from differential activation in striatal regions.

3.2 PVS: Reward Learning

The RDoC Reward Learning construct consists of three proposed sub-constructs: probabilistic and reinforcement learning, reward prediction error, and habit learning. These represent different processes by which one learns about stimulus-reward contingencies and updates one's internal schematic based on differences between expected and actual reward. These vary in their cognitive intensiveness, e.g., habits can result from reward learning, require little effort, but often do not update to changing contingencies. To the best of our knowledge, studies have not explicitly examined reward prediction error or habit learning in relation to STBs.

Probabilistic and reinforcement learning tasks have examined how individuals learn uncertain reward/punishment conditions and adapt to changing contingencies. Computational models can be used to ascertain latent parameters of behavior and estimate expected value of choices on a trial-by-trial basis. Adults, ages 60 years and older, with an attempt history showed impaired probabilistic reversal learning compared to depressed and nondepressed participants. Specifically, computational modeling suggested that adults with an attempt history discounted information about previous reward outcomes in favor of basing choice on prior trial outcomes (Dombrovski et al. 2010). In a probabilistic reversal learning study on late-life depression, participants with an attempt history exhibited weaker ventromedial PFC response to high expected reward and their pregenual cingulate responses tracked reinforcement history less reliably compared to depressed and nondepressed

participants with no attempt history (Dombrovski et al. 2013). Meta-analyses suggest worse performance on the Iowa Gambling Task among individuals with an attempt history compared to those without any attempt history (Perrain et al. 2021; Richard-Devantoy et al. 2014; Sastre-Buades et al. 2021). Though work is limited and largely in late-life adults, findings suggest potential deficits in reward learning in relation to suicide attempts.

3.3 PVS: Reward Valuation

The RDoC Reward Valuation construct consists of three proposed sub-constructs: delay discounting, probability discounting, and effort discounting. These represent processes by which the value of a reward is computed as a function of its magnitude versus the time, chance/risk, or effort required to obtain it. Anhedonic deficits may stem from alterations in these valuation processes, e.g., an individual may devalue the potential enjoyment of an activity because of the perceived effort it requires.

Delay discounting paradigms present participants with choices between sooner but smaller rewards versus later but larger rewards. Though delay discounting also has been conceptualized within an impulsivity framework or in relation to future orientation, RDoC places this process within a reward valuation context, i.e., how one weights/discounts the value of a potential reward based on the time required to obtain it. Interestingly, meta-analytic work suggests that steeper delay discounting (preference for sooner, smaller rewards) is seen across numerous disorders, including mood disorders, schizophrenia, and eating disorders (Amlung et al. 2019). This is similarly observed among individuals with self-harming or suicidal behaviors (McHugh et al. 2019; Bryan and Bryan 2021; Liu et al. 2012; Dougherty et al. 2009; Mathias et al. 2011). This could be accounted for by associations between stress and delay discounting (Fields et al. 2014, 2015) or potentially, thoughts of death and mortality salience, which can shift delay discounting to favor sooner, smaller rewards (Kelley and Schmeichel 2015). Work in older adults also suggests differences in delay discounting as a function of attempt lethality and planning (Dombrovski et al. 2011) and related delay discounting to putamen structure (Dombrovski et al. 2012). Suicide attempts also associated with deactivation of the lateral PFC in response to value difference favoring the immediate option (Vanyukov et al. 2016). Overall, despite a common focus on impulsivity, delay discounting differences in suicidal behavior may be more related to inconsistent reward valuation rather than a true preference for immediate reward (Tsypes et al. 2022).

Probability discounting paradigms present participants with choices between surer but smaller rewards versus riskier but larger rewards. Though preference for surer, sooner rewards have been observed in a number of psychiatric conditions (Dai et al. 2016; Hart et al. 2019), and a number of studies have examined decision making under probabilistic conditions (reward learning), to the best of our knowledge, only one study has examined probability discounting in relation to suicide.

Compared to adults with depression but no attempt history and psychiatrically healthy adults, adults with an attempt history exhibited greater discounting under conditions of potential monetary loss but not monetary gain, i.e., more often chose definite, but smaller loss over the probability of a larger loss (Baek et al. 2017). Similarly, there is some work suggesting greater risk aversion among depressed adults with an attempt history compared to depressed adults with no attempt history and psychiatrically healthy controls, in related paradigms (e.g., Balloon Analogue Risk Task) with less explicit probability frameworks (Ji et al. 2021). Though, other work does find lower loss aversion among adolescents with an attempt history compared to those with no attempt history (Hadlaczky et al. 2018). In other paradigms, adults with an attempt history also exhibited decreased frontal response to risky versus safe choices (Olie et al. 2015; Jollant et al. 2010). Taken together, although probability discounting has not been seen with monetary gains, there is some evidence for altered discounting with losses among individuals with an attempt history.

Effort discounting paradigms present participants with choices between smaller versus larger rewards that require less or more physical effort, respectively, e.g., number of button presses or intensity of grip strength. Although effort discounting deficits have been examined in relation to anhedonia in depression (Treadway 2016; Treadway et al. 2009, 2012a; Treadway and Zald 2013) and schizophrenia (Reddy et al. 2015; Horan et al. 2015; Green et al. 2015; Gold et al. 2013), research is very limited in STBs. In our prior work, we found that depressed attempters were less willing to choose the difficult option for reward than ideators, but only when rewards were uncertain. Further, while ideators were significantly more likely to choose the difficult option on trials proceeding winning money, attempters did not show this effect (Auerbach et al. 2015).

3.4 PVS: Molecular Pathways

PVS functioning and anhedonic deficits implicate a number of neurotransmitters and fronto-striato-limbic brain systems. Herein, we will expand on dopaminergic systems in relation to the PVS, particularly as it relates to a potential pathway to STBs; in spite of such focus, it is important to note the growing evidence for the involvement of other systems, including glutamate (Der-Avakian and Markou 2012), in PVS-related circuitry.

Initial theories suggested that dopamine is central to the experience of pleasure, but our understanding has since been refined (Wise 2008). Pleasure or "liking" is not fully contingent on dopamine, as alterations in dopaminergic systems are intimately involved in reward anticipation ("wanting"), modulation of striatal reward response, motivation, stimulus-reward pairing, and reward prediction errors (Wise 2008; Berridge and Kringelbach 2015; Bressan and Crippa 2005; Glimcher 2011). Dopamine is primarily synthesized by midbrain neurons, specifically the ventral tegmental area and substantia nigra pars compacta. Tegmental neurons project

widely to the PFC and critically to the nucleus accumbens in the ventral striatum (Glimcher 2011), while substantia nigra dopamine neurons project mainly to the dorsal striatum (Ilango et al. 2014). The majority of dopamine neurons respond to positive rewards (Schultz 2010), including carrying tonic signal encoding average reward rate during task, via the accumbens (Niv et al. 2007). Phasic dopamine responses occur on top of tonic dopamine levels, which are modulated by cortico-striatal control (Grace 1991), and play a key role in building associations between predictive stimuli and rewards (Wise 2008). Particularly, dopamine neurons encode reward prediction error signals that are used to guide learning (Glimcher 2011).

In human research, dopaminergic systems have been linked to RDoC PVS function. Striatal regions, receiving dopaminergic innervation, are centrally implicated in reward responsiveness in numerous human neuroimaging paradigms, particularly nucleus accumbens response to rewards relative to loss (Delgado et al. 2000; May et al. 2004). A meta-analysis of fMRI studies has shown robust blunting of reward-related responses in youth and adult depression that was localized to the striatum (Keren et al. 2018). Further, midbrain dopamine transporter availability correlates with ventral striatal fMRI activation during initial responsiveness to reward (Dubol et al. 2018). Midbrain neural activation has been shown to track with reward prediction errors calculated through temporal difference models (Klein-Flugge et al. 2011). Further, increased dopamine enhances willingness to exert physical effort to obtain reward, mediated by fronto-striatal mechanisms (Chong et al. 2015; Treadway et al. 2012b; Wardle et al. 2011). Behavioral and neuroimaging work also suggests an adolescent peak in reward responsivity, increasing over childhood into the adolescence (Galvan 2010; Luking et al. 2016, 2019), which may contribute to adolescent increases in depression and STBs.

A variety of studies have observed dopaminergic deficits in adult STBs, though work in youth is notably limited. For example, adults with an attempt history exhibited reduced peripheral metabolites of dopamine compared to those with no attempt history (Lester 1995; Roy et al. 1986, 1989; Träskman et al. 1981), which also predicted re-attempt within 5 years (Roy et al. 1989). Additionally, there is post-mortem evidence among people who died by suicide of reduced striatal dopamine turnover (Bowden et al. 1997a) and striatal receptor differences (Bowden et al. 1997b; Fitzgerald et al. 2017). Relatedly, STB increases can be noted with dopamine agonists and dopamine disruption in Parkinson's (Flament et al. 2011; Struhal et al. 2012). Adults with major depression with elevated suicide risk and who died by suicide showed lower striatal dopamine transporter availability via single photon emission computed tomography (Pettorruso et al. 2020; Pizzagalli et al. 2019). Finally, STBs have been linked to polymorphisms in dopamine pathway genes, including those involved in dopamine synthesis, degradation, and receptors (Brezo et al. 2008; Kia-Keating et al. 2007; Suda et al. 2009). Together, this provides evidence for dopaminergic deficits in suicide risk in adults, which underscores the importance of probing dopamine deficits in vivo in youth using less invasive methods.

4 Contextualizing Anhedonia in Leading Suicide Theories

Current suicide theories have not directly accounted for anhedonia as a risk factor; however, as anhedonia is a transdiagnostic symptom that cuts across a wide range of psychiatric disorders and profoundly shapes social behavior, it may play a prominent role in both the diathesis-stress (Mann et al. 1999) and interpersonal frameworks (e.g., Interpersonal Theory of Suicide [IPTS], Three Step Theory [3ST] (Joiner 2005; Klonsky and May 2015)). Further, preliminary evidence suggests that including anhedonia as a construct within leading theories of suicide may enhance our understanding of STBs (Yang et al. 2020a, 2021).

4.1 Anhedonia and Diathesis-Stress Model

Within the diathesis-stress model of suicide (van Heeringen and Mann 2014), the diathesis, generally believed to be a psychiatric disorder, is necessary but not sufficient for a suicide behavior to occur. Though mood disorders, substance use, and schizophrenia are observed among the majority of people who attempt or die by suicide (Conner et al. 2019; Mullins et al. 2022), only 5–8% of those diagnosed with psychiatric disorders die by suicide (Nordentoft et al. 2011). The diathesis, however, heightens the likelihood that a stressful event, typically interpersonal in nature, triggers a suicidal behavior (van Heeringen 2012). Although the diathesis-stress framework emphasizes the importance of the disorder, each disorder is characterized by extraordinary heterogeneity in terms of the symptom constellation. That is, the symptoms one experiences both within and across disorders vary significantly from patient to patient. Yet, within each of these disorders, anhedonia is a prominent transdiagnostic symptom (Whitton et al. 2015), and for major depression alone, 37–70% of depressed cases exhibit clinically significant anhedonia (Pelizza and Ferrari 2009; Yorbik et al. 2004). Accordingly, anhedonia may be the key vulnerability factor within this diatheses-stress framework, rather than the presence of a disorder broadly, that potentiates risk for suicide following interpersonal stress exposure.

For example, it is well documented that chronic stress and early life adversity contribute to anhedonia (Pizzagalli 2014). When stress occurs, the hypothalamic-pituitary-adrenal axis secretes glucocorticoids (i.e., cortisol), negatively affecting reward-based dopaminergic pathways. Prolonged stress, which may be common among high-risk patients, further reduces dopamine neuron availability in the ventral tegmental area (Douma and de Kloet 2020; Sugama and Kakinuma 2016), and is believed to reduce motivation, impair incentive-based learning, and increase social withdrawal (Lloyd and Dayan 2016). As social withdrawal increases, associated reductions in social support may occur, which may increase sensitivity to future stress and enhance STB vulnerability. This is consistent with preliminary findings showing that the co-occurrence of blunted cortisol levels (in response to a social stress task) and peer stress exposure together increased risk for suicidal behaviors,

above and beyond depression symptom severity (Eisenlohr-Moul et al. 2018). A critical next step for future research will be to test whether anhedonia – inclusive of PVS phenotypic, biological, and molecular markers – increases vulnerability to suicide attempts or death following stress exposure, and further, whether models focusing on anhedonia specifically versus psychiatric disorders generally are more predictive.

4.2 Anhedonia and Interpersonal Theories of Suicide

Interpersonal theories of suicide have expanded upon the diathesis-stress model by highlighting factors central to the transition from suicidal ideation to behaviors. The IPTS (Joiner 2005; Van Orden et al. 2010) disaggregates specific interpersonal elements – namely, thwarted belongingness and perceived burdensomeness – that hasten the transition from ideation to action. Thwarted belongingness is comprised of loneliness (i.e., feeling disconnected from others) or a lack of interpersonal support (e.g., social withdrawal, family conflict), whereas perceived burdensomeness reflects feeling expendable (Van Orden et al. 2010). According to the IPTS, the highest risk for suicidal ideation occurs when thwarted belongingness and perceived burdensomeness are both elevated, and risk for suicidal behaviors increases when there also is the capability to act on suicidal thoughts. Similarly, the 3ST (Klonsky and May 2015) separates components contributing to suicidal ideation versus behaviors. Psychache (i.e., psychological pain (Shneidman 1993)) and hopelessness are believed to be critical potentiators for suicidal ideation, and acquired capability (e.g., enhanced tolerance of pain), for some, increases risk for suicidal behaviors. Although not specified in these models, anhedonia, and particularly social anhedonia, pervades across key elements within these interpersonal frameworks.

Social anhedonia impacts interpersonal relationships (Llerena et al. 2012) and thus, may heighten risk for STBs. Recent research has shown that a loss of interest in friends was the only type of anhedonia that related to suicidal ideation severity (Yang et al. 2021), and interestingly, anhedonia moderated the relationship between thwarted belongingness and suicide attempts (Loas et al. 2018). In the context of the IPTS model, it is possible that thwarted belongingness leads to social anhedonia (e.g., social withdrawal), thereby augmenting feelings of disconnectedness. A continued cycle of disconnectedness and social withdrawal – perhaps due to perceptions of being a burden – may increase hopelessness and intensify suicidal ideation. Another possibility more consistent with the 3ST is that hopelessness and psychache may override feelings of connectedness with others. This lack of connectedness over time may contribute to anhedonic behaviors and exacerbate the risk for severe suicidal ideation. Moreover, social anhedonia (e.g., not engaging with a relationship, apathy about social closeness) may increase vulnerability to experiencing interpersonal stress. Across frameworks, interpersonal stress typically precedes suicidal behaviors (Paul 2018; Stewart et al. 2019b). Consequently, for those who have acquired capability (e.g., desensitization to pain, prior attempts), social anhedonia may be a key contributor to suicidal behaviors.

5 Targeting Anhedonia in Treatments for Suicide

Currently, there are several treatments that reduce the intensity of STBs (e.g., cognitive behavior therapy, dialectical behavior therapy, antidepressant medication); however, these approaches were not specifically designed to target anhedonia. In our recent systematic review (Mann et al. 2021), we detailed preventative intervention strategies most effective for reducing suicidal behaviors. The majority of scalable approaches relate to enhanced screening, particularly within non-psychiatrist physician settings. Consistent with precision medicine initiatives (Manchia et al. 2020), increasingly there is a need to match discrete clinical presentations with optimal treatments. Given the equifinal nature of suicide – it is unlikely that a single approach will be effective for all patients, underscoring the importance of developing anti-anhedonic approaches in the service of reducing the needless loss of life.

For example, Positive Affect Treatment (PAT) targets constructs within the RDoC PVS ((Craske et al. 2016); for recent review, see Sandman and Craske 2022). This transdiagnostic treatment employs strategies focused on improving positive affect through normalizing reward anticipation, initial response to reward, and reward learning (Sandman and Craske 2022). In a recent randomized clinical trial, depressed and anxious adults were recruited from the community. Participants were randomized to either PAT or Negative Affect Treatment (NAT), which was a combination of strategies derived primarily from cognitive behavioral therapy approaches for depression and anxiety. At 6-months post-treatment, compared to NAT, participants receiving PAT reported greater positive affect as well as reductions in negative affect, depression, and anxiety. Interesting, there also was a reduction in suicidal ideation occurrence (derived through a 1-item self-report measure) (Craske et al. 2019). These findings are promising, and perhaps, provide a novel inroad to reduce STBs among high-risk, anhedonic patients.

Additionally, ketamine, an N-methyl-D-aspartate receptor antagonist and glutamatergic modulator, has received widespread attention given potential rapid anti-suicidal ideation effects. Indeed, across several investigations, infusion of a subanesthetic-dose ketamine rapidly reduced suicidal thoughts within hours (Diazgranados et al. 2010; Larkin and Beautrais 2011; Murrough et al. 2015; Zarate et al. 2012; Price et al. 2009; Grunebaum et al. 2018). Moreover, in a recent meta-analysis, ketamine reduced suicidal ideation for up to 1 week, which was independent of antidepressant effects (Wilkinson et al. 2018). Interestingly, within the context of treatment-refractory major depressive disorder, ketamine trials also showed reductions in anhedonia (DeWilde et al. 2015), which, in patients diagnosed with bipolar disorder, were independent of depressive symptoms (Lally et al. 2014). Accordingly, post-hoc analyses across several clinical trials tested whether ketamine's anti-suicidal effects corresponded to the attenuation of anhedonia. Among patients with treatment-resistant major depressive disorder or bipolar disorder, improved anhedonia related to reductions in suicidal ideation 1-day post-ketamine administration – an effect that was above and beyond changes in depression symptom severity (Ballard et al. 2017). Though the specific mechanism of

action for these effects remains unclear, there was some preliminary evidence that anti-anhedonic effects following ketamine administration may relate to decreased glucose metabolism in the OFC in patients diagnosed with major depressive disorder (Lally et al. 2015) or increased metabolism in the dorsal ACC among patients with bipolar disorder (Lally et al. 2014).

Addressing an alternative pathway, recent evidence has linked inflammation with the pathophysiology of anhedonia (Miller and Raison 2016), specifically showing that peripheral elevations in pro-inflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], C-reactive protein) associated with anhedonia severity, neural circuitry alterations related to the PVS, and suicide attempts (Pedigo et al. 2016; Yin et al. 2019; Felger et al. 2016; Janelidze et al. 2011). Interestingly, among patients diagnosed with bipolar I or II disorder in a current depressive episode, compared with a saline placebo, the use of infliximab – an anti-TNF-α agent – resulted in reduced anhedonia severity. Moreover, reductions in anhedonia severity for those receiving infliximab corresponded to decreased plasma concentrations of TNF-α (Lee et al. 2020). These preliminary effects on anhedonia may be a key first step toward developing innovative treatments for STBs.

6 Conclusion

Suicide remains a major clinical problem and definitive risk markers are lacking. Anhedonia represents a promising transdiagnostic factor that likely contributes to suicidal thoughts and may facilitate the transition from ideation to action. Given the heterogeneity within anhedonia (Treadway and Zald 2011; Der-Avakian and Markou 2012; Rizvi et al. 2016) as well as the diversity of disorders through which suicidal behaviors often manifest, a more refined approach to concretely link anhedonia to suicide is needed, particularly when integrating within our current theoretical models of suicide risk. Use of real-time approaches (e.g., ecological momentary assessment, mobile sensor tracking), which have the potential to capture state-based changes in anhedonia, in combination with probing PVS brain-behavior markers that increase vulnerability to anhedonia and susceptibility to suicidal behaviors will serve to enrich our understanding of patients who may be most at risk for suicide death.

Acknowledgments RPA (U01 MH116923, R01 MH119771) and DP (R01 MH126181) were partially supported through funding from the National Institute of Mental Health. RPA and DP also received support through the Tommy Fuss Fund, and DP received support through the American Foundation for Suicide Prevention (YIG-0-145-20). JSK was supported through the Bender-Fishbein Research Award in Child Psychiatry as well as a training fellowship awarded to the Division of Child and Adolescent Psychiatry at Columbia University (T32 MH016434-42). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures Dr. Auerbach is an unpaid scientific advisor for Ksana Health. DP and JSK do not have any biomedical financial interests or potential conflicts of interest.

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Part V
Treatments

Pharmacological Treatments for Anhedonia

Matthew E. Klein, Ariela Buxbaum Grice, Sahil Sheth, Megan Go, and James W. Murrough

Contents

Abstract Anhedonia – the reduced ability to experience or respond to pleasure – is an important symptom domain for many psychiatric disorders. It is particularly relevant to depression and other mood disorders and it is a diagnostic criterion of a major depressive episode. Developing safe and effective pharmacological interventions for anhedonia is a critical public health need. The current chapter will review the state of the field with respect to both the efficacy of currently available pharmacotherapies for anhedonia and the recent clinical research focusing on new brain targets, including the kappa-opioid receptor and the KCNQ2/3 receptors. The evidence for anti-anhedonic effects of ketamine and psychedelic agents will be reviewed, as well.

Keywords Anhedonia · Antidepressant · Depression · KCNQ · Ketamine · Opioid · Psychedelic · Reward

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Curr Topics Behav Neurosci (2022) 58: 467–490
https://doi.org/10.1007/7854_2022_357
Published Online: 1 May 2022

Anhedonia is defined as: "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day" (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-V]; American Psychiatric Association, 2013). Characterized by a reduced motivation to engage in pleasurable activities or an inability to experience pleasure, anhedonia is a common feature of many psychiatric disorders, including major depressive disorder (MDD), substance use disorders, psychotic disorders, post-traumatic stress disorder (PTSD), and personality disorders (Treadway and Zald 2011). The transdiagnostic nature of anhedonia and its prevalence across a range of psychiatric disorders encourages an understanding of anhedonia as its own psycho-biological process, which may be present alongside diagnosable psychiatric disorders, but has specific neural substrates underlying its pathology (Husain and Roiser 2018; Zhang et al. 2016). It follows, therefore, that pharmacologic treatment targeting anhedonia should consider the unique neurobiological substrates of anhedonia.

Anhedonia is particularly relevant to depressive disorders. Considered a core feature of the disorder, anhedonia is reported by 40–75% of individuals with MDD (Buckner et al. 2008; Pelizza and Ferrari 2009). The presence of anhedonia in association with MDD is clinically important, as anhedonic symptoms are a predictor of poorer treatment response to selective serotonin reuptake inhibitors (SSRIs) and worse functional outcomes, including increased risk of suicide (Spijker et al. 2001; Vrieze et al. 2013; Vinckier et al. 2017; McMakin et al. 2012; Winer et al. 2014; Fawcett et al. 1990). First-line treatments for MDD (e.g., SSRIs) have shown mixed efficacy for the treatment of anhedonia. While a positive treatment response with respect to overall depressive symptoms is generally associated with improved ability to experience pleasure, there are many cases in which anhedonic symptoms persist, even as other mood-related symptoms are restored (Nutt et al. 2007; Whitton et al. 2016). There is, in fact, potential for antidepressants (particularly SSRIs such as citalopram and fluoxetine) to exacerbate levels of anhedonia due to common side effects like emotional blunting, thereby leaving patients with a greater symptomatic burden (McCabe et al. 2010; Price et al. 2009).To improve clinical outcomes, there is a need for anhedonia-specific pharmacological approaches that are able to address these residual symptoms of anhedonia (Cao et al. 2019).

Anhedonia can manifest as deficits in multiple reward-related domains – including motivation, decision making, anticipation, and consummation of reward – each with its own complex pathophysiology (Treadway and Zald 2011). The reward processes involved in anhedonia – reward valuation, motivation, anticipation, and decision making – map to neural circuitry overlapping with the mesocorticolimbic circuit, including the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), and the striatum (Dillon et al. 2014; Keren et al. 2018; Treadway et al. 2012; Wise 1980). The mesocorticolimbic reward circuit, which connects the ventral tegmental area (VTA) and the nucleus accumbens (NAc) and projects onto the PFC, is the primary pathway for processing and modulating reward-seeking behavior (Dunlop and Nemeroff 2007). Normal functioning of reward-related behavior is sustained by the interplay of the striatum and the medial PFC (mPFC) via the dopaminergic transmitter system and restoration of activity in this system may result in anti-

anhedonic effects. Compounds that demonstrate circuit-engagement relating to these pathways could therefore target symptoms of anhedonia by reversing deficits in the underlying biology (Argyropoulos and Nutt 2013). Indeed, this approach is supported by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative, which prescribes a transdiagnostic and dimensional focus, based on neurobiological pathways, for psychiatric research, rather than a focus on psychiatric syndromes per se (Dillon et al. 2014; Insel et al. 2010).

In this chapter, we will review potential therapeutic interventions for the treatment of anhedonia in the context of mood disorders, with focus on the clinical pharmacology of interventions, as well as their potential therapeutic efficacy. We will explore clinical trials conducted in adults with mood disorders, in which anhedonia is an endpoint, measured by a standardized anhedonia rating scale such as the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995). Some clinical trials relating to anhedonia have utilized functional imaging techniques to probe the effects of potential anti-anhedonic pharmacotherapies on the activity within brain regions related to reward processing. We will consider whether evidence supporting the anti-anhedonic effect of a compound is determined by improvement of clinical symptoms specific to anhedonia or by demonstrating circuit-engagement of anhedonia-related brain regions. While pharmacotherapeutics typically target a range of receptors and pathways, we have grouped agents by their primary mechanisms of action for the purpose of this review. Overall, this chapter will present the current state of the field of pharmacologic agents and their putative anti-anhedonic effects.

1 Kappa-Opioid Receptor Antagonists

The mesolimbic circuit, including the ventral striatum (VS, which includes the NAc) and the VTA, is integral in generating motivation and reward-related behaviors. Both the preclinical work from animal models and the clinical imaging studies implicate abnormal dopaminergic neural activity in the pathophysiology of anhedonia (Nestler and Carlezon 2006), so pharmacotherapies that can alleviate this abnormal neural activity in midbrain circuitry may have anti-anhedonic properties. Two compounds, the kappa-opioid receptor (KOR) antagonist JNJ-67953964 (discussed in this section) and the potassium channel modulator ezogabine (discussed below), have demonstrated anti-anhedonic properties in recent clinical trials. In both cases, the reduction in anhedonic symptoms was correlated with changes in VS activity, suggesting that the compounds exert their therapeutic effects by restoring normal function within dopaminergic mesolimbic reward circuitry.

The κ-opioid system is a neuromodulatory system that can influence mesolimbic circuitry activity related to reward and motivation. Antagonism of KORs modulates the balance of neurotransmitter release onto VS and VTA neurons, resulting in improved reward-related functioning and amelioration of anhedonic symptoms and behaviors (Brooks and O'Donnell 2017; Carlezon and Krystal 2016; Tejeda and

Bonci 2019; Tejeda et al. 2017). The therapeutic potential of targeting the κ-opioid system as a novel approach for the treatment of mood and anxiety disorders was tested within the context of the NIMH FAST-FAIL initiative in a study of JNJ-67953964 (Aticaprant), an orally available, high-affinity ($Ki = 0.8 \pm 0.24$ nM, $IC_{50} = 3.0 \pm 4.6$ nM) KOR antagonist with modest activity at mu and delta opioid receptors (Krystal et al. 2018; Margolis et al. 2020; Rorick-Kehn et al. 2014a, b; Zheng et al. 2013). In a double-blinded, randomized controlled trial, participants were administered JNJ-67953964 10 mg/day or a placebo for the 8-week trial duration (Krystal et al. 2020). The participant group included 89 individuals with MDD, bipolar disorder, anxiety disorders, or PTSD, plus some level of anhedonia (SHAPS $\geq$20), who were free of concurrent medication treatment for their primary psychiatric disorder. The primary outcome was change in VS activation, as measured by functional magnetic resonance imaging (fMRI) during a monetary incentive delay (MID) task. Brain activation is estimated during the reward or penalty conditions compared to a neutral condition to produce the contrasts of interest during the task. Researchers also compared baseline and post-treatment scores on mood-related scales, such as SHAPS and the Hamilton Depression Rating Scale (HDRS). Relative to placebo group, those treated with the study drug had statistically significantly greater VS activation during anticipation of both gain and loss (gain: $F(1,86) = 5.58$, $p < 0.01$, Hedges' $g = 0.58$, loss: ($F(1,86) = 11.7$, $p < 0.001$; $g = 1.12$)), as well as a greater reduction in mean SHAPS score relative to baseline scores ($F(1,86) = 3.35$, $p = 0.0345$; $g = 0.44$; baseline 36.4 ± 8.5 (drug group), 33.4 ± 5.9 (placebo group)) that was correlated with the VS activation changes during reward anticipation. Secondary analysis demonstrated baseline VS activation significantly predicted which participants would show a response to treatment. Interestingly, treatment did not seem to improve symptoms of depression (as measured by HDRS scores; mean baseline HDRS 16.3 ± 5.2 (drug group), 14.8 ± 5.9 (placebo group)), although authors note the study participants represented a mixed diagnostic population, and the study was not designed to determine the effects of KOR antagonism on depression.

In a follow-up report on the NIH FAST-FAIL trial described above, investigators performed a secondary analysis of the effects of treatment with the KOR antagonist, compared to placebo, on reward learning, measured using the Probabilistic Reward Task (PRT) (Pizzagalli et al. 2005). Used by several laboratories, the PRT provides a measure of the effect of prior reinforcement on behavior, an adaptation which appears to be modulated by dopamine signaling through the mesocorticolimbic system (Kaiser et al. 2018; Pizzagalli et al. 2008). While the initial report described improved reward learning after treatment with JNJ-67953964 compared to placebo, the secondary analysis determined that the group differences in reward learning following treatment were driven by an increased propensity to select the stimulus previously paired with more frequent rewards, and a higher learning rate in the KOR antagonist group relative to placebo group (Pizzagalli et al. 2020). Interestingly, while the treatment groups differed on learning rate (which, unlike reward sensitivity, has been linked the DA manipulations in prior computational modeling), they

did not differ on reward sensitivity, suggesting a specificity of KOR treatment on discrete aspects of reward dysfunction and anhedonia (Huys et al. 2013).

2 KCNQ Channel Modulators

Preclinical work in rodent social defeat models – a well-validated chronic stress model of depression and anhedonic behaviors – implicates abnormal firing of VTA neurons in the pathophysiology of the stress-induced anhedonic phenotype (Krishnan et al. 2007; Tye et al. 2013). In this preclinical model paradigm, inbred, docile mice are subjugated to repeated agonistic confrontations with a larger, aggressive, dominant male, which can result in the development of maladaptive behaviors in the subjugated mice, alongside pathological neural activity in their dopaminergic circuitry. Some mice, however, do not develop these maladaptive behaviors after exposure to chronic social defeat, and are termed "resilient" to repeated stress. Unlike susceptible mice, resilient mice appear able to restore normal patterns of midbrain neural activity by engaging homeostatic gene expression mechanisms, including upregulation of membrane-bound ion channels (Friedman et al. 2014). In that vein, pharmacotherapies that engage homeostatic pathways to ameliorate pathological dopaminergic hyperactivity may have similarly anti-anhedonic properties.

A promising mechanism to restore normal dopamine neuron firing is by altering membrane excitability through modulation of membrane-bound ion channels (Russo et al. 2012). Voltage-gated potassium channels of the KCNQ (Kv7) family, which pass the muscarinic current (M-current), alter neuronal excitability and are a potential target for anti-anhedonic pharmacotherapies. The KCNQ family of receptors is comprised of five subtypes (KCNQ1-5 or Kv7.1-5), of which subtype KCNQ2/3 (Kv7.2/3) heteromers are highly expressed throughout the brain and are thought to primarily mediate the M-current (Jentsch 2000). In preclinical studies, stress-resilient mice displayed an upregulation of these KCNQ2/3 channels, which increased M-current and led to the restoration of phasic firing of the VTA and, subsequently, absence of anhedonic symptoms. Daily peripheral administration of the selective KCNQ2/3 channel opener ezogabine was able to restore VTA homeostasis in defeated animals, with improvements in anhedonic and pro-depressive behaviors (Friedman et al. 2016). Ezogabine is a first-in-class KCNQ-selective potassium (K+) channel opener approved by the U.S. FDA for the adjunctive treatment of partial-onset seizures in the 600 to 1,200 mg/day range (Brodie et al. 2010). Ezogabine selectively binds to and activates KCNQ transmembrane K+ ion channels, thereby enhancing transmembrane potassium currents mediated by the KCNQ (KCNQ2/3) family of ion channels. These results highlight the importance of KCNQ channels in the pathology of the helpless phenotype, and the translational potential of channel modulators as pharmacotherapeutic agents for anhedonia.

To date, two clinical trials have been conducted demonstrating the effects of ezogabine on anhedonia-related endpoints in individuals with mood disorders.

The first study was a small, single-arm, open-label clinical trial of ezogabine, in which baseline performance and mood scores were compared to post-treatment at the 10-week trial endpoint. The study group included 18 adults with a primary diagnosis of MDD, plus clinically significant symptoms of anhedonia, as operationalized by a score of at least 20 on the SHAPS at baseline (Tan et al. 2020). Participants were administered ezogabine $\leq$900 mg/day over the trial duration, with the primary outcome being treatment-associated changes in connectivity of the brain reward circuitry and reward learning. Resting-state fMRI was used to compute functional connectivity (RSFC) at baseline vs post-treatment, and reward learning was measured (again, at baseline and after treatment) by the PRT (described above). Mood and mental affect was also quantified across the study duration; depression was quantified by the Montgomery-Åsberg Depression Rating Scale (MADRS) and anhedonia by the SHAPS. Reward learning increased with treatment, and participants' symptoms of both depression and anhedonia decreased from baseline to the 10-week treatment endpoint (MADRS: -13.7 ± 9.6, $t_{17} = -6.01$, $p < 0.001$, Cohen's $d = 2.08$, SHAPS -6.06 ± 5.34, $t_{17} = -4.81$, $p < 0.001$, Cohen's $d = 1.00$). The improvement in SHAPS was noted throughout the study as a function of time ($F(5,85) = 11.84$, $p < 0.001$, partial-$\eta^2 = 0.41$), and the difference remained significant after controlling for depression severity (change in MADRS). The improvement in SHAPS scores was associated with reduced connectivity between the ventral caudate (VCa) – an important reward-related region of the ventral striatum – and the mid-cingulate cortex (MCC) ($z = -4.87$, $k = 411$, $p = 0.004$). Treatment-driven improvements in anhedonia that are demonstrated by this study of ezogabine (which activates KCNQ) suggest that KCNQ modulation may affect a striatal-mid-cingulate circuit involved with affective and cognitive processing. Indeed, the MCC is highly connected to the caudate and the midbrain dopaminergic system and is responsive to appetitive and aversive stimuli (Haber and Knutson 2010; Shackman et al. 2011). However, given the open-label nature of this study, as well as its small size, additional work is needed to determine the effect of KCNQ modulation on brain systems that modulate reward processing, and its efficacy for treating anhedonia.

Building on these pilot findings, the authors initiated a two-site, randomized, controlled trial with 45 participants to test the neurocircuit and clinical effects of ezogabine in adults with a primary depressive disorder (MDD or other unipolar depressive disorder), plus elevated anhedonic symptoms (baseline SHAPS $\geq$20) (Costi et al. 2021). The primary outcome of the study was the drug-treated-vs. placebo-treated group differences in bilateral VS activation while anticipating a potential reward during a monetary incentive flanker task (IFT) after 5 weeks of treatment. A version of the monetary incentive delay task (described in the preceding sections), the IFT allows for measurement of neural activity relating to different aspects of reward-based decision making, including cue presentation and receipt of feedback (Stern et al. 2011). Clinical outcomes included baseline to post-treatment reported symptoms of depression and anhedonia measured by MADRS, SHAPS, and the Temporal Experience of Pleasure Scale (TEPS). The ezogabine group, compared to the placebo group, showed greater improvement in clinical symptoms

of depression (MADRS; baseline 28.3 ± 6.1 (ezo) and 26.8 ± 5.1 (placebo), outcome 12.7 ± 8.7 (ezo) and 18.5 ± 10.1 (placebo), $t = -4.04$, df = 213, $p < 0.001$), hedonic capacity (SHAPS; baseline 38.7 ± 8.1 (ezo) and 33.7 ± 6.0 (placebo), outcome 27.5 ± 8.5 (ezo) and 30 ± 10.9 (placebo), ($t = -4.1$, df = 212, $p < 0.001$)), and ability to anticipate pleasure (TEPS). There was trend-level association between treatment and an increased VS response to reward compared to the placebo, but it did not reach significance (estimate = 0.52, SEM = 0.28; $t = 1.85$, df = 38, $p = 0.07$, Cohen's $d = 0.58$). Of note, however, was a positive correlation, only in the ezogabine group, between the change in VS response to reward and change in anticipatory anhedonia (as measured by TEPS). This may suggest that increased VS activity is associated with increased self-reported anticipation of pleasure. The imaging results, together with the observed clinical improvement in anhedonic symptoms, further support the preclinical mechanism proposing that modulating KCNQ channel activity may restore normal functioning of mesolimbic reward-related circuitry.

Treatment with both JNJ-67953964 and ezogabine resulted in improvement of anhedonic symptoms, suggesting that both therapies hold promise as pharmacological interventions in the treatment of anhedonia, and that restoring pathological activation patterns related to reward functioning could be a target for anti-anhedonic pharmacotherapies. The VS and the VTA – as well as their cortical connections – are regions of interest for bettering our understanding of anhedonia and targeting such regions – particularly with respect to dopaminergic reward circuitry – is a potential avenue for future effective pharmacological treatments for anhedonia.

3 Ketamine

Ketamine is a glutamatergic modulator with substantial clinical evidence supporting its efficacy in the treatment of depression and suicidal ideation (Aan Het Rot et al. 2012; Wilkinson et al. 2018; Witt et al. 2020). The antidepressant mechanism of action of ketamine likely involves NMDA-receptor mediated inhibition of inhibitory GABAergic interneurons in the PFC (Zanos and Gould 2018a; Zanos et al. 2018). The resulting temporary elevation in synaptic glutamate leads to increased AMPA receptor activation and subsequent short- and long-term synaptic plasticity via activation of BDNF and the mTOR pathway (Zanos and Gould 2018b). The result of this cascade is a decreased inhibition and increased synaptic plasticity, which may promote therapeutic neural activity of reward circuitry or increase dopaminergic tone in the mesocorticolimbic pathway (Kokkinou et al. 2018; Pulcu et al. 2021). Several clinical studies have examined the potential anti-anhedonic properties of ketamine, which may be separate from its antidepressant and anti-suicidal effects. The clinical studies described below demonstrate acute and chronic effects of ketamine on neural activity in both cortical regions (ACC, orbitofrontal cortex [OFC], hippocampus) and midbrain regions (striatum), that correlate with its anti-anhedonic effects.

In one of the first clinical studies to investigate the anti-anhedonic mechanisms of ketamine, 36 adults with treatment-resistant bipolar depression were recruited for a randomized, double-blind, placebo-controlled, crossover trial (Lally et al. 2014). All participants received both a single intravenous infusion of racemic ketamine (0.5 mg/kg) and a placebo infusion, separated by 2 weeks. The primary outcome of the study was the difference between baseline to post-treatment MADRS scores, with a secondary outcome being the difference in anticipatory anhedonia (measured by SHAPS). Compared to placebo, injection with ketamine resulted in a greater reduction of SHAPS score, as observed by a main effect of the drug after controlling for change in depressive symptoms by entering the total MADRS score minus item 8 as a covariate in the linear mixed model ($F(1,123) = 7.71$, $p = 0.006$). In this model there was no overall main effect of time ($F(9,176) = 1.42$, $p = 0.18$), nor drug-by time interaction ($F(9,219) = 1.49$, $p = 0.15$), but post-hoc analyses demonstrated a significant reduction in SHAPS scores between ketamine and placebo at days 1-, 3-, 7-, and 14 post-treatment. These results suggest that ketamine has specific anti-anhedonic benefits, in addition to more general antidepressant effects, which can occur as soon as 1 day after treatment and last up to 2 weeks. A subset of patients (21 out of 36) also underwent fluorodeoxyglucose positron emission tomography (FDG-PET) to measure brain glucose metabolism 2 h after infusion. In the imaging outcome, reduction in SHAPS score following ketamine infusion was correlated with increased glucose metabolism in the VS. However, post-hoc analyses found this correlation was primarily explained by change in MADRS score, indicating that reduction in depressive symptoms – but not anhedonic symptoms – was associated with changes in VS activity. Whole-brain and subsequent ROI analyses revealed correlations specifically between improved SHAPS scores (corrected for change in MADRS) at 230 min, but not SHAPS scores at 14 days, and clusters in the dorsal anterior cingulate cortex (dACC), and putamen. Overall, this study suggests a mechanism involving the dACC and putamen that is temporarily connected with the anti-anhedonic effects of ketamine, which may be separate from its antidepressant mechanism of action.

In a secondary analysis, the same group studied the anti-anhedonic effects of ketamine in an open-label study of IV ketamine with either adjunctive oral riluzole or placebo (Lally et al. 2015). In this study, 52 adults with unipolar treatment-resistant depression (TRD) received a single IV dose of racemic ketamine (0.5 mg/kg), followed by oral riluzole or placebo for 4 weeks. A rapid reduction in anhedonia (SHAPS) was observed in both groups, beginning 40 min after infusion and lasting up to 3 days. There was no main effect of the adjunct, indicating that riluzole did not provide additional anti-anhedonic effects compared to ketamine, alone. In a subset of patients, (19 out of 52), whole-brain analyses of FDG-PET imaging were performed, revealing a trend-level association between increased VS activity and decreased SHAPS score. After controlling for reduction in MADRS, changes in activity of two regions – the hippocampus and OFC – remained significantly associated with reduced anhedonia at 230 min following treatment. The authors were also able to replicate their previous findings of significant association between increased dACC activity and improvement in SHAPS, when controlled for total change in MADRS.

A recent study by the same group extended these findings, demonstrating that, in patients with TRD, ketamine improved functional connectivity at 2 days post-infusion in a fronto-striatal network composed of PFC, OFC, and perigenual ACC (Mkrtchian et al. 2021). Post-ketamine increases in connectivity were correlated with reduction in SHAPS scores at both 2 and 10 days after infusion. A secondary outcome of the study investigated the effect of inflammation (as measured by plasma C-reactive protein levels) on ketamine-induced changes in brain connectivity. No significant correlations were observed between post-ketamine changes in connectivity and CRP levels in TRD patients.

Building on these findings, a two-part study investigated reward-based activity in the subgenual anterior cingulate cortex (sgACC) in cases vs. healthy controls (HC), and then tested the effect of ketamine administration on sgACC activation (Morris et al. 2020). Research in non-human primates has implicated over-activation of the sgACC in the neuropathology of anhedonia (Alexander et al. 2019). In the first leg of this study, activation was tested for a group of 48 individuals – 28 with MDD (cases) and 20 without (HC) – by the IFT. Compared to HC, individuals with MDD displayed sgACC hyperactivity in response to positively or negatively-valenced feedback (positive, $t(45) = 2.21$, $p = 0.032$; negative, $t(42) = 3.04$, $p = 0.004$). Furthermore, patients with greater anticipatory anhedonia (TEPS) had greater levels of sgACC hyperactivity in response to positive feedback. In the study's second leg, a group of adults with MDD were administered a single infusion of ketamine (0.5 mg/kg). Ketamine treatment improved symptoms of anhedonia and reduced sgACC hyperactivation in response to positive feedback. Together, these findings are consistent with preclinical findings, suggesting that modulation of ACC activity may be an important mechanism for the anti-anhedonic effects of ketamine.

Several recent, retrospective, post-hoc analyses also provide evidence for a specific anti-anhedonic effect of both racemic ketamine and the *S*-enantiomer, esketamine, which displays slightly higher affinity for NMDAR than the racemic form. A secondary analysis of 203 individuals with MDD assessed anhedonia (SHAPS) before and after treatment with four IV infusions of racemic ketamine (0.5–0.75 mg/kg) over the course of 1–2 weeks; findings revealed a reduction in total SHAPS score (controlled for baseline depression severity) following the first infusion, that remained significant until at least 1 week after treatment (SHAPS, baseline 8.82 ± 0.27, post-infusion 6.26 ± 0.39, $F(2, 235) = 31.6$, $p < 0.001$, Cohen's $f = 0.50$) (Rodrigues et al. 2020). The authors also observed improvements in symptoms of depression, anxiety, and suicidal ideation following treatment, which were partially mediated by the reduction of anhedonic severity. A second study collected data from a group of 45 inpatients and outpatients with either uni- or bipolar depression, who were treated with up to six semi-weekly infusions of racemic ketamine (0.5 mg/kg) in order to assess its effects on anhedonia, as measured by the Beck's Depression Inventory (Thomas et al. 2018). Overall, remission of anhedonia with treatment was achieved for ~35% of patients, and baseline anhedonia was found to be correlated with a reduction in symptoms of depression following treatment. Two additional studies of IV esketamine treatment in adults with uni- or bipolar depression also reported an anti-anhedonic effect of the

enantiomer, which was similar in magnitude to that of racemic ketamine (Delfino et al. 2021; Lins-Silva et al. 2021).

Preliminary results from clinical trials demonstrate that ketamine appears to be rapidly efficacious in reducing anhedonia in patients with both uni- and bipolar depression, potentially accounting for some of its observed efficacy in treating MDD, including treatment-resistant forms. Imaging results from patients with mood disorders that received ketamine treatment implicate both the VS and ACC in the anti-anhedonic effects of ketamine. Independent of reductions in depressive symptoms, post-treatment reduction of ACC hyperactivity or increase in VS activity may partially explain ketamine's acute anti-anhedonic effects. Modulating activity in the VS may represent a common mechanism for anti-anhedonic pharmacology, as increases in reward-related VS activity are observed following treatment with both ketamine and KCNQ modulators (or KOR antagonists). Further research will clarify both the efficacy and mechanisms of ketamine, specifically for treating anhedonia.

4 Psychedelics

A developing area of research is a renewed interest in the use of psychedelic compounds for the treatment of depression and other psychiatric disorders. Psilocybin, a serotonergic psychedelic agent and serotonin receptor agonist, acts on the same neurotransmitter system as classical SSRIs. Unlike the classical antidepressants, however, which increase serotonin in the synaptic cleft by inhibiting serotonin transporters, psilocybin acts as a direct agonist on the serotonin 2A (5-HT2A) receptor to elicit psychedelic effects (Carhart-Harris and Nutt 2017). Several studies examining psilocybin for its antidepressive properties additionally noted anti-anhedonic effects.

Given reports of recreational psilocybin having antidepressant effects, Carhart-Harris et al. designed a feasibility study to assess the potential for psilocybin use in the treatment of patients with unipolar TRD (Carhart-Harris et al. 2016). The open-label, non-blinded study with no control group enrolled 12 participants with moderate-to-severe MDD – defined by a HAM-D score >17 – that did not improve after at least 6 weeks of treatment with at least two different classes of antidepressants. Participants were administered two doses of psilocybin: a "test" dose of 10 mg on dosing day 1, then a "high" dose (the treatment dose) of 25 mg a week later. Participants also received several psychotherapy sessions in the form of: a 3–4 h preparatory session, supportive therapy during the two 4–6 h dosing days, as well as integration sessions after dosing and during follow-up. Treatment efficacy was quantified by the change from baseline (pre-dosing) QIDS and SHAPS scores to scores collected 1, 2, 3, and 5 weeks after the treatment dose (25mg), as well as 3 months from treatment dose administration. Scores on both scales showed improvement after treatment, compared to baseline. The most pronounced QIDS score decrease was observed 2 weeks after administration (QIDS, baseline 19.2 ± 2.0, 2 weeks 6.3 ± 4.6, Hedges' $g = 3.2$, $p < 0.002$). Anhedonia, which

was measured by the SHAPS score, significantly decreased from baseline, both 1 week and 3 months after treatment (SHAPS, baseline 7.5 ± 3.7, 1 week 1.4 ± 2.7, Hedges' $g = 1.9$, $p < 0.002$, 3 months 2.8 ± 3.7, Hedges' $g = 1.3$, $p < 0.002$).

Carhart-Harris et al. concluded from their 2016 study that psilocybin was indeed a potential therapeutic intervention for depressive and anhedonic symptoms in their cohort of individuals with TRD. To further this initial inquiry, the original (2016) study plan was modified to follow participants through 6 months after administration of the psilocybin treatment dose (Carhart-Harris et al. 2018). The study group was composed of 20 patients with unipolar, treatment-resistant, moderate-to-severe depression; of this 20 study cohort, most participants ($n = 12$) had also been in the feasibility study. As before participants were administered two doses of open-label psilocybin – a 10 mg test dose followed week later by a 25 mg treatment dose. QIDS-SR-16 scores were significantly decreased from baseline at all post-treatment test points, with the most significant change occurring between baseline and 1 week from treatment. Anhedonia was assessed by the SHAPS at baseline, then 1 week and 3 months after treatment. The average baseline SHAPS score was 6.6 (SD = 4.1) and showed significant improvement with treatment; SHAPS scores were significantly improved from baseline at both post-treatment follow-ups: −4.6 (CI = 95%) 1 week after treatment and −3.3 (CI = 95%) 3 months after treatment. The SHAPS was scored traditionally, using a scale of 0 to 14, unlike in the ezogabine or FAST-MAS trials, where a 0 to 56 scale was used. Although the study population was relatively small, the preliminary study and its 6-month extension found treatment with psilocybin to be well-tolerated and effective for treating anhedonia for duration of up to 3-months. Further research is needed to disambiguate the relative contributions of psychotherapy and psilocybin to the observed therapeutic effects. Though, as the authors note, a certain level psychological support may be necessary to maintain safety during a clinical trial of psychedelics.

Another study of psilocybin in patients with MDD compared the efficacy of treatment with psilocybin to treatment with an SSRI. Researchers at the Centre for Psychedelic Research at Imperial College London compared the depressive symptoms in patients with MDD before and after treatment with either psilocybin or escitalopram. The phase 2, double-blind trial randomly placed 59 participants (out of 1,000 screened) with long-standing, moderate-to-severe MDD into one of two treatment groups to compare treatment efficacies over 6 weeks (Carhart-Harris et al. 2021). On the two "dosing days", which occurred 2 weeks apart, individuals in the psilocybin group ($n = 30$) were administered 25 mg psilocybin; individuals in the escitalopram group ($n = 29$) were also administered psilocybin on dosing days, but were given a "placebo" dose of 1 mg both times. Participants were then given either a placebo (psilocybin group) or escitalopram (escitalopram group) to take daily for 6 weeks. The primary score of treatment efficacy was the difference between the QIDS-SR-16 score at baseline and post-treatment (6-weeks). At baseline, the psilocybin group had an average QIDS-SR-16 score of 14.5, and a change -8.0 ± 1.0 after 6 weeks. The escitalopram group averaged a baseline QIDS-SR-16 score of 16.4, and a change -6.0 ± 1.0 after 6 weeks. Although not a major

consideration in this study, and, as the authors note, the confidence intervals were not corrected for multiple comparisons, the change between baseline and 6-week scores on the SHAPS (0–14 scale) measurement of anhedonia was greater in the psilocybin group (-4.7 ± 0.6), than the escitalopram group (-2.5 ± 0.6), by a difference of -2.2 (-3.8 to -0.6, 95% CI).

5 Conventional Antidepressants

Conventional antidepressants have demonstrated mixed results in the treatment of anhedonia (Nutt et al. 2007). In some cases, conventional antidepressants exacerbate anhedonic symptoms, due to a commonly observed side effect of emotional blunting (Price et al. 2009). Up to 50% of patients taking SSRIs or serotonin-noradrenaline reuptake inhibitors (SNRIs) for MDD report side effects of emotional numbness or blunted affect (Goodwin et al. 2017). Interestingly, some findings suggest that antidepressants with relatively more activity on noradrenergic, dopaminergic, or melatonergic receptors may have superior benefits with respect to the treatment of anhedonia, compared to agents that are primarily serotonergic. For example, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) may be relatively better for reducing anhedonia, compared to SSRIs. Data also suggest that dopaminergic agonists such as pramipexole can alter activity in the mesocorticolimbic circuit, with corresponding changes in reward-related behaviors (Pizzagalli et al. 2008; Whitton et al. 2020).

Several clinical studies have provided evidence of an anti-anhedonic effect of the melatonin analog agomelatine (AGO). Agomelatine is a melatonin receptor (MT1 & MT2) agonist and a serotonin receptor (5HT2c & 5HT2b) antagonist. Preclinical studies suggest that both the melatonergic and serotonergic activities contribute to the antidepressant and anxiolytic effects of agomelatine, perhaps by altering circadian rhythms, or by increasing availability of dopamine and norepinephrine (Stahl 2014). Two prospective studies of outpatients with MDD examined the ability of agomelatine to reduce symptoms of anhedonia. In the first study, 257 outpatients were given agomelatine (25–50 mg/day) for 8 weeks (Gargoloff et al. 2016). Significant reductions in anhedonia were observed in the 143 individuals who completed the study, though these results were not corrected for changes in depression scores. Significant reduction began as early as 1 week into treatment, and continued through the end of treatment (SHAPS (0–14 scale), baseline 8.5 vs. 8 weeks 4.1, $p < 0.001$). Similar reductions in QIDS scores were observed, and changes in QIDS and SHAPS were positively correlated. In a larger prospective study, outpatients with MDD were treated with agomelatine (25–50 mg/day) and changes in depressive and anhedonic symptoms were measured after 10–14 weeks (mean time to endpoint 81.7 ± 12.3 days) of agomelatine treatment ($n = 1{,}570$); similar reductions in MADRS and SHAPS scores (MADRS, change -16.5, $p < 0.0001$; SHAPS (change -7.2, $p < 0.0001$) were observed (Vinckier et al. 2017). This study also observed an improvement in psychosocial functioning as measured by the Questionnaire of Social Functioning (QSF). Improvement of anhedonia was the

strongest predictor of improvement in psychosocial functioning, and mediation analysis revealed that reduced anhedonia over time was linked to improvement in depression and recovery of psychosocial functioning. The authors conclude that anhedonia represents an important target in restoring psychosocial functioning in patients treated for MDD, suggesting that a treatment such as agomelatine – which has both antidepressant and anti-anhedonic properties – may be particularly effective in restoring psychosocial functioning in patients with MDD and moderate anhedonia.

Agomelatine has demonstrated comparable efficacy to SSRIs in the treatment of depression, but several studies have shown that it is more effective than oral antidepressants in the treatment of anhedonia (Hickie and Rogers 2011). An open-label, parallel-group pilot study was conducted to compare anti-anhedonic effects in a cohort of 60 adults with MDD, who were randomized to treatment with agomelatine (25–50 mg/day, $n = 27$) or venlafaxine XR (75–150 mg/day, $n = 21$) over 8 weeks (Martinotti et al. 2012). Both compounds demonstrated similar antidepressant efficacy, but the anti-anhedonic efficacy for agomelatine was significantly greater than for VLX (SHAPS (0–14 scale), VLX, baseline 6.4, endpoint 5.1; AGO, 6.5, endpoint 3.4, difference -1.7 $p < 0.01$). Interestingly, the decrease in SHAPS score associated with agomelatine treatment was significant after just 1 week of treatment, suggesting it had a rapid anti-anhedonic effect.

A multi-site, double-blind, randomized head-to-head study between agomelatine and escitalopram (AGO, $n = 164$, 25–50 mg qd; escitalopram (LEX), $n = 160$, 10–20 mg qd) measured antidepressant efficacy, along with emotional side effects, in a population of adults with MDD over the course of 24 weeks (Corruble et al. 2013). The clinical improvements in depression for AGO were statistically significant and non-inferior to LEX (HAMD, AGO, baseline 26.8 $\pm$ 3.1, change at 12 weeks -18.7 ± 6.9 vs. LEX, baseline 26.6 $\pm$ 2.5, change at 12 weeks -18.3 ± 6.8), as well as in percent response (AGO, 82.6% vs. LEX, 81.3%). A subset of patients (AGO, $n = 25$; LEX, $n = 20$) completed the Questionnaire on the Emotional Side-Effects of Antidepressants (OQESA), a self-report that asks the extent to which participants have experienced a series of emotional events. On certain questions related to anhedonia, the AGO group reported greater improvement than the LEX group at 24 weeks ("Things that I cared about before my illness/problem don't seem important to me anymore," AGO = 16%, LEX = 53%; "My emotions lack intensity," AGO = 28%, LEX = 60%). While not a validated metric for anhedonia, the significant difference in response to these questions between the groups may suggest a superior anti-anhedonic effect of AGO over LEX. Together, these two head-to-head studies demonstrate that AGO has comparable antidepressant effects to standard treatments, with the additional and unique effect of improving may also uniquely improve symptoms of anhedonia.

Two studies have also probed potential mechanisms underlying the anti-anhedonic effects of agomelatine. An 8 week, open-label study, including 27 adults with MDD on agomelatine (25–50 mg PO QD), found that increases in peripheral Brain-Derived Neurotrophic Factor (BDNF) were correlated with improvement in symptoms of depression (HAM-D) (Martinotti et al. 2016). Additionally, variation in BDNF levels was more prominent in participants with greater anhedonia at baseline, suggesting that agomelatine may be preferentially efficacious in this

group. Another study measured changes in C-reactive protein (CRP) levels in 30 adult outpatients (12 males, 18 females) with MDD on agomelatine (25–50 mg QD) for 12 weeks (De Berardis et al. 2017). A significant reduction was observed for SHAPS (baseline, 6.6 ± 2.2, endpoint, 3.1 ± 2.0, $p < 0.001$) along with a significant reduction in mean serum CRP levels (baseline, 2.5 ± 0.6 mg/L; week 12, 1.8 ± 0.5 mg/L) in remitters.

Several mechanisms have been proposed for agomelatine's anti-anhedonic properties. Agomelatine can increase both serotonin and dopamine levels through antagonism of 5HT2C receptors, which may result in a reduction of both depressive and anhedonic symptoms (Racagni et al. 2011). Additionally, treatment with agomelatine may increase central BDNF levels leading to hippocampal neurogenesis and an anti-anhedonic effect. The clinical evidence supports both antidepressant and anti-anhedonic effects of agomelatine, though larger RCTs are necessary to clinically confirm agomelatine's anti-anhedonic properties.

Boyer et al. proposed that the different classes of antidepressants (i.e., whether the drug mediated dopaminergic, serotonergic, or noradrenergic activity) might correspond to stronger clinical outcomes for certain clusters of depressive symptoms (Boyer et al. 2000). The authors characterized the "effect profile" of one antidepressant – sertraline – in the treatment of patients with MDD. Sertraline was chosen for its ability in vitro to mediate the activity of both serotonin and dopamine, thereby potentially allowing it to treat a broader range of symptoms than a typical SSRI. Researchers hypothesized that treatment with sertraline would improve both depressive and anhedonic symptoms. To test this hypothesis, this open-label study enrolled 140 participants with MDD and monitored patient response to sertraline (50–150 mg daily) over an 8-week period, in which the primary metric of medication efficacy was HAM-D score across the study duration. Anhedonia was measured using a predefined subscale of the patient-rated symptom checklist (SCL-90) (Derogatis et al. 1973). Both average HAM-D and anhedonia subscale scores significantly improved throughout the treatment course, with improvements in both noted as early as 1 week. The subscale scores for both depression and anhedonia displayed similar reductions over the course of the study, suggesting that improvements in anhedonia may be related to the reduction of overall depressive symptoms. The relationship between anhedonia and decreased dopamine activity, coupled with in vitro findings that sertraline acts on the dopaminergic system, led researchers to conclude that the role of sertraline in the stimulation of dopaminergic activity improved anhedonia. Vortioxetine is a serotonergic antidepressant with multiple other effector neurotransmitter systems, including norepinephrine (NE), dopamine (DA), amino acids, histamine (HA), and cholinergic systems. A pooled analysis of 11, double-blinded RCTs suggested that treatment with vortioxetine was effective in reducing symptoms of anhedonia (McIntyre et al. 2021).

Several head-to-head trials have been conducted between the SNRI venlafaxine and other oral antidepressants in the treatment of anhedonia. In a double-blind RCT, Light et al. reported no significant difference in the reduction of anhedonic symptoms between treatment with venlafaxine and treatment with fluoxetine (Light et al. 2011). Reporting similar results, and as mentioned in the preceding section,

Martinotti et al. demonstrated both venlafaxine and agomelatine were able to reduce symptoms of anhedonia (SHAPS) in patients with depression. In a post-hoc analysis of five RCTs, McIntyre et al. investigated the anti-anhedonic effects of the serotonin and norepinephrine reuptake inhibitor (SNRI) levomilnacipran, using a four-item subscale of the MADRS to measure anhedonic symptoms: 5 [Reduced Appetite], 7 [Lassitude], 8 [Inability to Feel], and 10 [Suicidal Thoughts] (McIntyre et al. 2016). While these studies were not designed to measure the effectiveness of levomilnacipran for anhedonia, specifically, the improvement in the anhedonia symptoms cluster for the treatment group was significantly different than placebo.

Studies of oral antidepressants with the ablity to increase dopaminergic tone – including dopamine and norepinephrine reuptake inhibitors (DNRIs) and TCAs have demonstrated anti-anhedonic effects of these agents. Bupropion is an antidepressant that acts as both a dopamine and norepinephrine reuptake inhibitor. In a 6-week RCT conducted by Tomarken et al., patients treated with bupropion showed a consistent linear decline in anhedonia, whereas the placebo group initially showed improvement, but trended back toward baseline as the 6 weeks progressed, suggesting that the bupropion lead to a more lasting improvement of anhedonia (Tomarken et al. 2004). Amitifadine is a triple reuptake inhibitor, which can inhibit the reuptake of serotonin, norepinephrine, and dopamine (SNDRI). A 6-week, multicenter, randomized, double-blind, parallel, placebo-controlled study evaluated the efficacy and tolerability of amitifadine in 63 patients with MDD (Tran et al. 2012). Treatment with amitifadine improved scores in an anhedonia grouping of MADRS items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel). A study by Jouvent et al. compared the anti-anhedonic effects of the monoamine oxidase inhibitor (MAO-I A) moclobemide to the tricyclic antidepressants (TCA) clomipramine (Jouvent et al. 1998). While both antidepressants showed positive efficacy in reducing anhedonia, patients treated with moclobemide seemed to have a greater and faster improvement of anhedonic symptoms within 1 week compared to clomipramine, where effects were not seen until 4 weeks.

6 Conclusion

Anhedonia is a transdiagnostic symptom of reduced capacity to experience pleasure or lack of reactivity to pleasurable stimuli; it has core relevance to mood disorders such as MDD and is also associated with many other psychiatric disorders. Anhedonia in the context of MDD is associated with poor functional outcomes, increased suicide risk and treatment-resistance; first-line antidepressant agents appear to have only limited efficacy against anhedonia. Research indicates that anhedonia can arise through dysregulation with brain systems that control response to reward, with the VTA-NAc dopamine system appearing to be of central importance. In this chapter, we reviewed the data available concerning the efficacy of pharmacotherapy for anhedonia, with a focus on depressive disorders. We began by

summarizing recent experimental medicine approaches to identify pharmacotherapy targeting anhedonia, including work involving the KOR and the KCNQ2/3 systems. We then reviewed data concerning ketamine, psychedelic agents – such as psilocybin – and, finally, conventional antidepressant agents and agomelatine. While the data for the effects of conventional antidepressants on anhedonia are limited, it is likely that agents with activity at systems other than serotonin will be important for the development of future anti-anhedonic agents. In terms of treatment response prediction, baseline reward processing and VS DA function were recently reported to be associated with response to the DA drug pramipexole in adults with depression (Whitton et al. 2020). In a separate recent study, baseline reward sensitivity and fronto-striatal resting-state functional connectivity were related to therapeutic response to atypical antidepressant bupropion in adults with depression who had failed to respond to the SSRI, sertraline (Ang et al. 2020). Both of these studies suggest the potential of reward-related behavioral or brain-based biomarkers to predict response to agents that may preferentially target reward systems (i.e., via their DA- related activity). Work in this area is still in early stages and requires replication. Hopefully, additional research focused on targeting brain systems that mediate reward function will speed the development of safe and effective treatment of anhedonia across psychiatric diagnoses.

Study	Measure	Group	Baseline mean (SD)	Outcome mean (SD)	*N*	Time	Effect size
A randomized proof-of-mechanism trial applying the "fast-fail" approach to evaluating kappa-opioid antagonism as a treatment for anhedonia	HAM-D	JNJ-67953964	16.3 (5.2)	10.8 (4.0)	45	8 weeks	Hedges' $g = 0.44$, $p = 0.03$
		Placebo	14.8 (5.9)	11.1 (3.9)	44	8 weeks	
	SHAPS	JNJ-67953964	36.4 (8.5)	30.8 (3.7)	44	8 weeks	Hedges' $g = 0.09$, $p = >0.10$
		Placebo	33.4 (5.9)	32.4 (3.6)	44	8 weeks	
Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder	MADRS	Ezogabine	29.5 (4.9)	−13.7 (9.6), mean change	18	10 weeks	Cohen's $d = 2.08$, $p < 0.001$
						10 weeks	
	SHAPS	Ezogabine	27 to 51	−6.06 (5.34), mean change	18	10 weeks	Cohen's $d = 1.00$, $p < 0.001$
						10 weeks	
Impact of the KCNQ2/3 channel opener ezogabine on reward circuit activity and clinical symptoms in depression: Results from a randomized controlled trial	MADRS	Ezogabine	28.3 (6.1)	12.7 (8.7)	21	5 weeks	Cohen's $d = 0.76$, $p < 0.001$
		Placebo	26.8 (5.1)	18.5 (10.1)	24	5 weeks	
	SHAPS	Ezogabine	38.7 (8.1)	27.5 (8.5)	21	5 weeks	Cohen's $d = 0.64$, $p < 0.001$
		Placebo	33.7 (6.0)	30 (10.9)	24	5 weeks	
Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression	MADRS	Ketamine	33.92 (5.01)		36	1–14 days	
		Placebo			36	1–14 days	
	SHAPS	Ketamine	37.19 (7.25)		36	1–14 days	
		Placebo			36	1–14 days	
Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: Results from the Canadian Rapid Treatment center of excellence	QIDS	Ketamine	18.55 (0.33) standard error	13.43 (0.50), (SE)	138	1 week	
					138	1 week	
	SHAPS	Ketamine	8.82 (0.27)standard error	6.26 (0.39), (SE)	139	1 week	Cohen's $f = 0.50$, $p < 0.001$
					139	1 week	

(continued)

(continued)

Study	Measure	Group	Baseline mean (SD)	Outcome mean (SD)	*N*	Time	Effect size
Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study	QIDS	Psilocybin	19.2 (2.0)	7.4 (4.9)	12	1 week	Hedges' $g = 3.1$, $p = 0.002$
					12	1 week	
	SHAPS	Psilocybin	7.5 (3.7)	1.4 (2.7)	12	1 week	Hedges' $g = 1.9$, $p = 0.002$
					12	1 week	
Trial of psilocybin versus escitalopram for depression	QIDS	Psilocybin	14.5 ± 3.9	−8.0 (1.0), mean change (SE)	30	6 weeks	
		Escitalopram	16.4 ± 4.1	−6.0 (1.0), mean change (SE)	29	6 weeks	
	HAM-D	Psilocybin	19.2 ± 2.3	−10.5 (1.0), mean change (SE)	30	6 weeks	
		Escitalopram	18.4 ± 3.4	−5.1 (1.0), mean change (SE)	29	6 weeks	
	SHAPS	Psilocybin	Not reported	−4.7 (0.6), mean change (SE)	30	6 weeks	
		Escitalopram	Not reported	−2.5 (0.6), mean change (SE)	29	6 weeks	

Disclosure In the past 5 years, Dr. Murrough has provided consultation services and/or served on advisory boards for Allergan, Boehringer Ingelheim, Clexio Biosciences, FSV7, Global Medical Education (GME), Otsuka, Sage Therapeutics, and Engrail Therapeutics. Dr. Murrough is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders and on a patent pending for the use of KCNQ channel openers to treat depression and related conditions. The Icahn School of Medicine (employer of Dr. Murrough) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine or esketamine for the treatment of depression. The Icahn School of Medicine is also named on a patent related to the use of ketamine for the treatment of PTSD. Dr. Murrough is not named on these patents and will not receive any payments. The other authors do not have any disclosures to report.

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Psychological Treatments for Anhedonia

Christina F. Sandman and Michelle G. Craske

Contents

Abstract Anhedonia, a loss of interest or pleasure in activities, is a transdiagnostic symptom that characterizes many individuals suffering from depression and anxiety. Most psychological interventions are designed to decrease negative affect rather than increase positive affect, and are largely ineffective for reducing anhedonia. More recently, affective neuroscience has been leveraged to inform treatments for anhedonia by targeting aspects of the Positive Valence Systems, including impairments in reward anticipation, reward responsiveness, and reward learning. In this chapter, we review the efficacy of treatments and, when possible, highlight links to reward constructs. Augmented behavioral approaches and targeted cognitive interventions

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Curr Topics Behav Neurosci (2022) 58: 491–514
https://doi.org/10.1007/7854_2021_291
Published Online: 22 December 2021

designed to target reward anticipation, responsiveness, and learning show preliminary efficacy in reducing anhedonia, while there is a relative lack of treatments that target positive emotion regulation and reward devaluation. In addition to developing treatments that address these targets, the field will benefit from establishing standardized measurement of anhedonia across units of analysis, mapping mechanisms of change onto aspects of reward processing, and examining anhedonia outcomes in the long-term.

Keywords Anhedonia · Depression · Intervention · Positive affect · Reward

1 What Is Anhedonia?

Anhedonia is defined in the *Diagnostic and Statistical Manual of Mental Disorders* as markedly diminished interest or pleasure in activities (American Psychiatric Association 2013). Anhedonia is a multifaceted set of symptoms characterized by deficits in positive affect, which can be further understood by examining impairments in the reward system (Treadway and Zald 2011). Up to 75% of individuals with major depressive disorder report anhedonia (Franken et al. 2007). Anhedonia is a transdiagnostic symptom, in that it extends beyond major depression to social anxiety disorder and generalized anxiety disorder (Kashdan et al. 2011), as well as schizophrenia (Watson and Naragon-Gainey 2010) and substance use disorder (Thomsen et al. 2015). Although anhedonia is also relevant to other disorders, this chapter focuses on psychological treatments for anhedonia primarily in the context of depression and anxiety.

Anhedonia, assessed via low positive emotionality, prospectively predicts both depression and anxiety, even when controlling for baseline symptoms (Kendall et al. 2015; Khazanov and Ruscio 2016). Once disorders emerge, anhedonia is a robust predictor of poorer longitudinal course of major depression (Morris et al. 2009). Anhedonia predicts poor psychosocial functioning after improvements in depressed mood (Vinckier et al. 2017) and recurrence of depression (Wichers et al. 2010). Moreover, anhedonia is a substantial predictor of suicidal ideation and behavior (Winer et al. 2014; Ducasse et al. 2018), even when controlling for other cognitive and affective symptoms of depression (Fawcett et al. 1990; Ballard et al. 2017) as well as other risk factors such as history of suicide attempts, childhood trauma, marital status, sex, and age (Ducasse et al. 2020).

2 Traditional Treatments Are Ineffective for Anhedonia

Most psychological treatments are designed to reduce negative affect rather than enhance positive affect, and have a relatively limited impact on anhedonia. Existing evidence-based psychotherapies, such as cognitive behavioral therapy and mindfulness-based cognitive therapy, have limited effects upon positive affect (Boumparis et al. 2016). For example, whereas cognitive therapy and antidepressant medication normalized elevations in negative affect on the Positive and Negative Affect Schedule (PANAS; Watson et al. 1988) to adult population norms (percentile changes from 88% to 59% for cognitive therapy and 87% to 49% for medication), positive affect levels remained lower than typical for general adult populations (from 9% to 28% for cognitive therapy and 5% to 31% for medication) (Dunn et al. 2020).

2.1 Behavioral Activation

Even behavioral activation, which aims to increase response-contingent positive reinforcement through engagement in activities (Manos et al. 2010), is relatively ineffective for addressing anhedonia. With roots in Lewinsohn's theory that depression arises due to a lack of positively reinforcing experiences (Lewinsohn 1974), there have been several variants including most notably Behavioral Activation (BA; Lejuez et al. 2011), which emphasizes values, and Behavioral Activation for Depression (BATD; Martell et al. 2010), which takes a contextual approach and emphasizes overcoming patterns of avoidance. Although behavioral activation treatments vary slightly, common components include activity monitoring and activity scheduling (Kanter et al. 2010). According to a meta-analysis, activity scheduling has a large effect size on depressive symptoms when compared to control conditions (Cuijpers et al. 2007). However, very few studies report the effect of behavioral activation upon positive affect, and the ones that do show limited effects for improving anhedonia and positive affect (Dichter et al. 2009; Moore et al. 2013). When looking at broader constructs of well-being, behavioral activation results in only medium effect sizes (Mazzucchelli et al. 2010).

This is perhaps not surprising since relatively little attention has been given to how to conduct behavioral activation in a manner that maximizes positive emotional experience (Dunn 2012; Forbes 2020). Only recently has affective neuroscience been leveraged to inform targeted treatments for anhedonia. For example, more recent approaches aim to improve behavioral activation by incorporating strategies such as savoring via "attention to experience," as reviewed below (e.g., McCauley et al. 2016; Craske et al. 2016; Taylor et al. 2017). Efforts to deliberately target aspects of the Positive Valence Systems, such as reward anticipation, responsiveness, and learning, have led to the refinement of existing treatments (i.e., augmented behavioral activation) and development of novel therapeutics for anhedonia.

3 Positive Valence Systems

Historically, two major systems have been thought to guide behavior, cognition, and affect: the appetitive system, which motivates behavior to approach rewards and is associated with positive emotions, and the defensive system, which motivates avoidance of aversive stimuli and is associated with negative emotions (Watson et al. 1995). These core systems broadly map onto the Positive Valence Systems (PVS) and Negative Valence Systems (NVS) respectively, which are dimensional constructs for studying psychopathology put forth by the National Institute of Mental Health's Research Domain Criteria Initiative (Insel et al. 2010; Sanislow et al. 2019). By primarily targeting the NVS, the vast majority of treatments fail to address the underlying processes most relevant to anhedonia. Recent advances in the conceptualization of anhedonia as related to deficits in the PVS have led to the development of more targeted behavioral and cognitive treatments, which are critically reviewed in this chapter (see Table 1 for a comparison of treatment components).

As of 2019, the PVS consists of three constructs: (1) reward responsiveness (with subconstructs of reward anticipation, initial response to reward, reward satiation), (2) reward learning (probabilistic and reinforcement learning, reward prediction error, habit), and (3) reward valuation (reward [probability], delay, effort) (Sanislow et al. 2019). Across models of reward processing, most converge upon components of reward anticipation, initial response to reward, and reward learning. Disruptions in these three components are associated with anhedonia across multiple units of analysis (Der-Avakian and Markou 2012; Thomsen et al. 2015; Borsini et al. 2020).

In brief, reward anticipation (sometimes referred to as reward wanting) is associated with dopaminergic signaling and recruitment of the ventral striatum (VS), and less consistently, the orbitofrontal cortex (OFC) (Der-Avakian and Markou 2012; Oldham et al. 2018). Meta-analyses suggest that depressed individuals show reduced VS activation during anticipation of reward (Zhang et al. 2013; Keren et al. 2018), which is particularly strongly associated with symptoms of anhedonia (Greenberg et al. 2015; Ubl et al. 2015; Stringaris et al. 2015). Behaviorally, depressed individuals expend less effort for rewards than healthy controls (Treadway et al. 2012), and the motivational effort they expend correlates negatively with anhedonia (Sherdell et al. 2012; Treadway et al. 2012; Yang et al. 2014). At the level of self-report, depressed individuals expect to feel less positive emotions during future positive events (MacLeod and Salaminiou 2001; Wu et al. 2017; Hallford et al. 2020b) and report less state positive emotion in anticipation of a monetary reward (McFarland and Klein 2009) compared to healthy controls.

Initial response to reward (also referred to as reward attainment, liking, consumption, or hedonic capacity) is related to opioid and endocannabinoid pathways (Mahler et al. 2007) and activation of the VS (particularly the nucleus accumbens) and the OFC (Peters and Büchel 2010; Berridge and Kringelbach 2015; Thomsen et al. 2015). Depressed individuals show striatal hypoactivation and altered OFC responding during reward attainment (Pizzagalli et al. 2009; Pizzagalli 2014; Admon

Table 1 Treatment components from reviewed psychological treatments for anhedonia

	Activity scheduling/ Pleasant event scheduling	Prosocial activities (acts of kindness, generosity)	Values	Savoring through the senses	Positive memory/mental imagery training	Metta mindfulness practices (LKM, compassion, etc.)	Imagining positive future outcomes	Identifying one's contribution to positive outcomes
BA	X		[a]	[a]				[a]
PAT	X	X	X	X	X	X	X	X
VR-RT				X	X			
AMP	X	X	X	X	X		X	X
ADepT	X		X	X	X			
BATA	X		X	X				
PMET				X	X			
Imagery CBM					X			
EFT/ FeST				X	X		X	
PASS					X		X	X

BA behavioral activation, *PAT* positive affect treatment, *VR-RT* virtual reality-reward training, *AMP* amplification of positivity, *ADepT* augmented depression treatment, *PMET* positive memory enhancement training, *Imagery CBM* imagery cognitive bias modification, *EFT* episodic future thinking, *FeST* future specificity training, *PASS* positive affect stimulation and sustainment, *LKM* loving-kindness meditation

[a] Not required, although some versions of behavioral activation incorporate values (e.g., Lejuez et al. 2011), paying "attention to experience" akin to savoring (McCauley et al. 2016), and identifying one's contribution as a part of response-contingent reinforcement (Martell et al. 2010)

and Pizzagalli 2015; Keren et al. 2018; Ng et al. 2019), and such patterns are specifically related to anhedonic symptoms in some studies (Keedwell et al. 2005; Epstein et al. 2006; Wacker et al. 2009). Self-reported trait consummatory pleasure is lower in depressed versus non-depressed individuals (Liu et al. 2011; Li et al. 2015; Yang et al. 2017), and weaker positive emotions to positive stimuli are more strongly related to anhedonia than other symptoms of depression (Clepce et al. 2010).

Reward learning is associated with dopaminergic signaling and neural regions such as the caudate and anterior cingulate cortex (Der-Avakian and Markou 2012). During reward learning tasks, depressed individuals fail to develop a typical bias in behavioral responding in favor of more frequently rewarded stimuli, a pattern which is particularly prominent in those with high anhedonia (Pizzagalli et al. 2008; Vrieze et al. 2013). Individuals with depression also demonstrate striatal and frontal hypoactivation during positive feedback in reward learning tasks (Borsini et al. 2020), which has also been associated specifically with anhedonia in some studies (Rothkirch et al. 2017; Geugies et al. 2019).

4 Treatments Consistent with the Positive Valence Systems

4.1 Positive Affect Treatment (PAT)

Positive Affect Treatment (PAT) is a transdiagnostic treatment designed to increase positive affect by targeting deficits in reward anticipation, initial response to reward, and reward learning (Craske et al. 2016). PAT is a 15-session treatment consisting of three modules: (1) pleasant event scheduling augmented with imaginal recounting, (2) attending to the positive through cognitive exercises, and 3) cultivating the positive through loving-kindness, generosity, appreciative joy, and gratitude.

The first module includes modified pleasant event scheduling, which consists of three components for each pleasant activity: designing, conducting, and imaginal recounting. *Designing* targets reward anticipation, and involves planning pleasant events that are inherently enjoyable, provide a sense of mastery, or are consistent with one's values. *Conducting* targets initial response to reward by training clients to savor positive aspects during the activity, and targets reward learning by monitoring positive emotions before, during, and after the activity to reinforce behavior-mood relationships. *Imaginal recounting* involves therapist-guided visualization of pleasant events completed between-sessions, with a focus on recalling specific positive sensations (sounds, smells, sights), thoughts, emotions, and situational details, using a first-person perspective while re-living the events in the present tense. Imaginal recounting is intended to help clients savor pleasurable moments in order to enhance their hedonic impact (initial response to reward) and reinforce their positive mood-inducing effects (reward learning). Imaginal recounting draws from the literature on mental imagery and memory biases in depression (Holmes et al. 2016), and resembles other approaches such as directed imagery for rumination (Watkins 2018) and

memory specificity training (Raes et al. 2009; described below), but exclusively focuses on positive details.

The second module involves attending to the positive via cognitive exercises including: *finding the silver lining*, *taking ownership of the positive*, and *imagining the positive.* Finding the silver lining guides clients to identify at least six positive aspects of a positive, neutral, or negative situation. By "over-practicing," this skill intends to address attentional biases in depression by training attention to positive stimuli. *Taking ownership of the positive* involves identifying one's behavioral contributions to positive outcomes, with the goal of recognizing behavior-mood associations (reward learning) and savoring positive emotions (initial response to reward). Lastly, *imagining the positive* involves therapist-guided visualization similar to imaginal recounting, but focuses on envisioning future positive events and outcomes to train reward anticipation.

In the third module, cultivating the positive, clients deepen positive feelings toward themselves and others through four experiential exercises: *loving-kindness, generosity, appreciative joy*, and *gratitude*. These exercises aim to target initial response to reward and reward learning through recording of mood ratings before and after exercise completion. Loving-Kindness Meditation (LKM) can be conceptualized as the mental act of giving, and involves mentally sending happiness, health, peace, and freedom from suffering to others and oneself. In PAT, this LKM is facilitated through in-session therapist-guided meditation and between-session practices with an audio guide. Generosity, or the physical act of giving, involves completing daily acts of kindness without expecting anything in return. Appreciative joy, conducted via therapist and audio guided meditation, involves mentally wishing happiness, joy, and good fortune to oneself and others. Finally, clients engage in gratitude practices including making lists, journaling, and carrying a "gratitude rock" to prompt thinking about gratitude throughout the day.

In a randomized controlled trial that included adults with elevated depression, anxiety, or stress and functional impairment ($n = 91$), PAT resulted in greater improvements in positive affect at a six-month follow-up ($d = 0.67$) in comparison with cognitive behavioral therapy focused solely upon reductions in negative affect (Craske et al. 2019). Interestingly, effects were not specific to positive affect: participants in PAT also reported greater reductions in negative affect ($d = 0.52$), depression ($d = 0.34$), anxiety ($d = 0.30$), stress ($d = 0.43$), and a lower probability of suicidality (1.7% vs 12%) at six-month follow-up. An ongoing trial from our group is investigating whether PAT leads to changes in subconstructs of the PVS (reward anticipation, initial response to reward, and reward learning) at multiple units of analysis (subjective self-report, clinician-rated, behavior, psychophysiology) in a transdiagnostic sample of patients with anhedonia.

4.2 Virtual Reality-Reward Training (VR-RT)

Low levels of motivation characteristic of anhedonia make it difficult for many individuals to complete pleasant activities as part of behavioral activation. Virtual reality offers a potential solution by serving as a vehicle through which rewarding experiences can be delivered to anhedonic individuals. Virtual Reality-Reward Training (VR-RT) is a 13-session treatment over 7 weeks that involves exposure to 360° virtual reality scenes combined with imaginal recounting. VR content shifts from highly positive during early sessions to increasingly more neutral content in later sessions in order to train attention to positive aspects in more difficult situations. Each session involves viewing 12–15 min of VR scenes, followed by recounting (via written exercises and guided audio) of both the VR scene and a positive autobiographical memory to transfer savoring skills to personally relevant experiences.

Our lab has tested VR-RT in an open trial using Oculus Rift with six participants who met cutoffs on self-report measures for low reward sensitivity, moderate or severe depression, and significant functional impairment. From pre-treatment to 1-month follow-up, VR-RT resulted in reduced anhedonia, depression, anxiety, and functional disability (Chen et al. 2021). Whereas negative affect decreased both pre-post session and pre-post intervention, increases in positive affect were only apparent throughout the last half of treatment. This is a proof-of-concept trial in need of replication with controlled comparisons. Whereas VR-RT primarily targets initial response to reward through passive viewing of pleasant scenes, future adaptations may more directly address other processes such as reward anticipation and learning by having participants interactively search for rewards in the virtual environment, for example.

4.3 Amplification of Positivity (AMP)

Combining multiple positive psychological interventions, Amplification of Positivity (AMP) is a 10-session transdiagnostic treatment that includes behavioral activation, gratitude, acts of kindness, and identifying and using strengths, among other activities (Taylor et al. 2017). Compared to most other interventions reviewed in this article (with the exception of PAT), a relatively unique component of AMP is its explicit focus on prosocial behavior and social connection, as well as amplification of positive experiences by sharing with others. Potential processes plausibly targeted include reward anticipation (via imagining a "best possible future"), initial response to reward (e.g., by noticing positive events, engaging in pleasurable and meaningful activities) and positive emotion regulation (savoring, appreciation, sharing with others as an amplification strategy).

In a small sample of treatment-seeking adults with clinically impairing anxiety and/or depression, AMP ($n = 16$) led to larger reductions in negative affect, depression, and anxiety, as well as greater increases in positive affect and

well-being that were sustained at a six-month follow-up compared to a waitlist control condition ($n = 13$). Notably, in the AMP group, post-treatment levels of positive affect and well-being were comparable to general population norms. Participants in the same sample also completed the monetary incentive delay task during functional magnetic resonance imagining (fMRI) at pre- and post-treatment (Kryza-Lacombe et al. 2021). No findings emerged for activation analyses. In exploratory analyses of functional connectivity, the AMP group demonstrated changes compared to the waitlist control condition in three networks: (1) increased ventral striatum, anterior insula, and anterior cingulate connectivity with occipital regions, which may reflect enhanced stimulus-driven attention, (2) increased anterior insula connectivity with the ventral striatum and lateral prefrontal cortex, which may reflect decreased loss aversion and increased reward anticipation, and (3) increased anterior cingulate connectivity with the ventral striatum and lateral prefrontal cortex, which may reflect improved emotion regulation. Interestingly, many of these findings emerged during the loss anticipation (rather than gain anticipation) contrast, suggesting that AMP may reduce risk aversion, which the transdiagnostic sample of anxious or depressed patients may find more salient and rewarding than gain itself (Bishop and Gagne 2018). While findings from this pilot demonstrate initial clinical efficacy and shed light onto processes that change with treatment, they are limited by small sample size and comparison to a non-active control condition. Future research on positive psychology interventions such as AMP is needed using larger samples and formal mediation analyses to test treatment mechanisms.

4.4 Augmented Depression Therapy (ADepT)

Augmented Depression Therapy (ADepT) is a 15-session "solution-focused, cognitively augmented behavioral activation" treatment that is designed to simultaneously target both negative and positive valence systems (Dunn et al. 2019a). Initial sessions focus on values and goals, mood monitoring, diary exercises to train specific positive memory and attentional style, and mindful engagement in everyday activities. Later sessions include coping skills to reduce negative affect including behavioral experiments and "acting opposite" of depressogenic behaviors (avoidance, self-criticism, rumination, negative biases). In a multiple baseline mixed methods case series of 11 adults with a current major depressive episode, ADepT resulted in improvements in NVS outcomes, such as depression and anxiety symptoms, with large effect sizes comparable to those achieved by BA or CBT for depression, as well as large effect sizes for PVS outcomes such as anhedonia, positive affect, and well-being that were sustained (or even continued to improve) over a 1-year follow-up (Dunn et al. 2019a).

The multi-component nature of ADepT that addresses both PVS and NVS makes it difficult to tease apart the active ingredients or determine whether changes in reward processing per se are responsible for treatment effects. A planned RCT (Dunn et al. 2019b) comparing ADepT with CBT will help to shed light on

mechanisms of action and whether unique aspects of ADepT that target reward lead to superior comparative efficacy.

4.5 Behavioral Activation for Anhedonia (BATA)

Adapted from Behavioral Activation for Depression (Lejuez et al. 2011), Behavioral Activation for Anhedonia (BATA) is a 15-session, transdiagnostic treatment that aims to target approach motivation, initial responsiveness to reward, and reward learning (Nagy et al. 2020). Treatment components consist of psychoeducation about anhedonia (e.g., anticipatory vs consummatory pleasure), streamlined activity monitoring, "dabbling" to initiate novel behaviors, and savoring in the present moment (similar to PAT; Craske et al. 2016, 2019). Results from an ongoing RCT comparing BATA to mindfulness-based cognitive therapy (MBCT) are pending; however, preliminary results in a subsample ($n = 38$ BATA, $n = 35$ MBCT) demonstrated improvements in anhedonia (as measured by the Snaith-Hamilton Pleasure Scale; Snaith et al. 1995) to a comparable extent in both treatment groups (Cernasov et al. 2021). To probe neural mechanisms, resting state functional connectivity was examined at pre-, mid-, and post-treatment. Contrary to hypotheses that BATA would lead to greater changes in reward and salience network connectivity than MBCT, both treatment groups resulted in attenuated connectivity within the default mode network, as well as decreases in connectivity between the default mode network and frontoparietal network (Cernasov et al. 2021). Changes in frontoparietal, rather than reward, network connectivity corresponded to changes in anhedonia. These findings may suggest common, rather than distinct, neural processes that change with treatment related to cognitive control and emotion regulation. Future research should investigate whether positive affect treatments target shared or unique (i.e., reward) mechanisms compared to other psychosocial treatments.

5 Targeted Cognitive Approaches

Individuals with depression demonstrate overgeneral autobiographical memory, less detailed positive mental imagery, and a bias for observer (vs. field) perspective (Holmes et al. 2016), all of which have consequences for diminishing positive emotional experience. Overgeneral autobiographical memory (OGM) refers to a failure to generate specific memories that take place within a span of a day (Williams et al. 2007). According to meta-analyses, OGM predicts onset and poorer course of depression (Hallford et al. 2020a; Sumner et al. 2010), and often remains even after depressed mood has improved (Raes et al. 2006). Depressed individuals also exhibit deficits in generating detailed past- (Werner-Seidler and Moulds 2011) and future-oriented positive mental images (Parlar et al. 2016; Hallford et al. 2020b), which

have been associated with reduced anticipatory pleasure in anhedonic samples (Yang et al. 2018). Lastly, depressed individuals demonstrate a bias for observer (third-person) versus field (first-person) perspective when recalling positive memories (Lemogne et al. 2006; Bergouignan et al. 2008). Imagining positive experiences through field perspective can cause a boost in positive mood, whereas use of observer perspective leads to diminished positivity (Holmes et al. 2008). Although further research is necessary to link these deficits with anhedonia specifically rather than depression generally, recent approaches described below that translate these findings to clinical interventions hold promise for improving positive affect (Blackwell et al. 2015; Arditte Hall et al. 2018; Hallford et al. 2020e).

5.1 Memory Specificity Training

In recent years, several interventions have been developed to target deficits in memory and mental imagery in an emerging field of "memory therapeutics" (Dalgleish and Werner-Seidler 2014; Holmes et al. 2016). To address OGM, Memory Specificity Training (MeST) involves psychoeducation and generation of specific (<24 h) negative, neutral, and positive autobiographical memories, with standard delivery in a group format over 4 weeks (Raes et al. 2009). According to a recent meta-analysis, memory specificity interventions for emotional disorders lead to short-term significant improvements in overgeneral memory, depression, hopelessness, and problem solving (Barry et al. 2019).

With relevance for anhedonia, more recent approaches involve training exclusively on positive stimuli. For example, Positive Memory Enhancement Training (PMET) involves vividly recalling positive memories in field perspective, and was tested in a single session format with individuals with major depressive disorder ($n = 27$) (Arditte Hall et al. 2018). PMET resulted in greater memory specificity, improved perceived ability to "relive" positive memories, and repaired positive and negative affect after a negative mood induction. This study demonstrates preliminary support for improving emotion regulation in the short-term, but further work is necessary to test whether PMET alone results longer-term change in reward processing and anhedonic symptoms over time.

5.2 Positive Imagery Training

Positive imagery training has also been incorporated into cognitive bias modification (CBM) interventions, with some beneficial effects for anhedonia. In imagery CBM, participants are trained to resolve ambiguous scenarios by imagining positive outcomes, which has resulted in greater increases in positive affect than verbal CBM in nonclinical samples (Holmes et al. 2006, 2009). In a large randomized control trial in a depressed sample, imagery CBM performed as well as a control condition in

decreasing depressive symptoms, but resulted in greater reductions in anhedonia (Blackwell et al. 2015) and a faster increase in behavioral activation as measured by the Behavioral Activation for Depression Scale (Kanter et al. 2007; Renner et al. 2017). In another study, the effects of positive imagery CBM on anhedonia were only partially replicated, depending on the measure. For instance, positive imagery CBM led to greater reductions in anhedonic symptoms as measured by the Beck Depression Inventory (BDI-II; Beck et al. 1996) compared to control CBM and a waitlist control condition; however, changes in other measures of hedonic experience (Snaith-Hamilton Pleasure Scale and the Temporal Experience of Pleasure Scale; Snaith et al. 1995; Gard et al. 2006) were only superior to the waitlist control group (Pictet et al. 2016). Future work should tailor CBM to target facets of anhedonia, including reward constructs.

With a similar goal of shifting cognitive biases in depression, attention bias modification (ABM) aims to train attention away from negative stimuli. Meta-analyses reveal mixed results for ABM in reducing depressive symptoms (Cristea et al. 2015; Fodor et al. 2020). One reason may be that most ABM programs involve shifting attention toward neutral stimuli and do not emphasize directing attention toward positive stimuli. One exception is an attention training program designed for children with anxiety disorders, which explicitly trains attentional engagement with positive stimuli, and has resulted in reduced depressive and anxiety symptoms (Waters et al. 2015, 2016). Similar approaches that train attention toward positive elements should be examined for adults with anhedonia.

5.3 Episodic Future Thinking (EFT)

Resembling memory specificity training, future episodic thinking (EFT) interventions have been recently developed and may target deficits in reward anticipation characteristic of anhedonia. Depressed individuals simulate future positive events with less use of first-person perspective, which in turn is associated with lower vividness and anticipatory pleasure (Hallford et al. 2020b). Enhancing reward anticipation may have downstream effects for increasing motivation to engage in pleasurable activities. For instance, guided episodic thinking of future events increased vividness, anticipatory pleasure, and behavioral intention to engage in activities in healthy controls (Hallford et al. 2020c).

Resembling MEST, Future Specificity Training (FeST) is a 2-session treatment delivered in a group format that involves generation of specific future events in response to cue words (both neutral and positive), with a focus on anticipating positive emotions. In a randomized control trial comparing FeST to a waitlist control in a community sample, FeST led to greater increases in detail, mental imagery, anticipated pleasure (i.e., how pleasurable it is to just think about the event) and anticipatory pleasure (i.e., prediction of how pleasurable the activity will be), perceived control, and likelihood of engagement in future activities (Hallford et al. 2020e). A similar episodic future thinking (EFT) intervention was tested in a

randomized single-case series trial with seven depressed outpatients who were sent daily writing exercises via mobile phone over 2 weeks and were instructed to vividly imagine upcoming enjoyable activities using field perspective, including thoughts, emotions, and contextual details (Hallford et al. 2020d). EFT exercises led to increases in detail and imagery, which positively correlated with increases in anticipatory and anticipated pleasure. EFT led to increased self-reported behavioral activation but did not result in change in depressive symptoms or trait anticipatory pleasure, which may be explained by the brief and remote nature of the intervention. Future work should examine EFT training in an anhedonic sample over longer periods of time and examine measures of anticipatory reward as a potential mechanism.

6 Neurofeedback

Consistent with the notion that positive stimuli are less salient in depression, depressed individuals demonstrate decreased amygdala connectivity with regions of the salience network (anterior and posterior cingulate cortex) when recalling positive memories (Young et al. 2016). Using real-time fMRI neurofeedback, depressed patients were trained over two sessions to increase their hemodynamic response in either the amygdala or a non-emotion processing control region (intraparietal sulcus) while recalling positive autobiographical memories. Compared to the control condition, amygdala neurofeedback resulted in reduced depressive symptoms and increased memory specificity (Young et al. 2017). Amygdala activity during memory recall mediated the association between positive memory specificity and depressive symptoms at a 1-week follow-up, highlighting amygdala engagement during positive emotion processing as a potential treatment target. Future research could also examine the effect of neurofeedback during positive memory recall on other regions, including those central to reward processing deficits in anhedonia. Further, neurofeedback could be used during future episodic thinking to potentially target reward anticipation.

7 Regulation of Positive Affect

Positive emotion regulation refers to the ways in which individuals attempt to change the intensity or duration of positive emotional experience. Dampening of positive affect (e.g., via appraisals such as “this is too good to last” or “I don’t deserve this”) has been associated with depressive symptoms both concurrently (Nelis et al. 2015) and prospectively (Raes et al. 2012), as well as with anhedonia in particular (Werner-Seidler et al. 2013; Nelis et al. 2015), even when controlling for other depressive symptoms (Werner-Seidler et al. 2013). Further, instructed use of dampening decreases positive affect and increases negative affect during pleasant

activities (e.g., taking a walk, Burr et al. 2017) and positive memory recall (Dunn et al. 2018). Difficulties with positive emotion regulation are also reflected at the neural level, with diminished nucleus accumbens activation over time in depressed individuals (Heller et al. 2009). Taken together, dampening of positive emotions may be a key mechanism that drives anhedonia and could help to explain why clinical interventions that attempt to raise positive affect, such as behavioral activation, can sometimes have a limited effect (Dichter et al. 2009; Moore et al. 2013) or even backfire (Burr et al. 2017).

7.1 Positive Emotion Regulation Treatments

Few interventions directly target regulation of positive affect over time. One exception is Positive Affect Stimulation and Sustainment (PASS) (McMakin et al. 2011), which was developed to extend the temporal impact of positive experiences through memory recall and identification of how one's contribution could lead to future positive events. Participants complete a 20-min written disclosure paradigm three times over 2 weeks. In a study of women with elevated depressive symptoms, PASS resulted in moderate decreases in depression and negative affect relative to a control condition that involved writing about experiences in an objective manner. While positive affect improved from before to after a given PASS session, it did not significantly change from pre to post intervention. Given the brief nature of the intervention, it is possible that longer periods of time to practice skills may be necessary to produce change in positive affect. Another explanation for limited effects is that PASS does not focus on responses to positive affect such as dampening.

Due to the robust link between dampening appraisals and anhedonia, it may be warranted to explicitly target dampening. To the best of our knowledge only one treatment for anhedonia, ADePT, explicitly purports to target elevated dampening appraisals as a mechanism. ADePT resulted in reductions in levels of dampening at 1-year follow-up (Dunn et al. 2019a), although it is not clear which of the multiple treatment components are hypothesized to contribute to the effects. In addition, there is a lack of treatments that target reward devaluation related to a fear of positive emotion (Werner-Seidler et al. 2013). Through learned associations, individuals may come to devalue positivity if it is repeatedly paired with negative outcomes (e.g., disappointment after getting one's hopes up), which may influence regulatory goals and cause depressed individuals to actively avoid or down-regulate positive experiences (Vanderlind et al. 2017, 2020). Interventions may directly target positive emotion regulation and reward devaluation through psychoeducation (about the role of dampening appraisals in blunting rewarding experiences), mindful awareness of dampening and redirection back to pleasant present-moment sensations, and cognitive restructuring of unhelpful beliefs surrounding positive emotions. These suggestions require formal testing and linkage to reward constructs such as reward valuation within the context of anhedonia.

8 Conclusions and Recommendations for Future Research

In sum, recently developed psychological treatments that target the Positive Valence Systems show preliminary efficacy for improving anhedonia. However, most interventions reviewed in this article have been tested in relatively small samples of individuals primarily with depression, rather than anhedonia specifically. Positive affect treatments require replication and extension in larger, transdiagnostic samples with anhedonia as a primary presenting problem with longer follow-up periods to assess how long treatment-gains are maintained over time. By using translational research from affective neuroscience, more targeted treatments can be refined and developed to map onto specific deficits in reward processing central to anhedonia. The field will benefit from establishing gold standard measurement of anhedonia across units of analysis (self-report, behavioral, neural), and by investigating which aspects of reward processing are changed through treatment (e.g., anticipation, attainment, learning). Given that depression and anhedonia often emerge in adolescence (Lee et al. 2014), there is a need for treatments to take into account the developmental trajectories and maturation of the reward system (Forbes and Dahl 2012; Auerbach et al. 2014). Additionally, there is a relative lack of interventions that address regulation of positive affect and reward devaluation. Finally, innovations in technology such as neurofeedback and virtual reality have potential to augment and facilitate the delivery of treatments that target the Positive Valence Systems.

Interestingly, the effects of treatments designed to target the Positive Valence Systems are not always specific to anhedonia or positive affective outcomes. Several treatments described above (PAT, VR-RT, AMP, PASS) improved negative affective outcomes (depression, anxiety, stress) as well (Taylor et al. 2017; Craske et al. 2019; Chen et al. 2021; Kryza-Lacombe et al. 2021). This pattern of findings begs the question: what are the mechanisms of action? One possibility is that treatments consistent with the Positive Valence Systems increase reward processing, which in turn reduces negative affective outcomes. This pathway is consistent with models that propose that positive affect acts as a stress-buffer by activating neural reward systems which in turn dampen brain regions involved in signaling threat (e.g., anterior cingulate, insula, amygdala) (van Steenbergen et al. 2021). A second possibility is that these treatments only indirectly reduce anhedonia by more directly decreasing stress and other types of negative affective experience. Stress has been proposed as a central contributing factor for anhedonia via blunted mesocorticolimbic dopaminergic pathways critical to reward processing (Pizzagalli 2014). Therefore, these treatments may alleviate general distress more broadly, which results in restoration of reward processing. A third possibility is that treatments exert changes upon the Positive and Negative Valence Systems in tandem, and that there are complex interactions between systems, as exemplified by the role of positive affect in fear extinction (see Zbozinek and Craske 2017). Fourth, treatments may exert effects on cognitive mechanisms, such as attention and cognitive control, which are important for regulation of both positive and negative

emotions (Joormann and Vanderlind 2014; Young et al. 2019). Importantly, these hypotheses about therapeutic mechanisms of action have yet to be tested and require further investigation.

Another important research topic is for whom do positive affect treatments work best? Is it the person who shows the most deficits in reward processes (e.g., Krystal et al. 2020) or strengths in reward processes who responds best, for example? Future research should investigate whether certain clinical, demographic, or neurobiological characteristics predict better response to treatments that target positive affect as opposed to negative affect. By taking a modularized treatment approach, it would also be useful to determine which modules within Positive Valence Systems treatments (e.g., behavioral activation, savoring, memory training, imagining the future) are most essential and which order of modules confers better long-term outcomes for anhedonia (e.g., first delivering components that target Positive Valence Systems, followed by those that target Negative Valence Systems as needed and vice versa).

In conclusion, psychological treatments that target the Positive Valence Systems are providing promise for anhedonia, for which traditional treatment approaches have been relatively ineffective. Nonetheless, much remains to be learned regarding the optimal delivery of these treatments that are often multi-component nature, for whom they are most likely to be effective, and the mechanisms accountable for change.

Acknowledgments The authors were funded by the National Institute of Mental Health R61 MH115138-1NIH/NIMH (PIs: Craske, Meuret, & Ritz). All authors report no financial interests or potential conflicts of interest.

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Circuit-Targeted Neuromodulation for Anhedonia

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Contents

Abstract Despite the prevalence of anhedonia across multiple psychiatric disorders, its relevance to treatment selection and prognostication can be unclear (Davey et al., Psychol Med 42(10):2071–81, 2012). Given the challenges in pharmacological and psychosocial treatment, there has been increasing attention devoted to

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Curr Topics Behav Neurosci (2022) 58: 515–536
https://doi.org/10.1007/7854_2022_350
Published Online: 24 May 2022

neuroanatomically-targeted treatments. This chapter will present a brief introduction to circuit-targeted therapeutics in psychiatry (Sect. 1), an overview of brain mapping as it relates to anhedonia (Sect. 2), a review of existing studies on brain stimulation for anhedonia (Sect. 3), and a description of emerging approaches to circuit-based neuromodulation for anhedonia (Sect. 4).

Keywords Circuit · DBS · Deep brain stimulation · Network · Neuromodulation · TMS · Transcranial magnetic stimulation

1 Introduction: Circuit-Targeted Therapeutics for Mental Illness

Multiple psychiatric symptoms can be treated via noninvasive or invasive brain stimulation techniques. Transcranial magnetic stimulation (TMS) can noninvasively modulate specific brain regions, and different TMS protocols have been cleared by the US Food and Drug Administration (FDA) to treat major depressive disorder (MDD) (O'Reardon et al. 2007), obsessive-compulsive disorder (OCD) (Carmi et al. 2019), nicotine use disorder (Zangen et al. 2021), and migraines (Zangen et al. 2021). Deep brain stimulation (DBS) is an invasive implant that can also modulate specific brain regions, and different protocols have been cleared by the FDA to treat Parkinson's disease (Deuschl et al. 2006), essential tremor (Flora et al. 2010), epilepsy (Fisher et al. 2010), dystonia (Kiss et al. 2007), and OCD (Denys et al. 2010) (the latter two under humanitarian device exemption). Multiple other brain stimulation techniques have been investigated but are not yet approved for clinical use. With our growing knowledge about neuroanatomy of mental illness, it has become increasingly evident that these treatments can modulate distributed brain circuits rather than individual brain regions. With careful mapping of the relevant brain circuitry, it may be possible to selectively target anhedonia and related symptoms.

1.1 A Brief History of Brain Circuit Therapeutics in Psychiatry

The concept of neurocircuitry in human mental illness dates back to at least the 1930s, when Antonio Egas Moniz introduced the concept of therapeutic lesioning of prefrontal white matter tracts for schizophrenia (Tierney 2000). This approach was refined over subsequent generations, particularly after James Papez described a circuit that generates human emotion (Papez 1937). Starting in the 1960s, neurosurgeons such as Geoffrey Knight and H. Thomas Ballantine created surgical lesions of the Papez circuit to relieve the symptoms of severe treatment-refractory MDD and OCD (Knight 1965; Ballantine et al. 1967). In contrast to therapeutic lesioning, in

1982 Robert Robinson showed that incidental lesions can cause depression, particularly in the left dorsolateral prefrontal cortex (DLPFC) (Robinson et al. 1984). The subsequent emergence of functional neuroimaging research added further evidence for this idea, as multiple studies showed that MDD was associated with hypoactivity in the DLPFC and hyperactivity in the limbic system (Mayberg et al. 1999).

Based on the idea that DLPFC hypoactivity may cause depression, in the 1990s multiple studies used TMS to increase activity in the DLPFC as a treatment for depression (George et al. 1995, 2000; Pascual-Leone et al. 1996). The most commonly used TMS protocols involved a 37-min session of 10 Hz stimulation every weekday for 4–6 weeks. This protocol was believed to be excitatory based on early motor plasticity studies, but this directionality has recently been shown to be less predictable with DLFPC stimulation.

DBS is a more precise and sustained approach to brain stimulation. Unlike TMS, it can be implanted to provide long-term stimulation at a precise location deep in the brain. In general, DBS is believed to exert inhibitory effects, partly because it mimics the effects of a brain lesion in treatment of tremor, dystonia, and Parkinson's disease (Chiken and Nambu 2016). Based on this reasoning, DBS for depression was first targeted to the limbic system (particularly the subgenual cingulate and nearby white matter), which is believed to be hyperactive in depression (Mayberg et al. 2005; Merkl et al. 2013; Riva-Posse et al. 2014). While these approaches showed some efficacy for anhedonia as well, some studies have specifically targeted reward processing by stimulating the ventral striatum or medial forebrain bundle with varying degrees of success (Sect. 3.2).

1.2 Clinical Applications of Circuit-Targeted Brain Stimulation in Psychiatry

The efficacy of TMS for MDD has been demonstrated in two large multi-center randomized trials, leading to FDA clearance and broad clinical use (George et al. 2010; O'Reardon et al. 2007). Multiple studies have shown that the antidepressant efficacy of TMS is dependent on the precise brain circuit that is targeted (Herbsman et al. 2009; Cash et al. 2020a; Fox et al. 2012). Building on these findings, more recent multi-center trials have successfully employed different TMS targets for OCD (Carmi et al. 2019) and nicotine use disorder (Dinur-Klein et al. 2014). Meanwhile, advances in TMS pulse parameters have led to the widespread implementation of intermittent theta burst stimulation (iTBS), which can achieve similar efficacy with only a three-minute treatment (Blumberger et al. 2018). This success also paved the way for other neuromodulation studies in depression, including studies on DBS (Mayberg et al. 2005) and transcranial direct current stimulation (tDCS) (Brunoni et al. 2013, 2017).

By contrast, DBS has shown inconsistent results as a treatment for depression. In addition to the subgenual cingulate, different studies have targeted various other regions involved in mood, including the ventral capsule/ventral striatum (or specifically the nucleus accumbens, which is part of the ventral striatum)

(Dougherty et al. 2015; Tyagi et al. 2019), the lateral habenula (Sartorius et al. 2010), the medial forebrain bundle (Fenoy et al. 2021), and the bed nucleus of the stria terminalis (BNST) (Fitzgerald et al. 2018). Some of these studies reported improvements in anhedonia along with depression. However, no DBS protocol has clearly shown superiority to sham for depression severity, possibly because its increased precision leads to increased dependence on careful targeting. Randomized trials have been more successful with various targets for OCD, including the nucleus accumbens (NAc), subthalamic nucleus (STN), and the BNST (Raviv et al. 2020; Mosley et al. 2021), but these studies have provided limited insights about anhedonia.

tDCS is a more diffuse treatment that can be used to increase or decrease cortical excitability rather than directly activating brain activity (Medeiros et al. 2012). Although it may be less potent than TMS or DBS, it has gained popularity because it is relatively inexpensive and easy to administer. Two recent single-center clinical trials in Brazil suggested that tDCS may be as effective as SSRIs for MDD (Brunoni et al. 2013, 2017), but this finding failed to replicate in a multi-center clinical trial (Loo et al. 2018). The importance of precise targeting for tDCS remains unclear – targeting may be less relevant given the more diffuse nature of the treatment, but this has yet to be investigated systematically. Due to these open questions, the role of tDCS in the treatment of anhedonia remains unclear.

Of note, neuromodulation is not always targeted to specific brain circuits. One of the most effective treatments for depression is electroconvulsive therapy, which induces a generalized seizure. Other convulsive therapies, such as magnetic seizure therapy and focal electrically administered seizure therapy, can create a more precise stimulation field but still induce a generalized seizure (Sackeim 2021). Vagal nerve stimulation can also exert robust antidepressant effects, possibly by modulating autonomic function (Rush et al. 2005). These techniques may improve anhedonia along with depression (Wade et al. 2020), but have not been used to selectively target reward circuitry.

1.3 Targeting Brain Circuits with TMS and DBS

TMS and DBS are generally thought to function by selectively modulating specific circuits in the brain. For instance, effective TMS targets for various disorders appear to be connected to the same brain networks as effective DBS targets for the same disorders (Fig. 1) (Fox et al. 2014). Furthermore, in multiple studies, the clinical efficacy of TMS and DBS was better predicted by the connectivity of the stimulation site than the location of the stimulation site alone (Weigand et al. 2018; Siddiqi et al. 2021a; Horn et al. 2017). Together, these findings suggest that TMS and DBS targets could potentially be improved by taking brain connectivity into account.

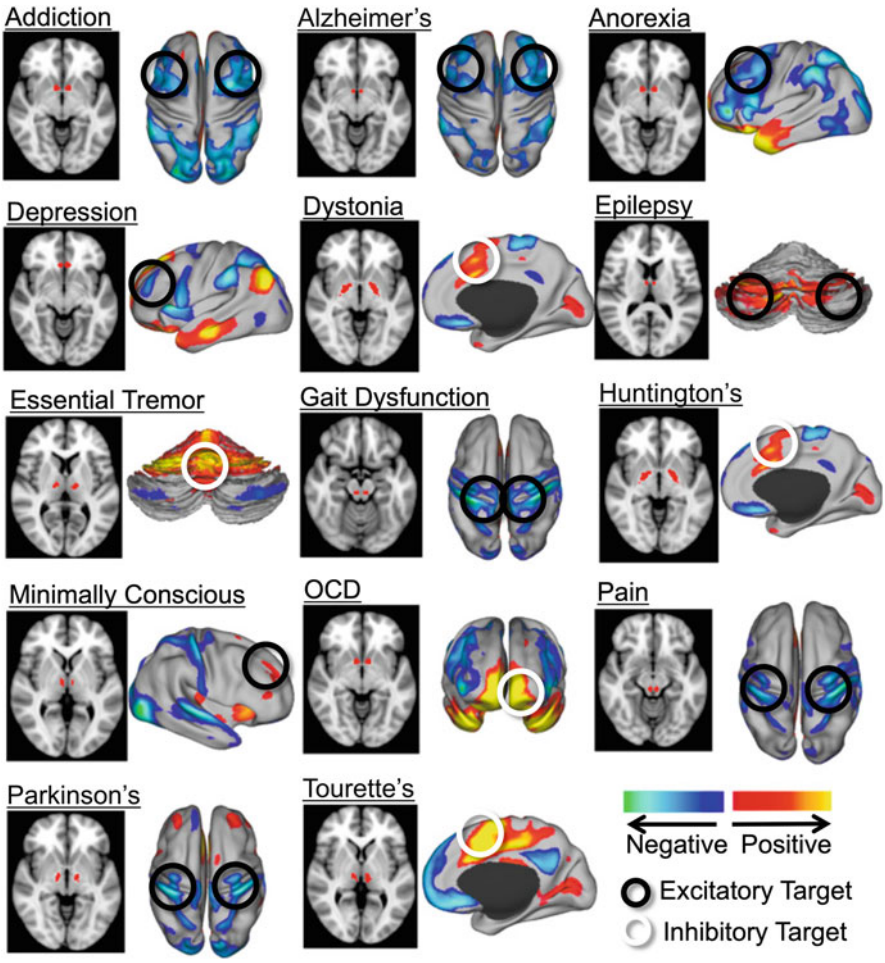

Fig. 1 Multiple studies have investigated the effects of TMS, tDCS, and DBS for different indications. These 14 examples depict neuropsychiatric disorders for which all three treatment modalities have shown efficacy. Effective excitatory TMS and tDCS sites were functionally anti-correlated with effective DBS sites, while effective inhibitory TMS and tDCS sites were positively correlated with effective DBS sites. (Reproduced with permission from Fox et al. *Proc Natl Acad Sci U S A* 2014)

2 Mapping Brain Circuits to Identify Treatment Targets for Anhedonia

2.1 Approaches to Brain Circuit Mapping

To interpret the literature on circuit-targeted neuromodulation, it is essential to first understand the techniques used to derive these circuit-based targets. Multiple tools

are commonly used to map circuits that are correlated with different psychiatric symptoms. Positron emission tomography (PET) can identify changes in local glucose metabolism, suggesting increased or decreased energy utilization. PET and arterial spin labeling (ASL) MRI can also be used to study changes in regional cerebral blood flow. Task-based functional MRI (fMRI) can be used to investigate how brain activity changes with different cognitive tasks. Resting-state fMRI uses spontaneous fluctuations in brain activity to map "functional" connectivity in the brain. Diffusion tensor imaging (DTI) measures water diffusion through axons to map "structural" connectivity in the brain. The results from any of these techniques can then be compared to clinical symptoms to identify neuroanatomical correlates of the symptom (Raichle 2009).

While these approaches can provide useful insights into the neuroanatomy of anhedonia, neuroimaging correlates may not translate into effective therapeutic targets. Different hypotheses have emerged to explain neuroimaging results and contextualize them along with clinical data, animal models, and other approaches to studying anhedonia. Each of these models has different strengths and weaknesses when attempting to identify neuromodulation targets.

2.2 Models of Anhedonia Derived from Correlative Neuroimaging

One of the most common models involves conceptualizing anhedonia as a dimensional construct that results from dysfunction in the brain's reward circuitry (Markou et al. 1998). This model would suggest that greater dysfunction in this circuit would lead to greater severity of anhedonia. Reward is processed by the dopaminergic reward system, which includes the ventral tegmental area, nucleus accumbens (NAc), and medial forebrain bundle. This system is partly regulated by the medial and lateral orbitofrontal cortex, whose functions are often conceptualized as reward-based learning and reward-motivated behavior, respectively (although alternative models also exist) (Fenoy et al. 2016). The neighboring ventromedial prefrontal cortex can attach emotional salience to these rewarding stimuli. Functional neuroimaging studies have implicated each of these regions in trait anhedonia, potentially supporting the reward deficiency hypothesis (Keller et al. 2013; Keedwell et al. 2005; Hamilton et al. 2012; Treadway and Zald 2011). This model has inspired the use of TMS targeted to sites connected to the reward circuit as a treatment for anhedonia (Wang et al. 2021).

By contrast, mental illness can also be conceptualized as a categorical construct. In this model, anhedonia is simply one of many symptoms that can incidentally arise in the context of certain discrete disorders. This approach builds on the plethora of research on mental illness in terms of categorical diagnoses with potentially overlapping symptoms (Kendler et al. 2010). If this is correct, then anhedonia would improve along with other symptoms when the "underlying" disorder is

treated. Indeed, dorsolateral prefrontal TMS for MDD leads to improvement in anhedonia as well as other depressive symptoms and baseline anhedonia does not predict its efficacy (Fukuda et al. 2021).

One possible compromise between the dimensional model and the categorical model involves identifying categorical "biotypes" made up of dimensional constructs. A particular biotype might comprise a discrete cluster of symptoms and neuroimaging findings (or other findings, such as cognitive/behavioral testing or blood/CSF biomarkers) that covary with one another. Biotypes for depression and anxiety are often described in terms of large-scale network dysfunction rather than abnormalities in specific brain regions. For instance, Williams et al. conceptualized anhedonia as a focal disruption of reward circuit function with relative sparing of threat, salience, attention, cognitive control, and default networks. Rather than characterizing anhedonia as a dimensional construct that correlates with the degree of reward deficiency, this model posits that a discrete state of reward deficiency leads to disorders that cause anhedonia. If this is correct, dopaminergic medications (i.e., pramipexole (Whitton et al. 2020)) and neuromodulation targeted to the striatum may be particularly beneficial in patients with anhedonia, regardless of etiology (Williams 2017).

Biotyping was most influentially applied to neuromodulation outcomes by Drysdale et al. who derived four distinct biotypes of depression based on functional connectivity and symptom patterns. The authors used canonical clustering analysis to divide patients with MDD into four distinct connectivity patterns associated with distinct symptom patterns. Patients in Biotype 1 (low anhedonia, high anxiety/insomnia/anergia) were most responsive to TMS targeting the DMPFC. Although the study did not identify a TMS target that is effective for anhedonia and related symptoms, it did illustrate that different clusters of symptoms and connectivity may respond better to specific TMS targets (Drysdale et al. 2016). To investigate this topic further, a subsequent study by Siddiqi et al. (see Sect. 4.1) derived different symptom clusters that respond better to different TMS targets. Consistent with Drysdale et al.'s results, targets connected to the DMPFC were more effective for "anxiosomatic" symptoms such as irritability and insomnia, while targets connected to the DLPFC were more effective for "dysphoric" symptoms such as anhedonia and sadness (Fukuda et al. 2021).

3 Treating Anhedonia with Circuit-Targeted Neuromodulation

3.1 TMS for Anhedonia

The evidence on TMS for anhedonia has primarily included studies in healthy controls, patients with MDD, and patients with schizophrenia. The existing results have been mixed, partly due to methodological heterogeneity. Most studies have

simply adapted treatment protocols designed for other disorders rather than developing targets specific to anhedonia. A circuit-based model of TMS targeting can explain many of the seemingly-inconsistent results.

At least three studies have attempted to modulate pleasure-seeking behavior using TMS in healthy controls, but each suffered from important methodological limitations. Duprat et al. used a single session of active or sham iTBS to the left DLPFC in 22 participants, finding no significant difference between groups on the temporal experience of pleasure scale (Duprat et al. 2016). In a more complex study, Hurlemann et al. applied active or sham continuous theta burst stimulation (cTBS, an inhibitory protocol) in separate sessions to left DLPFC and DMPFC. Relative to sham, both cTBS targets led to greater suppression of startle response to hedonic stimuli. However, these results are difficult to interpret because the sham device did not provide the same physical discomfort as active cTBS, and there was no assessment of efficacy of blinding (Hurlemann et al. 2015). Finally, Ulrich et al. applied 600 pulses of open-label iTBS (excitatory) and cTBS (inhibitory) to modulate fMRI responses to high- or low-calorie foods. They found no significant difference between excitatory and inhibitory stimulation (Ulrich et al. 2018). Of note, these studies are difficult to interpret because they applied only a single TMS treatment to modulate a normal behavior in healthy controls, while most successful TMS studies have applied daily treatment for several weeks to treat an abnormal symptom.

When using more standard treatment protocols in patients with MDD, multiple studies have lent useful insights into the role of TMS for anhedonia. In a naturalistic study of 47 patients receiving TMS to the DMPFC for MDD, Downar et al. showed that nonresponders were more likely to have high baseline anhedonia and reward circuit hypofunction (Downar et al. 2014). By contrast, in 144 patients receiving clinical TMS to the anterior DLPFC for MDD, Fukuda et al. found that improvement in anhedonia (58%) outpaced improvement in overall depression (45%), while baseline anhedonia was unrelated to clinical outcomes (Fukuda et al. 2021). Next, in 19 patients receiving active or sham TMS with precise neuronavigation to the anterior DLPFC for MDD, Light et al. reported significant improvement in anhedonia even after controlling for overall antidepressant effect (Light et al. 2019). Finally, Wang et al. randomized 56 patients to receive active or sham TMS with fMRI-guided neuronavigation to an anterior DLPFC site that is highly connected to NAcc. Active treatment led to significant improvement in multiple measures of anhedonia (Wang et al. 2021).

While some of these results may appear to be contradictory, they are likely explained by the distinct stimulation sites employed in each study. The importance of this distinction was highlighted by two recent influential brain circuit mapping studies. First, Drysdale et al. (see Sect. 2.2) showed that a connectivity-based biotype of MDD with low anhedonia and high anxiety/insomnia is more responsive to DMPFC stimulation (Drysdale et al. 2016). Of note, the existence of a discrete biotype has failed to replicate, potentially suggesting that this may be a continuous phenomenon that was artificially categorized. Supporting the continuous model, subsequent work by Siddiqi et al. (see Sects. 2.2 and 4.1) showed that TMS sites that relieve anxiety and somatic symptoms are more connected to the DMPFC, while

TMS sites that relieve anhedonia and dysphoric symptoms are more connected to the anterior left DLPFC (Siddiqi et al. 2020). This connectivity-based model could explain all four of the aforementioned clinical findings. Downar's results argue against TMS of the DMPFC for anhedonia, and a subsequent sham-controlled trial from the same group found this protocol to be ineffective for primary MDD without comorbid anxiety. By contrast, Fukuda's results argue in favor of TMS to the anterior left DLPFC for anhedonia, while Light and Wang's results further argue that precise targeting of the anterior DLPFC can selectively modulate anhedonia.

TMS studies in schizophrenia have also used heterogeneous methods and shown inconsistent results. Four clinical trials used a similar treatment target in the DLPFC, but applied different doses and observed different results. First, Prikryl et al. randomized 22 patients to receive 22,500 total pulses of active or sham TMS over 15 days, observing a large effect on negative symptoms overall (Cohen's $d = 1.03$, $p < 0.01$) (Prikryl et al. 2007). Building on this finding, the same group subsequently randomized 40 patients to receive 30,000 total pulses of active or sham TMS over 15 days, observing an even larger effect on negative symptoms overall ($d = 1.53$, $p < 0.01$) and anhedonia specifically ($d = 1.09$, $p < 0.01$) (Prikryl et al. 2013). Next, a large multi-center trial randomized 175 patients to receive only 15,000 total pulses of active or sham TMS over 15 days and failed to detect a significant effect on negative symptoms ($d = 0.09$, $p > 0.5$) (Wobrock et al. 2015). Finally, a more recent trial randomized 100 patients to receive 40,000 total pulses of active or sham TMS over 20 days, showing a significant effect on negative symptoms overall ($d = 0.61$, $p < 0.01$) and on anhedonia specifically ($d = 0.64$, $p < 0.01$) (Kumar et al. 2020). Of note, each of these doses is substantially lower than the typical TMS dose traditionally used for depression (90,000 pulses over 30 days). Given that higher TMS doses provide greater antidepressant efficacy in MDD patients, it may be reasonable to suspect that TMS can modulate anhedonia in schizophrenia when applied at an appropriate dose. Circuit-based TMS targeting may also add value, and its potential utility was illustrated in a recent pilot study of cerebellar stimulation for negative symptoms of schizophrenia (Brady et al. 2019).

3.2 DBS for Anhedonia

In contrast to most TMS trials for anhedonia, which have modeled their protocol after successful trials for MDD, DBS studies have sometimes employed a more targeted approach. In MDD patients, Schlaepfer et al. attempted to selectively treat anhedonia by targeting reward circuitry with DBS. They implanted DBS electrodes directly into the nucleus accumbens (NAc), the regulating center of the reward pathway, in patients with severe treatment-resistant depression. Although DBS is generally considered to be inhibitory, the authors reasoned that a sustained pattern of stimulation may restore normal activity in the NAc. The electrodes were methodically activated or inactivated in a double-blind manner. In all three patients, anhedonia preferentially improved when the stimulator was turned on, improved further

when the voltage was increased, and worsened when the stimulator was turned off. Stimulation also led to increased glucose metabolism in NAc along with consistent changes in the prefrontal cortex and limbic system (Schlaepfer et al. 2008). Follow-up studies from the same group showed that this antidepressant benefit was sustained in 5 out of 11 patients, but there was a high rate of complications, including agitation (3/11), pain (4/11), seizure (1/11), and suicide attempts (1 attempted but failed, one completed) (Bewernick et al. 2012). Thus far, no sham-controlled trials have specifically investigated NAc stimulation for depression and/or anhedonia.

More recent studies have investigated stimulation of the medial forebrain bundle (MFB), a white matter tract that connects important reward structures such as the NAc and the VTA to the prefrontal cortex. This was inspired partly by rat models showing that DBS to the MFB can improve depression-like symptoms, while optogenetic modulation of the nearby VTA can induce changes in reward processing. Initial studies on this target, also by Schlaepfer et al. showed rapid effects on reward motivation along with high response rates for overall depression (6/7 patients) (Schlaepfer et al. 2013). Since then, at least 33 cases of MFB-DBS have been reported in the literature with similar overall response rates. In many of these cases, the authors noted that anhedonia appears to be the symptom that improves most prominently with MFB-DBS. Randomized clinical trials are now underway to better characterize this effect (Fenoy et al. 2021).

4 Novel Approaches to Neuromodulation for Anhedonia

4.1 Identifying Neuromodulation Targets Using Causal Sources of Information

Most neuroimaging studies of MDD and anhedonia are focused on identifying correlates of symptoms. Such correlates are useful for conceptualizing and classifying the syndrome as a discrete circuit-based phenomenon, but provide limited knowledge about potential therapeutic targets. To determine which brain circuit should be targeted with an intervention, it would be ideal to know if that circuit is causally implicated in anhedonia (Etkin 2018, 2019).

The most rigorous way to establish the causal role of a circuit would be to randomize patients to be stimulated at different circuits. For instance, Tyagi et al. randomized six patients with OCD to receive DBS at the anteromedial subthalamic nucleus (amSTN) or the ventral capsule/ventral striatum (VC/VS). The amSTN target led to preferential improvement in cognitive flexibility, consistent with the role of the STN in associative cognition. The VC/VS target led to preferential improvement in mood, consistent with the role of these regions in reward processing (Tyagi et al. 2019). If replicated in a larger sample, this study would provide a clear rationale for stimulating different targets in different patients.

However, in practice, large comparative randomized trials are challenging to implement. Instead, we can sometimes infer causality by capitalizing on natural experiments that lead to incidental near-randomization. In clinical practice, TMS is targeted using scalp landmarks, leading to substantial variability in precise target locations. DBS is targeted using intraoperative responses, which also leads to inter-individual variability in stimulation location. Similar inference can also be made using focal brain damage, which occurs throughout the brain (Bates et al. 2003). We can map the connectivity of stimulation sites and lesion locations using normative connectivity – rather than using functional connectivity data for each individual patient (which is inherently noisy), this method assumes that patients are more similar than different and capitalizes on the substantial incidental variance in the precise stimulation site or lesion location. If stimulation sites or lesions that causally modify the same symptom are incidentally connected to the same circuit, then that circuit may be causally implicated in that symptom. This principle has been used to map the causal neuroanatomy of mood disorders (Fox et al. 2012; Siddiqi et al. 2021a; Padmanabhan et al. 2019; Cotovio et al. 2020; Cash et al. 2019; Irmen et al. 2020), anxiety-related disorders (Siddiqi et al. 2020; Baldermann et al. 2019; Li et al. 2020), psychosis (Kim et al. 2021; Boes et al. 2015; Darby et al. 2017), disorders of arousal/consciousness (Snider et al. 2020; Fischer et al. 2016; Joutsa et al. 2019), movement disorders (Horn et al. 2017; Irmen et al. 2020; Joutsa et al. 2018a; Corp et al. 2019; Joutsa et al. 2018b; Laganiere et al. 2016), and various other neuropsychiatric phenomena (Fox et al. 2014; Darby et al. 2018a, b; Cohen et al. 2019, 2021).

This approach holds a great deal of promise given the sheer number of patients who experience different types of symptoms after different types of stroke. If damage to a particular brain circuit can causally induce a particular symptom, then it may be reasonable to conclude that activating the same circuit would relieve that symptom. To test this hypothesis, Siddiqi et al. recently combined data from 14 datasets including 713 patients who were assessed for depression after TMS ($n = 151$), DBS ($n = 101$), or focal brain damage ($n = 461$). Each stimulation site or lesion location was localized and mapped to an underlying brain circuit using a normative connectivity database. This analysis revealed a common circuit that was preferentially connected to TMS sites that relieved depression, DBS sites that modified depression, and brain lesions that caused depression (Fig. 2). The circuit was consistent with the known neuroanatomy of depression, including positive correlations to the DLPFC and negative correlations to the subgenual cingulate and ventromedial prefrontal cortex. This effect was transdiagnostic – a similar depression circuit was identified from patients with MDD, Parkinson's disease, epilepsy, hemorrhagic stroke, ischemic stroke, and penetrating brain injury. Connectivity to this circuit also predicted out-of-sample antidepressant efficacy of TMS and DBS sites (Siddiqi et al. 2021a). This demonstrates that connectivity of causal brain lesions can reveal new therapeutic targets for specific symptoms, including symptoms such as anhedonia that transcend conventional diagnostic boundaries.

To translate this finding to a targeting framework for anhedonia and related symptoms, Siddiqi et al. used a similar approach to derive symptom clusters that preferentially respond to stimulation of different circuits with TMS. Across

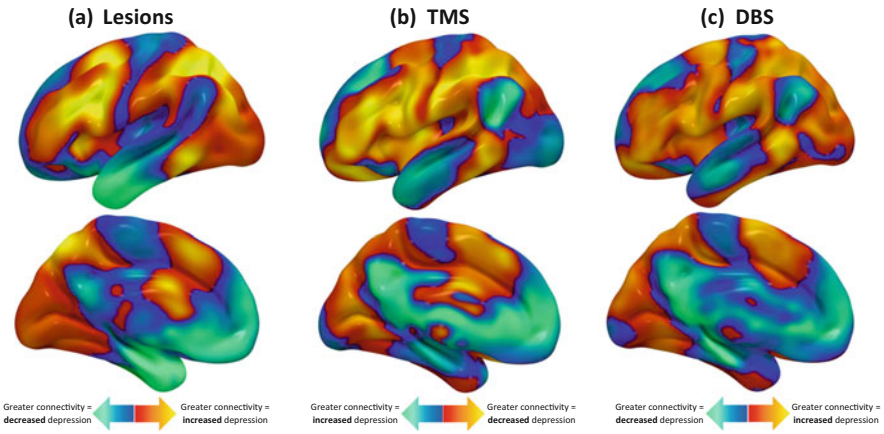

Fig. 2 (**a**) Lesions, (**b**) TMS sites, and (**c**) DBS sites can modify depression severity via connectivity to a common brain circuit. (Reproduced with permission from Siddiqi et al. *Nat Hum Behav* 2021)

independent datasets, this revealed two distinct circuit targets that were effective for two different symptom clusters (Fig. 3a). The "dysphoric" cluster included symptoms such as anhedonia, sadness, and suicidality, while the "anxiosomatic" cluster included symptoms such as anxiety/irritability, insomnia, and sexual dysfunction. The dysphoric circuit, which included positive connectivity to the DLPFC and anticorrelations to the subgenual cingulate and the limbic system, overlapped closely with the target used in multiple studies that showed improvement in anhedonia and other dysphoric symptoms (Fig. 3b). The anxiosomatic circuit, which primarily included the dorsomedial prefrontal cortex and other regions in the default mode network, overlapped closely with the target that was more effective for Drysdale et al.'s biotype with low anhedonia and high anxiety/insomnia/anergia (see Sect. 26.2.2) (Drysdale et al. 2016). It also overlapped with the target used in multiple studies that showed greater improvement in anxiety than in dysphoria (Fig. 3b) (Siddiqi et al. 2020).

4.2 Mapping Inter-Individual Variability to Personalize Neuromodulation

Treatment targets can also be personalized based on patient-specific brain mapping data rather than disease- or symptom-specific group-based data. For instance, individualized white matter tractography measurements can help to optimize the precise DBS target for depression (Howell et al. 2019). Similarly, individualized functional connectivity measurements may help to optimize the precise TMS target for

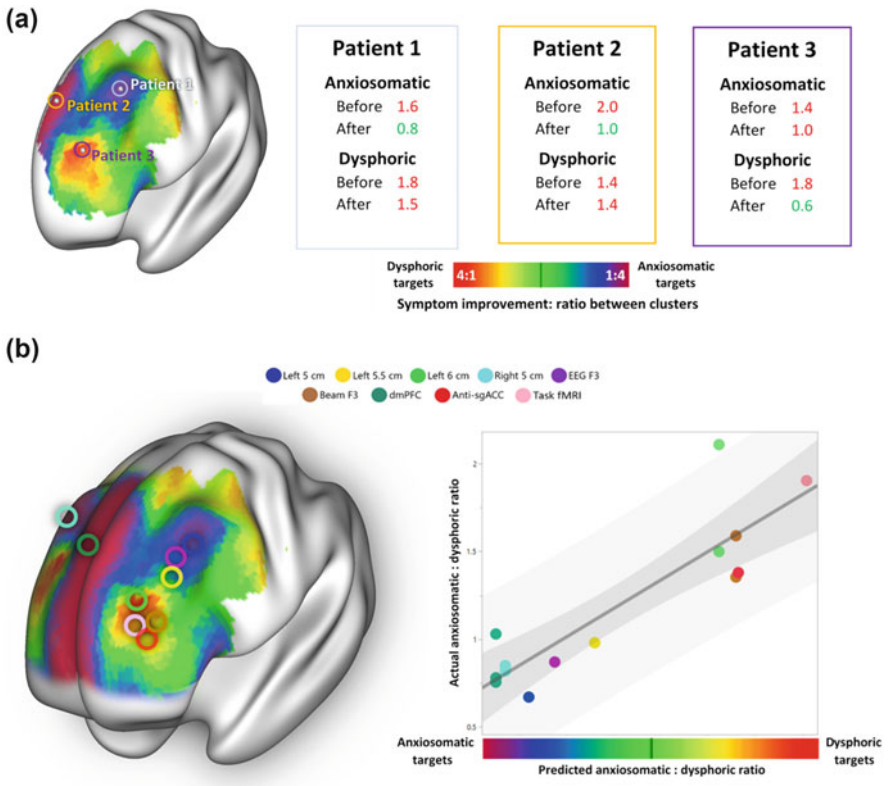

Fig. 3 Distinct circuit-based TMS targets for dysphoric versus anxiosomatic symptoms. (**a**) Patients receiving stimulation to dysphoric targets (orange) showed greater improvement in symptoms such as anhedonia and sadness. Patients receiving stimulation to anxiosomatic targets (magenta) showed greater improvement in symptoms such as insomnia and sexual dysfunction. (**b**) Prior published clinical TMS studies reported greater improvement in depression if their stimulation site overlapped with our dysphoric circuit, and reported greater improvement in anxiety if their stimulation site overlapped with our anxiosomatic circuit. (Reproduced with permission from Siddiqi et al. *Am J Psychiatry* 2020)

depression (Cash et al. 2020a, b; Drysdale et al. 2016; Downar et al. 2014; Siddiqi et al. 2019, 2021b).

However, before individualized brain mapping can be translated to the clinic, there is a need for increased methodological standardization. Several different approaches have emerged to map brain organization and personalize stimulation sites at different levels of precision (Boes et al. 2015; Yarkoni et al. 2011; Glasser et al. 2016; Schaefer et al. 2018; Gordon et al. 2016, 2017; Destrieux et al. 2010; Yeo et al. 2011; Power et al. 2011; Laumann et al. 2015; Wang et al. 2015; Hacker et al. 2013; Botvinik-Nezer et al. 2020). As a result, there are countless ways to map the circuits linked to any given lesion or stimulation site. In one recent study, when 70 different research teams were asked to test the same hypotheses in the same

neuroimaging dataset, no two teams chose the same analytical procedure (Yang et al. 2021).

Similarly, it remains unclear how to choose the optimal stimulation parameters to modulate any given node in a brain network (Opitz et al. 2016). First, the size of an individual node in a brain network remains unclear. Multiple studies have attempted to parcellate the cortex into individual subregions, and each has arrived at a different scheme with anywhere between 7 and 1,000 different parcels (Schaefer et al. 2018; Gordon et al. 2016; Destrieux et al. 2010; Yeo et al. 2011; Power et al. 2011). Second, the size of the electric field induced by TMS is a topic of active debate. Some studies have used finite element modeling to estimate the electric field distribution in individual patients (Butson et al. 2007; Fox et al. 2013), while other studies have used simplified models of electric field (Eisenstein et al. 2014; Cole et al. 2020). Third, dosing and pulse patterns have not yet been optimized, particularly for TMS. This leads to relatively slow clinical effects which may be too subtle to characterize thoroughly. This limitation might be addressed by the advent of high-dose accelerated TMS protocols, which greatly improve the short-term efficacy of clinical TMS (Williams et al. 2018).

5 Conclusions

Despite the extensive body of research on neuroimaging of anhedonia, the concept of circuit-targeted neuromodulation for anhedonia remains in its infancy. Although many early studies used speculative methods that led to inconsistent results, recent studies have developed more refined approaches to targeting anhedonia with TMS and DBS. With increasing data on TMS of the anterior DLPFC and DBS of the medial forebrain bundle, the field may soon approach a consensus treatment target for patients with anhedonia associated with MDD. Meanwhile, with the recent emergence of methods that can identify common treatment targets across modalities and diagnoses, there is a clear path to developing transdiagnostic neuromodulation approaches for anhedonia.

Disclosures SHS is a scientific consultant for Magnus Medical. SHS and MDF have jointly received investigator-initiated funding from Neuronetics Inc. SHS and MDF own independent intellectual property involving the use of brain connectivity to target TMS. None of these entities were directly involved in the present work.

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