Michael S. Ritsner *Editor*

Anhedonia: A Comprehensive Handbook Volume II

Neuropsychiatric And Physical Disorders

Springer

Anhedonia: A Comprehensive Handbook
Volume II

Michael S. Ritsner
Editor

Anhedonia: A Comprehensive Handbook Volume II

Neuropsychiatric And Physical Disorders

Springer

Editor
Michael S. Ritsner
Israel Institute of Technology
Haifa and Sha'ar Menashe Mental
Health Center
Israel

ISBN 978-94-017-8609-6 ISBN 978-94-017-8610-2 (eBook)
DOI 10.1007/978-94-017-8610-2
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2014932424

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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

About the Editor

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

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

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

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

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

1. Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders. New Perspectives on Research and Treatment. Ritsner, *Michael S.; Awad, A. George* (Eds.), Springer, Dordrecht. The Netherlands, 2007, 388 p.
2. Neuroactive Steroids in Brain Functions, and Mental Health. Novel Strategies for Research and Treatment. *Ritsner, Michael S.; Weizman A.* (Eds.), Springer Science + Business Media, B.V., 2008. 559 p.
3. The Handbook of Neuropsychiatric Biomarkers, Endophenotypes, and Genes. Volumes I–IV. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V., 2009.
   - *Volume I: Neuropsychological Endophenotypes and Biomarkers. 231 pp.*
   - *Volume II: Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers. 244 pp.*
   - *Volume III: Metabolic and Peripheral Biomarkers. 231 pp.*
   - *Volume IV: Molecular Genetic and Genomic Markers. 232 pp.*
4. Brain Protection in Schizophrenia, Mood and Cognitive Disorders. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2010. 663 p.
5. Handbook of Schizophrenia Spectrum Disorders. Volumes I–III. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2011.
   - *Volume I: Conceptual Issues and Neurobiological Advances. 494 pp.*
   - *Volume II: Phenotypic and Endophenotypic Presentations. 526 pp.*
   - *Volume III: Therapeutic Approaches, Comorbidity, and Outcomes. 461 pp.*
6. Polypharmacy in Psychiatric Practice. Volumes I–II. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2013.
   - *Volume I: Multiple Medication Use Strategies. 287 pp.*
   - *Volume II: Use of Polypharmacy in the "Real World". 321 pp.*
7. Anhedonia: A Comprehensive Handbook. *Ritsner, Michael S.* (Ed.), Springer Science + Business Media, B.V. 2014.
   - *Volume I: Conceptual Issues and Neurobiological Advances.*
   - *Volume II: Neuropsychiatric and Physical Disorders.*

Dr. Ritsner served as Associate Editor, Quality of Life Research (An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, Amsterdam, The Netherlands); Board Member, American Journal of Neuroprotection and Neuroregeneration (USA); CNS & Neurological Disorders-Drug Targets (Italy); member of the Scientific Committee, International Society for the Study of Neuroprotection and Neuroplasticity (Romania). Referee activity: CNS Drugs, Quality of Life Research, Psychiatry Research, Clinical Drug Investigation, Social Psychiatry and Psychiatric Epidemiology, Biological Psychiatry, etc.

Click here for PubMed: http://www.ncbi.nlm.nih.gov/pubmed/?term=ritsner

Preface

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

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

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

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

Haifa
January, 2014

Michael S. Ritsner
Editor

Contents

Contributors

Francesca Assogna Neuropsychiatry Laboratory, I.R.C.C.S. Santa Lucia Foundation, Rome, Italy

Neus Barrantes-Vidal University of North Carolina at Greensboro, Greensboro, NC, USA

Universitat Autònoma de Barcelona, Barcelona, Spain

Sant Pere Claver – Fundació Sanitària, Barcelona, Spain

Instituto de Salud Carlos III, CIBERSAM, Madrid, Spain

Placido Bramanti IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

Benjamin Buck Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Rocco Salvatore Calabrò IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

Carlo Caltagirone Department of Neuroscience, University "Tor Vergata", Rome, Italy

Department of Clinical and Behavioral Neurology, I.R.C.C.S. Santa Lucia Foundation, Rome, Italy

Raymond C.K. Chan Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Beijing, China

Eric F.C. Cheung Castle Peak Hospital, Hong Kong Special Administrative Region, China

Charlotte A. Chun University of North Carolina at Greensboro, Greensboro, NC, USA

Wendy D'Andrea Psychology (Clinical), The New School for Social Research, NY, New York

Jonathan M. DePierro Psychology (Clinical), The New School for Social Research, NY, New York

Anna R. Docherty Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, USA

Eduardo Fonseca-Pedrero Departamento de Ciencias de la Educación, University of La Rioja, Logroño, La Rioja, Spain

Paul Frewen Department of Psychiatry, The University of Western Ontario, London, ON, Canada

Department of Psychology, The University of Western Ontario, London, ON, Canada

Diane C. Gooding Departments of Psychology and Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

Georgina M. Gross University of North Carolina at Greensboro, Greensboro, NC, USA

Charlotte Keating Brain and Psychological Sciences Research Centre (BPsyC), Swinburne University of Technology, Melbourne, Australia

Monash Alfred Psychiatry Research Centre, Melbourne, Australia

Thomas R. Kwapil University of North Carolina at Greensboro, Greensboro, NC, USA

Albert F.G. Leentjens Department of Psychiatry, Maastricht University Medical Centre, Maastricht, The Netherlands

Serafín Lemos-Giráldez Department of Psychology, University of Oviedo, Oviedo, Spain

Center for Biomedical Research in the Mental Health Network, Madrid, Spain

Gwenolé Loas University Department of Psychiatry, Hôpital Erasme and ULB, Bruxelles, Belgium

Simon S.Y. Lui Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Beijing, China

Castle Peak Hospital, Hong Kong Special Administrative Region, China

Paul H. Lysaker Roudebush VA Medical Center, Indianapolis, IN, USA

Department of Psychiatry, Indiana University Medical School, Indianapolis, IN, USA

Ciara McCabe School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK

Marco Mula Division of Neurology Trinity Hospital, Borgomanero, Italy

José Muñiz Department of Psychology, University of Oviedo, Oviedo, Spain

Center for Biomedical Research in the Mental Health Network, Madrid, Spain

Mercedes Paino Department of Psychology, University of Oviedo, Oviedo, Spain

Center for Biomedical Research in the Mental Health Network, Madrid, Spain

Michael S. Ritsner Department of Psychiatry, Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, and Sha'ar Menashe Mental Health Center, Hadera, Israel

Susan L. Rossell Brain and Psychological Sciences Research Centre (BPsyC), Swinburne University of Technology, Melbourne, Australia

Monash Alfred Psychiatry Research Centre, Melbourne, Australia

Paul J. Silvia University of North Carolina at Greensboro, Greensboro, NC, USA

Letteria Spadaro IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

Gianfranco Spalletta Neuropsychiatry Laboratory, I.R.C.C.S. Santa Lucia Foundation, Rome, Italy

Scott R. Sponheim Mental and Behavioral Health, Minneapolis VA Medical Center, Departments of Psychiatry & Psychology, University of Minnesota, Minneapolis, MN, USA

Gregory P. Strauss Department of Psychology, State University of New York at Binghamton, Binghamton, NY, USA

Yi Wang Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Beijing, China

Chao Yan Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Beijing, China

Qi-feng Yin Department of Psychology, Renmin University of China, Beijing, China

Part I
Anhedonia in Psychotic Disorders

Chapter 1
Anhedonia in Schizophrenia: A Brief History and Overview of the Construct

Benjamin Buck and Paul H. Lysaker

Abstract Though studied for decades in relation to mood disorders, anhedonia has only more recently become widely discussed in relation to schizophrenia, despite being described in the earliest writings describing the phenomenon. In addition to being a self-evident detriment to quality of life, anhedonia is a predictor of a number of negative outcomes, including poor quality of life, social dysfunction and psychosis vulnerability. Recent research has generated many questions about the nature and course of anhedonia in schizophrenia, including questions about its elements and place within the larger picture of the psychopathology of schizophrenia. In the present chapter, we review two distinction between subtypes of anhedonia in schizophrenia: the social/physical distinction, as well as the anticipatory/consummatory distinction. We then review literature on the affective, cognitive and interpersonal components of anhedonia, and explore the possibility that there are two forms of anhedonia; one which is primarily a negative and associated with deficits in metacognition and one which is secondary to depressive symptoms. Finally, we discuss directions for future research.

Keywords Anhedonia • Depression • Schizophrenia • Negative symptoms • Metacognition • Social functioning

B. Buck (✉)
Department of Psychology, University of North Carolina at Chapel Hill,
CB #3270, Davie Hall, Chapel Hill, NC 27599, USA
e-mail: buck@unc.edu; buckbe@gmail.com

P.H. Lysaker, Ph.D.
Roudebush VA Medical Center, Indianapolis, IN, USA

Department of Psychiatry, Indiana University Medical School, Indianapolis, IN, USA
e-mail: plysaker@iupui.edu

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_1,

Abbreviations

BPRS	Brief Psychiatric Rating Scale
CAINS	Clinical Assessment Interview for Negative Symptoms
CPPS	Chapman Psychosis Proneness Scales
MAS-A	Metacognitive Assessment Scale Abbreviated
SANS	Scale for the Assessment of Negative Symptoms

1.1 Introduction

Anhedonia refers to the diminished ability to experience pleasure as a result of sensory experiences or social interactions [1]. While anhedonia has been well described as a integral symptom in major depression and other mood disorders for decades [2, 3], its presentation and course in schizophrenia has become an issue of research interest and scholarly debate more recently [4]. Despite the more recent interest, it has been a concern as a core feature of schizophrenia since the earliest writings of Bleuler [5] and Kraepelin [6]. In the latter half of the twentieth century, Paul Meehl [7] built on the writings of Rado and others [8], describing anhedonia in schizophrenia as "a marked, widespread, and refractory defect in pleasure capacity which, once you learn how to examine for it, is one of the most consistent and dramatic behavioral signs of the disease." (p. 829) In spite of the attention given to anhedonia by schizophrenia research, anhedonia is not included as a symptom of the illness according to DSM-IV [9], though some consider it related to some of the disorder's chronic negative symptoms [10]. The theoretical importance of anhedonia in the study of all forms of psychopathology is self-evident given a central aim of assessment and treatment of psychological phenomena is to reduce suffering and increase pleasure in one's life experiences.

To date, research on predictors of outcome in schizophrenia have offered an increasing amount of evidence that anhedonia may be a barrier to wellness and acceptable quality of life [11]. Anhedonia has been correlated with poorer social functioning [12–15], fewer social interactions [16], increased aggressive behaviors [17] and suggested as a barrier to communicating as well as receiving reinforcement from social interaction [18] resulting in social withdrawal [19]. Anhedonia may also make persons vulnerable to the development of psychosis as well [20]. Kwapil [21] has identified social anhedonia as a strong predictor of schizophrenia in the general population. Others have demonstrated that emotional disturbances are strong indicators of vulnerability to functional impairments associated with schizophrenia [22] or psychotic-like experiences [23]. This has been corroborated with potential genetic [24] and neurological mechanisms [25, 26].

While anhedonia seems to be an important predictor of recovery, models of the role anhedonia plays in the complex interplay between biological, social and

psychological processes dysfunction in have yet to emerge. Additionally, at present, it is unclear how it might be treated or addressed psychosocially. One of the barriers to creating more comprehensive models of the role of anhedonia concerns a lack of clarity regarding its components, dimensions, elements, and potential subtypes. For example, are there different forms of anhedonia? Are there different cognitive, emotional and interpersonal processes that underlie prolonged anhedonic experience? Furthermore, how should these be measured? How do the methods of measurement change the presentation of the phenomena in question?

An examination of the history and development of the conceptualization of anhedonia in schizophrenia is an important undertaking to capture and demystify this area. In this chapter, we seek to address these issues through a review of literature that will summarize some of the core issues related to the construct. Primary among these are the distinctions between physical and social anhedonia as well as the tension between anticipatory and consummatory anhedonia. These distinctions will be explored in the first two sections of the chapter. In a third section, we will explore the potential emotional, cognitive, and interpersonal components that underlie anhedonia in schizophrenia. In the fourth and final section, we will turn to the contemporary debate regarding whether anhedonia is best understood as a depressive or negative symptom of schizophrenia, or whether there may be both a depressive and non-depressive anhedonic subtype of schizophrenia.

1.2 The Physical-Social Distinction

Some of the earliest studies of anhedonia in schizophrenia distinguished lack of pleasure in physical activities such as tasting pleasurable food or smelling pleasurable odors from lack of pleasure in social exchanges. These studies used the Chapman Psychosis Proneness Scales (CPPS) [1] which include scales that assess physical [27] and social anhedonia [28]. Research using the CPPS has found social anhedonia is more closely related to negative symptoms than physical anhedonia [29–32]. Because negative symptoms are closely tied to a loosening of social connections with others, this has increased particular attention to deficits in pleasure processing in specifically social contexts. In fact, the Scale for the Assessment of Negative Symptoms (SANS) [33] collapses the distinction between anhedonia and asociality altogether, noting the two as closely related. Herbener and Harrow [34] note that anhedonia as assessed by the SANS [33] rates the "loss of interest in pleasurable activities, an inability to experience pleasure when participating in activities normally considered pleasurable, or a lack of involvement in social relationships of various kinds." (p. 237) Importantly, anhedonia is defined as a loss of previous level of attained pleasure, and focuses specifically on pleasure derived from social activities.

Blanchard, Horan and Brown [35] reported that social anhedonia persisted across 12-months in the schizophrenia sample while it did not in a depressed sample. They interpreted this as indicating that social anhedonia is a stable feature of schizophrenia. Non-diagnosed individuals who evidence elevations on social anhedonia scales show fewer affiliative behaviors and poorer social skills, as well as a self-reported attenuated experience of positive affect, and less willingness to engage in future social interactions compared to controls [36]. Social anhedonia has been demonstrated to be a unique predictor of aggressive behaviors among non-clinical controls [17]. Kwapil and colleagues [16] found that social anhedonia increases the likelihood an individual will prefer to and indeed spend time alone. Tully, Lincoln and Hooker [15] reported that social anhedonia has significant relationships with social functioning, as well as executive control of emotions. Ritsner and colleagues [11] found that social anhedonia was related to quality of life outcomes related to social relationships, life satisfaction and leisure time activities, though these relationships were attenuated compared to relationships with physical anhedonia.

Unlike social anhedonia, the presence of physical anhedonia does not require a comparison to prior levels of functioning [34]. Chapman, Chapman and Raulin's [1] original work on physical anhedonia showed that the construct had negligible correlations with demographic and clinical variables but was related to premorbid functioning. Schuck and colleagues [37] failed to find a unique link with of anhedonia and schizophrenia, however, and reported no differences in severity of physical anhedonia between participants with schizophrenia and affective disordered and non-clinical controls. They concluded instead that anhedonia is not a stable trait of schizophrenia but rather the consequence of some of the other factors associated with the illness like education level and poor premorbid status. Herbener and Harrow [34] have demonstrated that assessments of physical anhedonia were stable in a 10 year longitudinal study, and that they did not correlate with positive, negative or depressive symptoms. Loas and colleagues [38] also showed that physical anhedonia was not related to negative symptoms, but was correlated with the severity of disorganization symptoms. Ritsner and colleagues [11] found physical anhedonia was significantly correlated with a range of quality of life and functioning outcomes including physical health, leisure time activities, social relationships, general activities, and life satisfaction, and that these relationships were stronger than those of social anhedonia with each outcome variable. These relationships persisted while accounting for the influence of antipsychotic side effects as well as other symptoms of schizophrenia.

Ultimately, it seems that distinguishing physical from social anhedonia has helped researchers differentiate between individuals who fail to experience pleasure in relation to sensual experiences from those who fail to receive it from social interactions. It is unclear, however, whether these forms of anhedonia have fundamentally different roots. Is, for instance, social anhedonia the result of cognitive deficits, a specific organic deficit or a common neurobiological pathway [39]? Are there kinds of deficits for instance in metacognition and social cognition that are more specific to social anhedonia?

It is important to note as well that there are measurement issues. Factor analytic studies of the Chapman Social Anhedonia scale have been inconsistent [40]. Significant psychometric limitations have been noted including doublets, modest relationships between items, many items that showed little to no relationship with any overall factor, as well as cross-loadings in bi-factor solutions. While people with schizophrenia demonstrate elevations on measures of both forms of anhedonia, Blanchard, Bellack and Mueser [30] found that higher levels of social anhedonia were not related to hedonic ratings in response to an emotion-eliciting video, though they did predict performance overall on a social skills role play.

1.3 The Anticipatory-Consummatory Distinction

A second kind of distinction that has been made regarding different forms of anhedonia concerns the experience of pleasure in the moment (consummatory anhedonia) and the expectation that future experiences will be pleasurable (anticipatory anhedonia). This distinction was in part a response to findings that people with schizophrenia score highly on interview-rated measures of anhedonia and report lower levels of trait-like positive experience compared to controls [41–43], as well as reporting a similar amount of pleasant emotion in response to evocative stimuli in the moment [29, 44, 45]. This finding is referred to broadly as "the emotion paradox," and has been replicated using different methodologies, including experience sampling [46]. Aghevli and colleagues [47] reported that while people with schizophrenia rate their experience similarly to controls in role-plays, they are significantly less emotionally expressive during those interactions.

One potential solution to the emotion paradox is the division of anhedonia into its anticipatory and consummatory components. Klein [48] first divided anhedonia in this way and defined anticipatory pleasure as the motivated behavior and desire for a future stimulus, and consummatory pleasure as the positive emotional experience associated with satiation. The temporal model which combines anticipatory and consummatory pleasure argues that first, expectation of reward generates approach motivation and goal-directed behavior toward the rewarding stimulus [49]. Second, the expectation of the stimulus generates a positive emotion in itself, termed appetitive pleasure. Kring and Caponigro [50] add that consummatory pleasure when encoded in memory may trigger the anticipation of pleasure which then leads to future attempts to re-experience that pleasure.

Gard and colleagues [51] were among the first to apply this distinction in a schizophrenia population. Using a new measure called the Temporal Experience of Pleasure Scale (TEPS) [51], they have shown self-reported deficits in anticipatory but not consummatory pleasure among individuals with schizophrenia. These anticipatory deficits have been associated with behavioral activation, reward responsiveness, drive, negative symptoms, and family and role functioning [51]. The consummatory pleasure subscale of the TEPS has shown to correlate consistently only with physical anhedonia. Replicating this, Chan and colleagues [52] found that patients scoring highly on

negative symptom scales had greater levels of anticipatory anhedonia, and Favrod and colleagues [53] found a similar pattern using a French language version of the TEPS. Strauss and colleagues [54], on the other hand, found differences between participants with schizophrenia and controls only on measures of consummatory – and not anticipatory – anhedonia. Others have shown that there may be more deficits in anticipatory pleasure in cases of Kraepelinian compared to non-Kraepelinian schizophrenia [55]. Buck and Lysaker [56] showed that the anticipatory scale of the TEPS is more stable than the consummatory scale over 6 months, and also that it prospectively predicts emotional discomfort.

This pattern of results suggests that emotional disturbance in schizophrenia may present as a primary disruption of anticipatory pleasure mechanisms, while consummatory pleasure often remains intact. This would explain why persons experience pleasure in the moment but not expect it in the future. If this anticipatory component is the driving force in anhedonia and related deficits in schizophrenia, this could provide targets for specific remedial intervention, as has been proposed by Favrod and colleagues [53].

1.4 Cognitive, Emotional, and Interpersonal Components of Anhedonic Experience

In contrast to approaches that seek out different forms of anhedonia, other researchers have focused on the different cognitive, affective and interpersonal processes that culminate in a presentation of anhedonia. With the initial aim of addressing the state-trait emotion paradox in the assessment of anhedonia, Cohen and colleagues [57] suggested that anhedonia may involve three components in addition to the aforementioned social-specific deficits and deficits in anticipatory pleasure: (1) affective regulation deficits, (2) encoding-retrieval deficits, and (3) representational deficits.

First, regarding emotional processes that may contribute to anhedonia, one possibility is that anhedonia may be the result of a lessened ability to enhance pleasant emotions while regulating and tolerating negative emotional states (i.e. global affective regulation deficit) [58, 59]. For instance, an inability to manage painful emotions results in an absence of positive emotions and a reduced inclination to approach reinforcing positive stimuli. This is consistent with other findings demonstrating elevations in negative affect regardless of emotional stimuli. Strauss and Gold [60] also point out that people with schizophrenia report higher levels of negative emotions when exposed to unpleasant, neutral and pleasant stimuli compared to controls. This model is bolstered by the findings that when reporting current feelings, people with schizophrenia respond with increased aversive emotion regardless of type of stimuli [45].

Outside of difficulties regulating emotions, another possibility is that anhedonia emerges in schizophrenia as a result of impairments in the cognitive processes that enable encoding and retrieval of positive memories. In other words, a lack of pleasure may ensue when no context for the potentially pleasurable event occurs. People with

schizophrenia have demonstrated memory deficits related to autobiographical events [61]. It is possible that failing to recall context of a pleasurable event reduces persons motivation to seek that event in the future. One difficulty with this model is that rather than participants responding randomly, as one might assume someone with impaired memory might, people with schizophrenia tend to respond with a negative bias toward stimuli [45]. Also contradicting this, many of the self-report measures related to emotion demonstrate somewhat high test-retest reliability values, and therefore are unlikely to be responded to randomly. However, it might be the case that when lacking adequate information to respond to self-report questions, individuals with schizophrenia could respond with a negativistic bias, particularly in light of some of the other negativistic biases in schizophrenia, including attention toward threatening information [62, 63], and externalized and personalized bias for negative events [64].

Gold and colleagues [65] have proposed another cognitive mechanism underlying anhedonia. They suggest that the problem may not be in the processing or memory of the initial stimuli but instead in a disturbance in the pairing of the representation of the stimulus and a specific emotional valence leading to a reduction in the likelihood of approaching rewarding stimuli. For instance, if someone were unable to create a complex representation of oneself then it might be difficult to find more complex meaning in social interactions. Evidence supporting this view comes from one study in which in response to positive, negative and neutral stimuli, patients and controls gave similar subjective ratings of the stimuli, but significantly differed in behavioral responses which allowed them to choose whether they wanted to see it again. The correlation between behavioral change and subjective reactions was significantly higher in the control group than it was in the patient group [66]. More support for this possibility come from findings that people with schizophrenia have difficulty in tasks that require participants to keep an abstract representation of a stimulus and its reward, and to change behavior accordingly [67]. Assessments of a construct related to the ability to form complex representations of self and others, synthetic metacognition [68] has also been found to prospectively predict levels of negative symptoms [69].

Reflecting on the wide use of self-report measures to assess anhedonia, Strauss and Gold [60] conclude that the discrepant findings between current and non-current emotion assessments ought be no surprise given consistent findings that assessments of non-current and current emotions differ for control subjects [70, 71]. Strauss and Gold [60] review different assessments of non-current feelings and their associated findings, including retrospective self-report, hypothetical self-report, trait self-report, and prospective self-report. All of these assessments require individuals to reflect on or hypothesize about noncurrent feelings. When assessed in this way, individuals with schizophrenia consistently report less prospective *and* retrospective pleasure on overall trait assessments, indicating anhedonia may not be solely linked to motivational or anticipatory mechanisms.

Strauss and Gold [60] attribute this to either an underestimation of non-current positive emotions or a lack of an overestimation bias. Building on this model, they also point out that while current emotion assessments have no significant relationship

with cognitive variables, individuals with impaired working memory show lower levels of pleasure on hypothetical reports. This could indicate that anticipatory anhedonia is heavily influenced by or comprised of certain kinds of beliefs about pleasure [60, 72]. Others have noted the tendency to confuse negative emotion with affective blunting [73]. This possibility is consistent with recent findings that anticipatory pleasure deficits showed a predictive relationship only with negative mood symptoms, but not with negative symptoms [56].

Robinson and Clore [72] suggest that the report on non-current anhedonic feelings is rooted in four different sources of information: (1) experiential knowledge, (2) episodic memory, (3) situation-specific beliefs, and (4) identity-related beliefs. Based on the nature of the emotion assessment, individuals may make specific patterned errors because of differences between these sources of information. General populations have demonstrated a tendency to overestimate the impact of future events on emotions or "affective forecasting" [74]. Prospective and retrospective judgments involve use of semantic identity and situation-specific information (e.g. "I have great memories of vacations," "Going out with friends is lots of fun") that flows from individuals' beliefs that experiences are generally positive and that pleasure is attainable in the world. It has been shown in both patient and control groups that in-the-moment emotion assessments and non-current emotion assessments do not significantly correlate with one another [54, 60, 66].

Whether it be rooted in cognitive biases and attributions related to the attainability of pleasure in the world or cognitive impairment, one implication of this work is that anhedonia is not as much an "experiential deficit" but rather "a set of beliefs related to low pleasure that surface when one reports on noncurrent feelings" that also implicates both behavioral changes and elevations of negative emotions [60] (p. 372). Strauss [75] concludes that "recent research suggests that there is no diminished capacity for pleasure in schizophrenia" but rather that "self-reports typically interpreted as anhedonia reflect abnormal psychological processes, such as low-pleasure beliefs and reduced overestimation of past and future pleasure, as well as dysfunctional behavioral processes such as reduced pleasure-seeking behavior." (p. 249)

A final possible component of anhedonia that has received less attention is the ways in which it impacts interpersonal processes. The regulation of emotion and the production of autobiographic memory generally occur in regular life in the midst of interpersonal exchanges. It is possible that with weakened or atrophied social connection, persons with schizophrenia lose persons to share pleasure with. For instance, any number of achievements in life are pleasurable because there are people to share them with. It is thus possible that some of the previous correlations noted between anhedonia and social connection [36] reflect the effects of social distance on hedonic experience, and not only the other way around.

In sum, the work reviewed in this section has moved beyond looking at different forms of anhedonia experience and examined emotional, cognitive and interpersonal experiences that may influence the emergence of persistence of anhedonia. While each of these additional models require replication and development, they nonetheless provide a view of the different components which may contribute to

anhedonia in schizophrenia. It remains unclear the extent to which these different components are redundant or whether they interact or work together to produce different forms of anhedonic experience.

1.5 Is Anhedonia a Negative Symptom, a Depressive Symptom, or Something Else?

A final way researchers have sought to understand how anhedonia fits into the larger process of dysfunction in schizophrenia, has been to determine whether anhedonia is linked with some of the traditional forms of psychopathology in schizophrenia. One specific proposal has been to consider anhedonia as a negative symptom of schizophrenia, one specifically linked with reductions in the experience of emotion but not necessarily deficits in the expression of emotion [76]. Implied here is that anhedonia represents one of a series of losses of previous psychological processes not attributable to another set of symptoms. In the sense that the negative symptom asociality is the loss of interest in the world, anhedonia could reflect a loss of natural pleasure in daily life. Understanding anhedonia as a negative could allow for a more nuanced picture of how anhedonia interacts with others factors as the course of illness unfolds.

According to some theoretical accounts, anhedonia is considered a core negative symptom [76] along with asociality, avolition, blunted affect and alogia. Support for the conceptualization of anhedonia as a negative symptom can be found in work on the psychometrics of the SANS which, as noted above, found that items related to anhedonia and demonstrated high internal consistency [33]. Andreasen and colleagues [77] also found that the anhedonia item of the SANS correlated significantly with the negative symptom factor, including items for avolition and affective flattening. While some have continued to find relationships between trait anhedonia and other negative symptoms [78], others have failed to replicate this concurrently [79] and prospectively [34, 38].

Recent research has led to the development of a new assessment of anhedonia in schizophrenia, the Clinical Assessment Interview for Negative Symptoms (CAINS) [80]. Subjected to a large-scale and comprehensive psychometric validation, the CAINS was found to have a two-factor solution, including factors for both expressive and experiential negative symptoms. These two factors were moderately intercorrelated. Anhedonia was included in the experiential subscale, which also included asociality and avolition. The experience subscale had a small but significant correlation with negative symptoms as measured by the Brief Psychiatric Rating Scale (BPRS). Overall the measure demonstrated good discriminant validity, with the experience subscale showing small non-significant correlations with positive symptoms, depression and IQ. Two anhedonia items were removed from the experience subscale because of low factor loadings, including expected recreational intensity and physical expected intensity. In the final validation [81], the same factor structure was replicated, and it demonstrated test-retest reliability and rater agreement.

There were small but significant correlations between the experience subscale and both (anticipatory and consummatory) subscales of the TEPS. However, there were significant relationships with agitation and positive symptoms on the BPRS, but not with depressive symptoms.

While more factor analytic and longitudinal work with multiple methods could assist in developing a richer account of the relationship between anhedonia with negative symptoms, neglected is the possibility that anhedonia may sometimes be a primary negative symptom and other times a reflection of other psychopathological processes. One possibility pointed out by Cohen and Minor [45] is that anhedonia in some schizophrenia patients may be a reflection of depression or other forms of emotional discomfort which would presumably not be reflective of a primary negative symptoms. Empirical support for this possibility includes findings that anticipatory anhedonia is a predictor of future depressive symptoms though not necessarily negative symptoms [56]. Other research in persons without psychosis have suggested links between depression and anhedonia [31].

The point here is not to debate whether anhedonia is a primary negative or depressive symptom but to suggest that there may different kinds of anhedonic experience: somewhere loss of pleasure comes from the negative symptoms or perhaps specifically, the fragmentation of self-experience, and others where it emerges from emotional distress. This possibility, in addition to its intuitive appeal, would explain the equivocal findings described above. Support for this hypothesis can be found in a recent study by Buck et al. [82] that revealed that a group of patients with anhedonia without depression demonstrated less complex and integrated representations of themselves and other than a group with anhedonia and depression. Fragmented internalized experience was operationalized as poorer levels of synthetic metacognitive activity and measured using the Metacognitive Assessment Scale Abbreviated (MAS-A) [83]. Results were interpreted as suggesting that a subgroup of patient may exist who experience fragmented self-experience and heightened anhedonia in the absence of depression. Consistent with Gold et al. [65] one speculation is that barren self-experience is a potential cause of anhedonia among some with schizophrenia though a separate group may exist for whom anhedonia is a result of emotional distress.

1.6 Conclusion

One barrier to the understanding of the role of anhedonia in outcome in schizophrenia involves a lack of the understanding of the dimensions and components of anhedonia. To address this issue the present chapter has reviewed historical and theoretical developments regarding the understanding and assessment of anhedonia in schizophrenia. Examples of refinements which have deepened our understanding of anhedonia are the social/physical and anticipatory/consummatory anhedonia distinctions. We also examined various emotional, cognitive and interpersonal factors which likely interact and contribute to the development of anhedonia.

Furthering that discussion we finally examined the possibility that some forms of anhedonia in schizophrenia are related to impoverished self-experience.

In sum, research is needed to understand how the different domains and dimensions of anhedonia are related to one another. For instance, are cognitive factors more closely related to physical vs. social anhedonia than emotional processes? Do metacognitive disturbances predict more recalcitrant forms of anhedonia? Does heterogeneity in schizophrenia account for some of the puzzles and paradoxes in the study of emotional processing in schizophrenia? Do artifacts of measurement affect the field's understanding of the construct as a whole? Might there be separate but both clinically significant factors associated with both the report and the experience of pleasure?

Given the limitations of the literature as reviewed here, there nevertheless are some potential clinical implications that also deserve to be explored. For one, if there are distinctly different roots of anhedonia, specifically distressed mood and fragmented inner experience, then it may be that different forms of treatment should be investigated. In particular, it is possible that if fragmented internal experience leaves persons with little capacity to experience pleasure when engaging the physical or social world, they may respond to newly developing metacognitive forms of psychotherapy which target the ability to bring together elements of experience into richer representations of self and other [84–86]. Such treatments have been reported in an open trial and case studies to be linked to a range of both subjective and objective forms of recovery [87] and could potentially offer some access to a range of cognitive and emotional processes needed for interpersonal connection and the construction of the kinds of meaning needed for the experience of pleasure.

References

1. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374–82.
2. Feigner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry. 1972;26:57–63.
3. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55.
4. Wolf DH. Anhedonia in schizophrenia. Curr Psychiatry Rep. 2006;8:322–8.
5. Bleuler E. Dementia praecox or the group of schizophrenias. Oxford: International Universities Press; 1950.
6. Kraepelin E. Dementia praecox and paraphrenia. Translated by Barclay RM. Huntington, NY: Krieger; 1971(1919).
7. Meehl PE. Schizotaxia, schizotypy, schizophrenia. Am Psychol. 1962;17:827–38.
8. Rado S. Psychoanalysis of behavior. New York: Grune & Stratton; 1962.
9. American Psychiatric Association Task Force on DSM-IV, editor. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychiatric Publishing; 1994.
10. Horan WP, Blanchard JJ, Kring AM, et al. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32:259–73.
11. Ritsner MS, Arbtman M, Lisker A. Anhedonia is an important factor of health- related quality of life deficit in schizophrenia and schizoaffective disorder. J Nerv Ment Dis. 2011;199:845–53.

12. Chapman LJ, Chapman JP, Kwapil TR. Putatively psychosis-prone subjects 10 years later. J Abnorm Psychol. 1994;103:171–83.
13. Blanchard JJ, Mueser KT, Bellack AS. Anhedonia, positive and negative affect, and social functioning in schizophrenia. Schizophr Bull. 1998;24:413–24.
14. Cohen AS, Dinzeo TJ, Nienow TM, et al. Diminished emotionality and social functioning in schizophrenia. J Nerv Ment Dis. 2005;193:796–802.
15. Tully LM, Lincoln SH, Hooker CI. Impaired executive control of emotional information in social anhedonia. Psychiatry Res. 2012;197:29–35.
16. Kwapil TR, Silvia PJ, Myin-Germeys I. The social world of the socially anhedonia: exploring the daily ecology of asociality. J Res Pers. 2009;43:103–6.
17. Fanning JR, Berman ME, Guillot CE. Social anhedonia and aggressive behavior. Personal Individ Diff. 2012;53:868–73.
18. Keltner D, Kring AM. Emotion, social function, and psychopathology. Rev Gen Psychol. 1998;2:320–42.
19. Crespo-Facorro B, Paradiso S, Andreasen NC, et al. Neural mechanisms of anhedonia in schizophrenia: a PET study of response to pleasant and unpleasant odors. J Am Med Assoc. 2001;286:479–80.
20. Horan WP, Reise SP, Subotnik KL, et al. The validity of Psychosis Proneness Scales as vulnerability indicators in recent onset schizophrenia patients. Schizophr Res. 2008;100:224–36.
21. Kwapil TR. Social anhedonia as a predictor of the development of schizophrenia spectrum disorders. J Abnorm Psychol. 1998;107:558–65.
22. Erlenmeyer-Kimling L, Cornblatt BA, Rock D, et al. The New York high-risk project: anhedonia, attentional deviance, and psychopathology. Schizophr Bull. 1993;19:141–53.
23. Gooding DC, Tallent KA, Matts CW. Clinical status of at-risk individuals 5 years later: further validation of the psychometric high-risk strategy. J Abnorm Psychol. 2005;114:170–5.
24. Velthorst E, Meijer C. The association between social anhedonia, withdrawal, and psychotic symptoms in general and high-risk populations. Schizophr Res. 2012;138:290–4.
25. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry. 2010;67:902–11.
26. Harvey P, Armony J, Malla A, et al. Functional neural substrates of self reported physical anhedonia in non-clinical individuals and in patients with schizophrenia. J Psychiatr Res. 2010;44:707–16.
27. Chapman LJ, Chapman JP. Revised physical anhedonia scale. 1978. Unpublished test.
28. Eckblad M, Chapman LJ, Chapman JP, et al. Revised social anhedonia scale. 1982. Unpublished test.
29. Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. J Abnorm Pschol. 1992;101:37–44.
30. Blanchard JJ, Bellack AS, Mueser KT. Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. J Abnorm Psychol. 1994;103:719–28.
31. Loas G, Boyer P, Legrand A, et al. Anhedonia and negative symptomatology in chronic schizophrenia. Compr Psychiatry. 1996;37:5–11.
32. Loas G, Noisette C, Legrand A, et al. Is anhedonia a specific dimension in chronic schizophrenia? Schizophr Bull. 2000;26:495–506.
33. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. Arch Gen Psychiatry. 1982;39:784–8.
34. Herbener ES, Harrow M. The course of anhedonia during 10 years of schizophrenia illness. J Abnorm Psychol. 2002;111:237.
35. Blanchard JJ, Horan WP, Brown SA. Diagnostic differences in social anhedonia: a longitudinal study of schizophrenia and major depressive disorder. J Abnorm Psychol. 2001;110:363–71.
36. Llerena K, Park SG, Couture SM, et al. Social anhedonia and affiliation: examining behavior and subjective reactions within a social interaction. Psychiatry Res. 2012;200:679–86.
37. Schuck JR, Leventhal D, Rothstein H, et al. Physical anhedonia and schizophrenia. J Abnorm Psychol. 1984;93:342–4.

38. Loas G, Monestes JL, Ingelaere A, et al. Stability and relationships between trait or state anhedonia and schizophrenic symptoms in schizophrenia: a 13-year follow-up study. Psychiatry Res. 2009;66:132–40.
39. Germine LT, Garrido L, Bruce L, et al. Social anhedonia is associated with neural abnormalities during face emotion processing. Neuroimage. 2011;58:935–45.
40. Reise SP, Horan WP, Blanchard JJ. The challenges of fitting an item-response theory model to the social anhedonia scale. J Pers Assess. 2011;93:213–24.
41. Blanchard JJ, Cohen AS. The structure of negative symptoms in schizophrenia: implications for assessment. Schizophr Bull. 2006;32:238–45.
42. Horan WP, Green MF, Kring AM, et al. Does anhedonia in schizophrenia reflect faulty memory for subjectively experienced emotions? J Abnorm Psychol. 2006;115:496–508.
43. Horan WP, Blanchard JJ, Clark LA, et al. Affective traits in schizophrenia and schizotypy. Schizophr Bull. 2008;34:856–74.
44. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. Schizophr Bull. 2008;34:819–34.
45. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36:143–50.
46. Myin-Germeys I, Delespaul PA. Schizophrenia patients are more emotionally active than is assumed based on their behavior. Schizophr Bull. 2000;26:847–54.
47. Aghevli MA, Blanchard JJ, Horan WP. The expression and experience of emotion in schizophrenia: a study of social interactions. Psychiatry Res. 2003;119:261–70.
48. Klein D. Depression and anhedonia. In: Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1984. p. 1–34.
49. Depue RA, Iacono WG. Neurobehavioral aspects of affective disorders. Annu Rev Psychol. 1989;40:457–92.
50. Kring AM, Caponigro JM. Emotion in schizophrenia: where feeling meets thinking. Curr Dir Psychol Sci. 2010;19:255–9.
51. Gard D, Gard M, Kring AM, et al. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.
52. Chan RCK, Wang Y, Huang J, et al. Anticipatory and consummatory components of the experience of pleasure in schizophrenia: cross cultural validation and extension. Psychiatry Res. 2010;175:181–3.
53. Favrod J, Ernst F, Guiliuana C, et al. Validation of the Temporal Experience of Pleasure Scale (TEPS) in a French-speaking environment. Encéphale. 2009;35:241–8.
54. Strauss GP, Wilbur RC, Warren KR, et al. Anticipatory vs. consummatory pleasure: what is the nature of hedonic deficits in schizophrenia? Psychiatry Res. 2011;187:36–41.
55. Fertout E, Scoury D, Lefebvre O, et al. Anhedonia in Kraepelinian schizophrenia. Psychol Rep. 2012;111:755–60.
56. Buck B, Lysaker PH. Consummatory and anticipatory anhedonia in schizophrenia: stability, and associations with emotional distress and social function over six months. Psychiatry Res. 2013;205:30–5.
57. Cohen AS, Najolia GM, Brown LA, et al. The state-trait disjunction of anhedonia in schizophrenia: potential affective, cognitive and social-based mechanisms. Clin Psychol Rev. 2011;31:440–8.
58. Gross JJ. The emerging field of emotion regulation: an integrative review. Rev Gen Psychol. 1998;2:271–99.
59. Westen D, Muderrisoglu S, Fowler C, et al. Affect regulation and affective experience: individual differences, group differences and measurement using a Q-sort procedure. J Consult Clin Psychol. 1997;65:429–39.
60. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169:364–73.
61. Neumann A, Blairy S, Lecompte D, et al. Specificity deficit in the recollection of emotional memories in schizophrenia. Conscious Cogn. 2007;16:469–84.

62. Green MJ, Williams LM, Davidson D. Visual scanpaths to threat related faces in deluded schizophrenia. Psychiatry Res. 2003;119:271–85.
63. Phillips ML, Senior C, David AS. Perception of threat in schizophrenics with persecutory delusions: an investigation using visual scan paths. Psychol Med. 2000;30:157–67.
64. Aakre JM, Seghers JP, St-Hilaire A. Attributional style in delusional patients: a comparison of remitted paranoid, remitted nonparanoid, and current paranoid patients with nonpsychiatric controls. Schizophr Bull. 2009;35:994–1002.
65. Gold JM, Waltz JA, Prentice KJ, et al. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull. 2008;34:835–47.
66. Heerey EA, Gold JM. Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. J Abnorm Psychol. 2007;116:268–78.
67. Prentice KJ, Gold JM, Buchanan RW. The Wisconsin Card Sorting impairment in schizophrenia is evident in the first four trials. Schizophr Res. 2008;106:81–7.
68. Lysaker PH, Vohs JL, Ballard R, et al. Metacognition, self-reflection and recovery in schizophrenia. Future Neurol. 2013;8:103–15.
69. Hamm JA, Renard SB, Fogley F, et al. Metacognition and social cognition in schizophrenia: stability and relationship to concurrent and prospective symptom assessments. J Clin Psychol. 2012;68:1303–12.
70. Norris CJ, Larsen JT, Crawford E, Cacioppo JT. Better (or worse) for some than others: individual differences in the positivity offset and negativity bias. J Res Pers. 2011;45:100–11.
71. Ito T, Cacioppo JT. Variations on a human universal: individual differences in positivity offset and negativity bias. Cogn Emot. 2005;19:1–26.
72. Robinson MD, Clore GL. Belief and feeling: evidence for an accessibility model of emotional self-report. Psychol Bull. 2002;128:934–60.
73. Romney DM, Candido CL. Anhedonia in depression and schizophrenia: a reexamination. J Nerv Ment Dis. 2001;189:735–40.
74. Wilson TD, Gilbert DT. Affective forecasting. Adv Exp Soc Psychol. 2003;35:345–411.
75. Strauss GP. The emotion paradox of anhedonia in schizophrenia: or is it? Schizophr Bull. 2013;39:247–50.
76. Kirkpatrick B, Fenton WS, Carpenter WT. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006;32:214–9.
77. Andreasen NC, Arndt S, Alliger R. Symptoms of schizophrenia: methods, meanings, and mechanisms. Arch Gen Psychiatry. 1995;52:341–51.
78. Horan WP, Kring AM, Gur RE, et al. Development and psychometric validation of Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr Res. 2011;132:140–5.
79. Ritsner MS. Anhedonia of patients with schizophrenia and schizoaffective disorder is attributed to personality-related factors rather than to state-dependent clinical. Clin Schizophr Relat Psychoses. 2013;1:1–32.
80. Forbes C, Blanchard JJ, Bennett M, et al. Initial development and preliminary validation of a new negative symptom measure: the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr Res. 2010;124:36–42.
81. Kring AM, Gur RE, Blanchard JJ, et al. The Clinical Assessment Interview For Negative Symptoms (CAINS): final development and validation. Am J Psychiatry. 2013;170:165–72.
82. Buck KD, Hamish McLeod H, Gumley A, et al. Anhedonia and depression in schizophrenia: comparisons of levels of deficits in metacognition across three profiles. (Submitted).
83. Lysaker PH, Carcione A, Dimaggio G, et al. Metacognition amidst narratives of self and illness in schizophrenia: associations with neurocognition, symptoms, insight and quality of life. Acta Psychiatr Scand. 2005;112:64–71.
84. Lysaker PH, Buck KD, Fogley R, et al. The mutual development of intersubjectivity and metacognitive capacity in the psychotherapy for persons with schizophrenia with severe paranoid delusions. J Contemp Psychother. 2013;43:63–72.
85. Lysaker PH, Buck KD, Carcione A, et al. Addressing metacognitive capacity for self-reflection in the psychotherapy for schizophrenia: a conceptual model of the key tasks and processes. Psychol Psychother. 2011;84:58–69.

86. Salvatore G, Lysaker PH, Gumley A, et al. Out of illness experience: metacognition-oriented therapy for promoting self-awareness in individuals with psychosis. Am J Psychother. 2012;66:85–106.
87. Bargenquast R, Schweitzer RD. Enhancing sense of recovery and self reflectivity in people with schizophrenia: a pilot study of metacognitive narrative psychotherapy. Psychol Psychother. In press.

Chapter 2
Measuring Anhedonia in Schizophrenia-Spectrum Disorders: A Selective Update

Eduardo Fonseca-Pedrero, Diane C. Gooding, Mercedes Paino, Serafín Lemos-Giráldez, and José Muñiz

Abstract The main objective of this chapter was to carry out a selective review of the main measuring instruments used for the assessment of anhedonia and hedonic capacity. First, we briefly discuss the historical origins of the concept of anhedonia. Given that one's conceptualization of a given latent construct guides the development and/or selection of measurement instruments, we consider various conceptualizations and operational definitions of anhedonia and hedonic capacity. While doing this, we briefly discuss the hypothesized special relationship that is thought to exist between anhedonia and schizotypy, the latent construct underlying a diathesis for schizophrenia-spectrum disorders. Following this, we present some clinical interviews and self-report instruments used in the assessment of anhedonia. Some of the instruments are stand-alone measures of anhedonia and/or hedonic capacity (as an indirect measure of anhedonia), while other assays of anhedonia are obtained within the context of a more general assessment of negative symptoms. We have chosen to focus only on those interviews and self-report measures that are either new or of special relevance to research and clinical assessment of schizotypy, schizophrenia,

E. Fonseca-Pedrero, Ph.D. (✉)
Departamento de Ciencias de la Educación, University of La Rioja, Logroño, La Rioja, Spain
e-mail: eduardofonsecapedrero@gmail.com

D.C. Gooding
Departments of Psychology and Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

M. Paino • S. Lemos-Giráldez • J. Muñiz
Department of Psychology, University of Oviedo, Oviedo, Spain

Center for Biomedical Research in the Mental Health Network, Madrid, Spain

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_2,

and schizophrenia-spectrum disorders. For each of the measures reviewed, the main psychometric properties are described. Finally, some limitations are discussed and suggestions for future research directions are offered.

Keywords Anhedonia • Negative symptoms • Schizotypy • Assessment • Clinical interviewing • Self-report • Questionnaires

Abbreviations

ACIPS	Anticipatory and Consummatory Interpersonal Pleasure Scale
BIS/BAS	Behavioral Inhibition and Behavioral Activation Scales
BNSS	Brief Negative Symptom Scale
BPRS	Brief Psychiatric Rating Scale
CAINS	Clinical Assessment Interview for Negative Symptoms
CAPE-42	Community Assessment Psychic Experiences-42
CAT	Computerized Adaptive Testing
CTT	Classical Test Theory
ESQUIZO-Q	Oviedo Questionnaire for Schizotypy Assessment
ICC	Intra-Class Correlation
IRT	Item Response Theory
MAP-SR	Motivation and Pleasure Scale-Self-report
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MMPI	Minnesota Multiphasic Personality Inventory
NIMH	National Institute of Mental Health
O-LIFE (B)	Oxford-Liverpool Inventory of Feeling and Experiences (Brief)
PANSS	Positive and Negative Syndrome Scale
PAS	revised Physical Anhedonia Scale
PAS-B	revised Physical Anhedonia Scale-Brief
RDoC	Research Domain Criteria
RSAS	revised Social Anhedonia Scale
RSAS-B	revised Social Anhedonia Scale-Brief
SANS	Scale for Assessment of Negative Symptoms
SD	Standard Deviation
SOPS	Scale of Prodromal Symptoms
SPQ-B	Schizotypal Personality Questionnaire-Brief
SPQ-BR	Schizotypal Personality Questionnaire-Brief Revised
TEPS	Temporal Experience of Pleasure Scale
TEPS-ANT	Anticipatory subscale of the TEPS
TEPS-CON	Consummatory subscale of the TEPS
TPSQ	Thinking and Perceptual Style Questionnaire
VMPFC	Ventromedial Prefrontal Cortex
WCST	Wisconsin Card Sorting Test

2.1 Introduction

Schizophrenia is a serious and devastating mental disorder characterized by symptoms such as hallucinatory experiences, delusional ideation, negative symptoms, and disorganized speech and behavior, which usually has its onset during late adolescence or early adulthood [1–3]. Epidemiological data indicates that the median lifetime prevalence estimated for schizophrenia is 4.0 per 1,000 persons [4]. Schizophrenia and schizophrenia-spectrum disorders have a direct impact on the lives of individuals at the personal, educational, family and occupational levels. In fact, psychotic symptoms do not only have immense repercussions on the health and quality of life of patients, but also on health care costs and society [5, 6]. For example, patients with schizophrenia die approximately 12–15 years earlier than the average individual in the general population [7]. The main reason for this mortality increase, in addition to suicide, is related to physical causes and the increase in the frequency of risk factors such as the lack of physical activity, obesity, diabetes, and tobacco addiction [7–9].

Despite considerable advances in the management and treatment of schizophrenia and schizophrenia-spectrum disorders, negative symptoms have remained largely treatment-refractory. Indeed, for many individuals affected by schizophrenia, the negative symptoms, namely, restricted affect, emotional expression, poverty of speech, anhedonia, asociality and diminished motivation and sense of purpose, appear to be the rate-limiting steps in terms of quality of life and their achieving optimal functional outcomes (e.g., integration into the community and workplace). As such these negative symptoms have emerged as a treatment target in their own right, distinct from positive symptoms. Recently, anhedonia has been identified as an important factor that contributes to the health-related quality-of-life deficit observed in individuals with schizophrenia and schizoaffective disorder [10]. Anhedonia is the focus of considerable clinical research, though to date, there have not been any pharmacological and/or psychosocial breakthroughs.

The main objective of this chapter was to carry out a selective review of the main measuring instruments used for the assessment of anhedonia and hedonic capacity. This chapter deals with the assessment of anhedonia and hedonic capacity in individuals at risk for and/or affected by schizophrenia and schizophrenia spectrum disorders. First, we briefly discuss the historical origins of the concept of anhedonia. Given that one's conceptualization of a given latent construct guides the development and/or selection of measurement instruments, we consider various conceptualizations and operational definitions of anhedonia and hedonic capacity. While doing this, we briefly discuss the hypothesized special relationship that is thought to exist between anhedonia and schizotypy, the latent construct underlying a diathesis for schizophrenia-spectrum disorders [11]. Following this, we present some clinical interviews and self-report instruments used in the assessment of anhedonia. Some of the instruments are stand-alone measures of anhedonia and/or hedonic capacity (as an indirect measure of anhedonia), while other assays of anhedonia are obtained within the context of a more general assessment of negative symptoms. We have chosen to focus only on those interviews and self-report measures that are either

new or of special relevance to research and clinical assessment of schizotypy, schizophrenia, and schizophrenia-spectrum disorders. For each of the measures reviewed, the main psychometric properties are described. Finally, some limitations are discussed and suggestions for future research directions are offered.

2.2 The Construct of Anhedonia

2.2.1 The Origins of the Construct

The origins of the term "anhedonia" can be traced back to Ribot, a psychoanalytic psychologist [12, 13]. However, most clinicians associate the term with the writings of Rado [14, 15] and Meehl [11]. The literal translation of the word "anhedonia" is "without pleasure". However, because few people truly experience a complete lack of pleasure across all contexts, the term is typically used to denote a diminution or reduction in the capacity to experience pleasure. Interestingly, there seems to be a discrepancy in the way that some (predominantly depression) researchers operationally define anhedonia compared to other (predominantly schizophrenia) researchers. Some define anhedonia as a "decrease in the capacity to experience pleasure *from previously pleasurable activities*" (p. 123) [13]; there is an inherent state-like quality in that conceptualization. In keeping with Meehl [16], however many schizophrenia researchers regard schizotypy as a diminished ability to derive pleasure from typically pleasurable sources/stimuli. Note that the latter conceptualization does not assume that the individual ever found these stimuli pleasurable or had experience with them. These subtle distinctions in the operational definitions of anhedonia are noteworthy, in part because one's assessment of a construct is guided by one's conceptualization of the construct.

2.2.2 Operational Definitions of Anhedonia

Pleasure is, by definition, a multi-faceted trait, characterized by positive affect, anticipation of an experience that will evoke pleasure, recall of past satisfying experience, and willingness/motivation to increasingly exert effort to achieve such an experience in the future [17]. Anhedonia, the reduced capacity to experience pleasure, may be described in terms of the hedonic domains that are affected, such as the physical domain versus the social domain. Thus, we talk about the characteristics of individuals who experience physical anhedonia and those who experience social anhedonia.

The dimininuition of pleasurable experience may also be described in terms of the chronology of the affective experience. Animal, clinical, and affective neuroscience research suggest that approach-related, appetitive pleasure is distinct from consummatory pleasure [18]. Anticipatory pleasure states are more closely related

to the experience of "wanting", whereas consummatory states are more closely related to the "in the moment" experience of satiety [19]. In this regard, we might talk about the characteristics of patients who display anticipatory pleasure deficits, and question whether they also have consummatory pleasure deficits. Thus far, considerably more research has been conducted studying social and physical anhedonia. However there are several factors that render it likely for there to be a substantial increase in research examining the distinction between anticipatory and consummatory pleasure in both nonpatient and patient populations. First, there is evidence that the different components of pleasure have at least partially dissociable neural circuitry [20–22]. Secondly, in 2005, a NIMH-sponsored group [23] embraced the idea of incorporating the distinction between appetitive and experienced components of pleasure in the assessment of negative symptoms.

2.2.3 The Prevalence of Anhedonia

If one considers hedonic capacity as a trait characteristic that is normally distributed throughout the population, then it is possible to account for the presence of anhedonia, albeit at low base rates, in the general population. Furthermore, if one conceptualizes hedonic capacity as being bimodal, i.e., the normally hedonic group falling in one distribution and the anhedonic in the second, smaller distribution, then, again, the base rates would seem appropriate. In this way, anhedonia might best be considered on a continuum, rather than categorically [24].

Anhedonia has been observed in patients with various psychiatric disorders including mood disorders, particularly major depressive disorder [13, 22, 25], substance use disorders [26, 27], and drug-induced psychosis [28]. Indeed, there are reports of anhedonia in autism [29], eating disorders [30], and post-traumatic stress disorder [31]. There are also reports of anhedonia accompanying various other medical disorders, such as Parkinson's disease [32], coronary artery disease [33], and diabetes [34]. Although anhedonia is a prominent symptom in depression, a comparative study by Blanchard, Horan, and Brown [25] indicated that anhedonia is state-related in major depressive disorder, though trait-related in schizophrenia. A 10-year follow-up study by Herbener and Harrow [35] also indicated that anhedonia is a stable clinical feature of schizophrenia.

2.2.4 Issues of Specificity: The Special Relationship Between Anhedonia and Schizotypy

Several clinicians and theoreticians have posited a special relationship between anhedonia and schizotypy, the hypothesized latent trait underlying risk for schizophrenia and schizophrenia-spectrum disorders. Since the early writings of Rado [14, 15] and Meehl [11], anhedonia has been hypothesized as either a contributing or

potentiating factor in the development of schizophrenia-spectrum [11, 16, 36]. However, studies indicate that anhedonia is not present in all patients with schizophrenia and schizophrenia-spectrum disorders. Estimates vary, but up to 80 % of schizophrenia patients show at least moderate levels of anhedonia [37]. In summary, anhedonia is a common, stable trait-like condition for a substantial portion of the schizophrenia-spectrum and it is currently treatment-refractory.

2.3 The Assessment of Anhedonia

Anhedonia has been prominent in clinical descriptions of schizophrenia since Kraepelin [38] and Bleuler [39], Recently, however, there has been a resurgence of interest in assessing and describing it [40]. A 2005 meeting, sponsored by the NIMH [23], provided some of the impetus for the development of several of the measures described below.[1]

2.3.1 Clinical Assessment

There are several tools for the assessment of anhedonia and negative symptoms [41] in psychosis: the Scale for the Assessment of Negative Symptoms [42], Positive and Negative Syndrome Scale [43], Clinical Assessment Interview for Negative Symptoms [44] and Brief Negative Symptom Scale [45]. Also, there are structured interviews such as the Scale of Prodromal Symptoms [46] for the assessment at high risk mental states in help-seeking samples. After reviewing the SANS, we provide an in-depth analysis of the new developments in the assessment of negative symptoms, according to the NIMH negative symptoms consensus [23].

2.3.1.1 The Scale for the Assessment of Negative Symptoms (SANS)

The SANS [42] is an interview-based instrument designed to assess negative symptoms in schizophrenia and its related disorders. It consists of 25 items, which fall into five a priori symptom domains, namely, affective flattening, alogia, avolition-apathy, anhedonia-asociality and attention. The items are rated on a 6-point Likert scale (0 = *absent/not at all*; 5 = *severe/extreme*). For each of the subscales, there is a global subscale score as well. The SANS Anhedonia-Asociality subscale consists of 4 items that cover recreational interests and activities, sexual interest and activities, ability to feel intimacy and closeness, and relationships with friends and peers. In this way, anhedonia is operationally defined as encompassing a reduced ability to experience pleasure when participating in pleasurable activities

[1] Neither of the authors of this chapter were attendees of the NIMH-sponsored meeting.

as well as social withdrawal and lack of involvement in social relationships. The SANS includes queries regarding the frequency of the respondent's social engagement, as well as their interest in and enjoyment of their activities.

There have been other relatively recent discussions of the psychometric properties of the SANS (for a review see [40, 47]). There are relatively few published reports of systematic studies regarding the psychometric characteristics of the Anhedonia-Asociality subscale of the SANS [40]. Briefly, the reliability scores range between 0.63 and 0.83 and test-retest reliability ranging from 0.25 to 0.37. Also, the findings indicate good levels of rater agreement ranges from 0.75 to 0.92 (for total score). Factor analysis indicates that the SANS measures two fairly independent dimensions of schizophrenic symptomatology (diminished expression and combined anhedonia-asociality) [40, 44, 45, 47–50].

There have been some criticisms of the SANS. There is some concern that the Anhedonia-Asociality subscale may confound patients' hedonic capacity with other aspects of social functioning, such as level of interest and engagement in recreational and social activities. While all of this information is useful clinically, it would be helpful to differentiate the information in terms of targeting different aspects for appropriate types of intervention (e.g. pharmacological, vocational, social skills training, etc.). Due to its length, several researchers suggest that the SANS be shortened. For example, Levine and Leucht [50] tested the psychometric properties of the short research version of the SANS in a sample of 487 patients with schizophrenia. The results shown that the short version of the SANS is adequate to assess predominantly negative symptoms in chronic schizophrenia in research settings.

Despite its limitations, the SANS is one of the interviews recommended for use by the NIMH-MATRICS workgroup on negative symptoms [23]. An advantage of this measure is that there is a global score per each domain, so overall global/summary scores can be derived. Suggested interview questions and prompts are built into this measure, and it also contains explicit anchor points. Not surprisingly, the SANS has been translated into numerous foreign languages. At present, the SANS is considered to be the standard interview-based assessment that all other similar measures of negative symptoms are compared with. Indeed, the SANS is perhaps the most well-known interview-based measure for the assessment of negative symptoms in general, and especially, anhedonia.

2.3.1.2 The Clinical Assessment Interview for Negative Symptoms (CAINS)

The CAINS [44, 51] is an interview-based measure for the assessment of negative symptoms. The CAINS was purportedly designed to address limitations of extant measures, incorporate knowledge from affective neuroscience, and provide more comprehensive coverage of negative symptoms. For example, this semi-structured interview includes extensive prompts and follow-up questions for each item, as well as anchors, in order to guide interviewers in the administration and scoring of the measure. The CAINS items are scored on a 7-point Likert scale with higher scores

reflecting greater pathology. The CAINS distinguishes between the categorical (i.e., social, physical, and recreational/vocational) and temporal (experienced versus expected) aspects of pleasure. The CAINS also distinguishes between social anhedonia and asociality, operationally defined as the preference for being alone and low or lack of value placed on relationships. Out of 23 items, 9 items comprise an anhedonia subscale and 3 items comprise an asociality subscale.

Limited data indicated evidence of convergent validity for the CAINS-beta. The CAINS-beta anhedonia subscale correlated negatively with the TEPS-ANT and TEPS-CON, and positively with the SANS asociality subscale. However, the CAINS-beta anhedonia subscale failed to correlate significantly with the SANS anhedonia subscale. Internal consistency for the CAINS-beta anhedonia subscale was adequate (0.74). The developers of the interview acknowledged the difficulty of setting pathological thresholds for the anhedonia items assessing the frequency and intensity of pleasurable events in the absence of normative data.

Subsequent development of the CAINS was conducted, using the largest standardization sample of any scale developed for the assessment of symptoms in schizophrenia [44, 52]. The final 13-item version was empirically derived from the CAINS-beta using both CTT and IRT [51, 53]. Results from structural analyses yielded two general factors: expression (four items reflecting diminished outward expression and speech) and motivation pleasure. Across the four testing sites, the internal consistency for the CAINS ranged from 0.74 to 0.88. In terms of the motivation/pleasure and expression subscales, inter-rater agreement (0.93 and 0.77, respectively) and test-retest reliability (0.69 and 0.69) was good overall. The developers reported evidence of convergent validity for the CAINS. Ratings on the CAINS Motivation/Pleasure subscale correlated with the BPRS negative symptoms subscore, SANS asociality/anhedonia subscore, and the RSAS. The CAINS Motivation/Pleasure subscale ratings also correlated negatively with TEPS-ANT and TEPS-CON scores.

An accompanying training manual and videos are available to facilitate use of the CAINS. To date, the CAINS has been translated into Chinese and French, thereby allowing it to be used internationally. Thus far, the CAINS has only been administered to outpatients with schizophrenia or schizoaffective-disorder. It is unclear how amenable this measure is to its use in inpatient settings. Moreover, the instrument is quite lengthy, which may limit its usefulness in certain contexts, such as genetic studies, early intervention studies, and general psychiatric practice.

2.3.1.3 The Brief Negative Symptom Scale (BNSS)

The BNSS [45] is another interview-based measure for the assessment of negative symptoms. Like the CAINS, the BNSS was developed in response to a perceived need, following a NIMH Consensus Development Conference on Negative Symptoms held in 2005, to improve upon the assessment of negative symptom domains for use in clinical as well as research settings. The BNSS is a 13-item semistructured interview organized into 6 subscales, namely, Anhedonia, Distress, Asociality,

Avolition, blunted affect, and Alogia. All items in the BNSS are rated on a 7-point Likert scale, generally ranging from the absence of a symptom (0) to a symptom appearing severe (6). The BNSS anhedonia subscale consists of three items which assess the intensity of pleasure during activities, frequency of pleasure during activities, as well as the intensity of expected pleasure from future activities. In addition, there are two asociality items, measuring behaviour and inner experience, which may be related to social anhedonia.

The BNSS has good psychometric characteristics [45, 54, 55]. The internal consistency for the total scores ranges from 0.93 to 0.95. In schizophrenia and schizoaffective patients, the BNSS displays high temporal stability, with the total BNSS test-retest reliability being estimated at 0.81 and the subscales also showing good test-retest reliability, ranging from 0.76 to 0.90 (anhedonia r = 0.76). Also, the findings indicate good levels of rater agreement ranging from 0.77 to 0.95 (anhedonia ICC = 0.95). Principal axis extraction indicated two distinct components, namely, an Amotivation and Pleasure dimension, consisting of the items in the anhedonia, avolition, and asociality subscales, and an Emotional Expressivity dimension, consisting of the blunted affect, alogia, and lack of normal distress subscale [54]. Together, these two factors accounted for nearly 69 % of the variance.

Results indicated that the BNSS has good convergent and discriminant validity in its relationships with other symptom rating scales, functional outcome, self-reported anhedonia, and functional outcome. For example, it is encouraging that the BNSS Anhedonia subscale total score and SANS Anhedonia/Asociality subscale scores were positively and moderately highly correlated, as were the BNSS and SANS Anhedonia/Asociality scores [45]. Moreover, the BNSS anhedonia subscale was significantly correlated with the RSAS and PAS. Interestingly, both the BNSS Intensity of Pleasure and Frequency of Pleasure items were significantly correlated with both the RSAS and PAS. However, the Intensity of Future Pleasure item was only correlated with social anhedonia, as measured by the RSAS, not physical anhedonia, as measured by the PAS [45, 54, 55].

There are several advantages to this new interview-based measure. First, the BNSS is designed so that a clinician or researcher can administer the BNSS in approximately 15 min. The brevity of this measure contrasts with the SANS (typically requires 25–30 min) and the CAINS (estimated time required 45 min). A second advantage of the BNSS is its strong psychometric characteristics. For example, the BNSS has demonstrated good separation of its two-factor structure, namely motivation-pleasure and emotional expressivity; this has proven more difficult for the CAINS [53]. Although the instrument was designed primarily for use in treatment trials, due to its high test-retest reliability, it can also be used in clinical evaluations, to track clinical change.

It appears to be applicable to both inpatient and outpatient clinical use, though to date, it has only been piloted on outpatient schizophrenia-spectrum patients. The BNSS is accompanied by a training manual and workbook including suggested questions and scoring anchors in order to guide users of the instrument. In conclusion, the BNSS can be considered a promising new instrument for use in clinical trials.

Table 2.1 Measurement instruments for the assessment of anhedonia or hedonic capacity

Name	Main reference(s)	Abbreviation	N° items	Format
Scale for the assessment of Negative Symptoms	[42]	SANS	25	Likert 6
Positive and Negative Syndrome Scale	[43]	PANSS	30	Likert 7
Clinical Assessment Interview for Negative Symptoms	[44]	CAINS	13	Likert 7
Brief Negative Symptom Scale	[45]	BNSS	13	Likert 7
Motivation and Pleasure Scale-Self-report	[56, 57]	MAP-SR	15	Likert 5
Scale of Prodromal Symptoms	[46]	SOPS	19	Likert 7
Revised Physical Anhedonia Scale	[17]	PAS	61	True/False
Revised Physical Anhedonia Scale-Brief	[62]	PAS-B	15	True/False
Revised Social Anhedonia Scale	[58]	RSAS	40	True/False
Revised Social Anhedonia Scale-Brief	[62]	RSAS-B	15	True/False
Schizotypal Personality Questionnaire (Brief)	[59, 63]	SPQ (B)	74/ 22	True/False
Oxford-Liverpool Inventory of Feeling and Experiences (Brief)	[64, 65]	O-LIFE (B)	159/43	Yes/No
Community Assessment Psychic Experiences –42	[66]	CAPE-42	42	Likert 4
Thinking and Perceptual Style Questionnaire	[67]	TPSQ	99	Likert 5
Oviedo Questionnaire for Schizotypy Assessment	[60]	ESQUIZO-Q	51	Likert 5
Temporal Experience of Pleasure Scale	[19]	TEPS	18	Likert 6
Anticipatory and Consummatory Interpersonal Pleasure Scale	[33, 61]	ACIPS	17	Likert 6

2.3.2 Self-report Assessment

Several self-report measures have been used to measure anhedonia in individuals at risk for or affected by schizophrenia-spectrum disorders. These measures include: the Motivation and Pleasure Scale-Self-report (MPS-SR) [56, 57], Revised Physical Anhedonia Scale (PAS) [17] and Revised Social Anhedonia Scale (RSAS) [58], Schizotypal Personality Questionnaire (SPQ) [59], Oviedo Questionnaire for Schizotypy Assessment (ESQUIZO-Q) [60], Temporal Experience of Pleasure Scale (TEPS) [19] and Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) [61]. Although other measures within the psychometric high-risk paradigm and early intervention research traditions have been developed (see Table 2.1), we do not discuss them here. In the sections that follow, we critically review the extant literature regarding each of the aforementioned scales; where applicable, their abbreviated versions are discussed as well. Table 2.2 shows psychometric properties for the measurement instruments and Table 2.3 provides examples of items included in each of the scales reviewed.

Table 2.2 Psychometric properties for the measurement instruments

Name	Reliability	Interrater	Test-retest	Sources of validity	References
SANS	0.63/0.82	0.75/0.92 (global)	0.28/0.37	Internal structure and related with other measures	[40, 44, 45, 47–50]
PANSS	0.83/0.90	0.72/0.89	0.68	Internal structure and related with other measures	[40, 43, 45, 47, 68–72]
CAINS	0.74/0.88	0.77/0.93	0.69	Internal structure and related with other measures	[44, 51, 53]
BNSS	0.93/0.95	0.96 (0.76 anhedonia)	0.76/0.90	Internal structure, predictive, and related with other measures	[45, 54, 55]
MAP-SR	0.90	–	–	Internal structure and related with other measures	[56, 57]
SOPS	0.87/0.93	0.74/0.91		Internal structure, predictive, ecological and related with other measures	[73–79]
PAS	0.77/0.92	–	0.65/0.84	Internal structure, predictive, ecological and related with other measures	[10, 19, 80–93]
PAS-B	0.62/0.91	–	–	Internal structure and related with other measures	[62, 91]
RSAS	0.75/0.95	–	0.75/0.84	Internal structure, predictive, ecological, and related with other measures	[10, 44, 62, 81–90, 92–99]
RSAS-B	0.75/0.92	–	–	Internal structure and related with other measures	[62, 91]
SPQ[a]	0.57/0.82	–	0.41/0.70	Internal structure, predictive and related with other measures	[100–107]
O-LIFE (Brief)[b]	0.42/0.87	–	0.72–0.85	Internal structure and related with other measures	[108–116]
CAPE-42	0.78/0.93	–	0.64 (negative)	Internal structure, predictive, and related with other measures	[66, 111, 117–123]
TPSQ[c]	0.75–0.85	–	0.65–0.79	Internal structure and related with other measures	[67, 124–127]
ESQUIZO-Q[d]	0.66/0.77	–	–	Internal structure and related with other measures	[60, 128, 129]
TEPS	0.63/0.87	–	0.75–0.81	Internal structure and related with other measures	[19, 44, 83, 130–137]
ACIPS	0.87	–	0.78	Internal structure and related with other measures	[34, 35, 138, 139]

Note:
[a]No close friends and constricted affect (Social Anhedonia)
[b]Introvertive anhedonia
[c]Physical and social anhedonia
[d]Anhedonia dimension

Table 2.3 Examples of self-report items for assessment of hedonic capacity and anhedonia

Self-reports	Items
Motivation and Pleasure Scale-Self-report	In the past week, what is the most pleasure you experienced from being with other people?
	In the past week how motivated have you been to be around other people and do things with them?
Physical Anhedonia Scale (Brief)	I have often found walks to be relaxing and enjoyable
	A brisk walk has sometimes made me feel good all over
Revised Social Anhedonia Scale (Brief)	Having close friends is not as important as many people say
	I never had really close friends in high school
Schizotypal Personality Questionnaire	I find It hard to be emotionally close to other people
	Do you feel that you cannot get "close" to people?
Oxford-Liverpool Inventory of Feeling and Experiences-reduced	Are you much too independent to get involved with other people?
	Do you love having your back mass?
Oviedo Questionnaire for Schizotypy Assessment	I like to meet again with friends I have not seen in a while
Temporal Experience of Pleasure Scale	A hot cup of coffee or tea on a cold morning is very satisfying for me
	When I hear about a new movie starring my favorite actor, I can't wait to see it
Anticipatory and Consummatory Interpersonal Pleasure Scale	I enjoy watching films about friendships or relationships with my friends

2.3.2.1 Motivation and Pleasure Scale-Self-report (MAP-SR)

The MAP-SR [56, 57] is an 18-item self-report version of the CAINS Motivation and Pleasure subscale designed to assess the severity of the negative symptoms. An earlier version of the MAP-SR, called the CAINS-Self Report (CAINS-SR) [56] contained 30 items divided between an Experiential (avolition, anhedonia, asociality) and an Expressive (affect, alogia) subscale. The CAINS-SR included 9 items assessing the intensity and frequency of experienced (consummatory) and expected (anticipatory) pleasure across social, physical, and recreational/work domains. It also included 6 items assessing asociality. Despite high internal consistency (Cronbach's alpha = 0.90) for the overall measure, low levels of internal consistency values for the Expression subscale (0.40) led the authors to remove this subscale from the self-report version.

The MAP-SR [57] is a 15-item self-report measure of negative symptoms, which are rated on a 5-point Likert scale. The MAP-SR differs from the CAINS-SR in that it focuses exclusively on self-reported deficits in motivation and pleasure. Six items in the MAPS-SR assess the subject's experience of pleasure in both the past week as well as their expectations of future pleasure, and three items assess the subject's feelings and motivations about close, caring relationships. The internal consistency

for the MAP-SR in the sample of schizophrenia and schizoaffective patients was excellent (Cronbach's alpha = 0.90). As expected, the MAP-SR demonstrated good convergent validity with clinician ratings of motivation and pleasure on the CAINS. The MAP-SR also showed good convergent validity with other relevant self-report measures tapping social anhedonia such as the RSAS and the University of California, San Diego, Performance-Based Skills Assessment-Brief Version rating of social engagement. The MAP-SR was not significantly correlated with depressive symptoms or with the Positive Symptom or Depression/Anxiety subscales of the Brief Psychiatric Rating Scale, thereby demonstrating discriminant validity as well.

Overall, the MAP-SR's convergent and discriminant validity and internal consistency values indicate that the MAP-SR shows promise as a self-report measure of the severity of negative symptoms in schizophrenia. According to its developers, the MAP-SR is intended largely as way to screen people with elevated negative symptoms. Like its predecessor, the CAINS-SR, its psychometric properties have been evaluated on outpatients with schizophrenia and schizoaffective disorder. Thus far, however, the MAP-SR has not been evaluated in terms of its sensitivity or specificity for the detection of individuals with anhedonia. In addition, questions about the temporal stability of the MAP-SR scores have not been addressed. Future investigations of the MAP-SR across other patient groups, and in other populations are a necessary next step in order to realize the full potential of this measure.

2.3.2.2 Revised Physical Anhedonia Scale (PAS)

The PAS [17, 140] is a self-report questionnaire consisting of 61 items in a true/false format which measures the inability to experience pleasure from pleasant physical stimuli such as touch, taste, sight, smell, movement, sex, and sound. The PAS has been administered widely to schizophrenia outpatients [37, 80, 141] and inpatients [142]. Patients with schizophrenia report high levels of physical anhedonia on this measure [80, 141, 143–145]. It is noteworthy that a substantial proportion of schizophrenia patients produce PAS scores which overlap with those of healthy controls, leading some to question whether trait anhedonia is associated with a schizophrenia subtype, i.e., deficit syndrome schizophrenia [146].

The PAS has also been administered to first degree-relatives of patients [147, 148]. Overall, biological relatives report elevated rates of physical anhedonia [145, 149–151]. Some research indicates that PAS scores can distinguish between schizophrenia probands and their first-degree relatives [152] as well as distinguish between non-psychotic relatives of schizophrenia probands and controls [145, 149]. In the Roscommon Family Study, physical anhedonia scores were typically higher in relatives of schizophrenia patients with severe anhedonic symptoms [153].

The PAS has also been administered to college- and community-derived nonclinical samples [81, 82]. In nonpatient samples, the internal consistency of the PAS ranges from 0.77 to 0.92, and its test-retest reliability ranges from 0.65 to 0.84 (see Table 2.2). In the first longitudinal study of psychosis-proneness in recent-onset schizophrenia [80], the internal consistency of the PAS was 0.67 in the

patient group. The investigators found supportive evidence that schizophrenia and schizophrenia-spectrum patients' physical anhedonia is a vulnerability marker, i.e., their levels of physical anhedonia remained elevated across time and across assessments. These findings are consistent with those of longitudinal studies of chronic schizophrenia probands, which also indicate the trait-like nature of physical anhedonia [35, 154–156].

Physical anhedonia, as measured by the PAS, appears to have a taxonic structure in American and German samples [157]. Support regarding the concurrent validity of the PAS comes from investigations of nonclinical individuals with aberrantly high scores (i.e., greater than or equal to 2 SDs beyond the same-sex control group mean) who performed in similar, albeit attenuated patterns, as schizophrenia patients. For example, individuals identified as anhedonic on the basis of the PAS display smooth pursuit impairments, antisaccade task deficits and nailfold plexus visibility [158–160]. Moreover, Soliman et al. [161] demonstrated that physically anhedonic individuals show increased stress-induced striatal dopamine release. The measurement of trait anhedonia has increasingly included advances in neuroscience. Harvey et al. [162] obtained structural and functional imaging data from community-derived controls in order to examine correlates of individual differences in anhedonia. Trait anhedonia was inversely related to anterior caudate volume. In terms of functional neural correlates, the investigators noted an association between VMPFC activation and trait anhedonia during the processing of pleasant information [162]. Similarly, Dowd and Barch [163] noted a significant negative correlation within the VMPFC region between activation to reward-predictive cues and individual differences in PAS scores.

2.3.2.3 Revised Social Anhedonia Scale (RSAS)

The Revised Social Anhedonia Scale [58] is a self-report questionnaire consisting of 40 items true/false format which measures schizoid indifference, associability, lack of social enjoyment, and indifference towards others. The RSAS has been administered to college- and community-derived nonpatients [164–168] as well as psychiatric patients. In terms of patient samples, the RSAS has been administered to schizophrenia outpatients [25, 83, 154, 169, 170], schizophrenia inpatients [171], mixed groups of personality-disordered patients [172], patients with drug-induced psychoses [28], and eating-disordered patients [30]. First-degree relatives of schizophrenia patients have been assessed using this measure as well [173]. As such, the psychometric properties of the RSAS have been studied extensively (see Table 2.2). Briefly, the internal consistency of the measure ranges from 0.75 to 0.89, and test-retest reliability estimates range from 0.75 to 0.84.

The RSAS has high sensitivity (92 %) and moderately high specificity (75 %) [174]. Research findings continue to indicate that individuals with schizophrenia and schizophrenia-spectrum disorders report significantly greater levels of social anhedonia than do nonpsychiatric comparison participants (see, for example [25, 37, 40, 175]). In schizophrenia patients, the RSAS is correlated significantly and positively with their SANS total scores as well as their SANS 'anhedonia-asociality'

subscale scores. This elevation in social anhedonia is relatively independent of psychotic and depressive symptoms [25]. Moreover, in direct comparisons, individuals with schizophrenia report higher amounts of social anhedonia than individuals with schizophrenia-spectrum personality disorders [175]. Schizophrenia probands report significantly higher levels of social anhedonia than their siblings with nonpsychotic disorders and siblings without nonpsychotic disorders [152]. First-degree relatives of individuals with schizophrenia have reported significantly higher levels of social anhedonia compared to controls (Kendler et al. [176]).

Further supportive evidence regarding the concurrent validity of the RSAS can be derived from investigations of nonclinical individuals with aberrantly high scores (i.e., greater than or equal to 2 SDs beyond the same-sex control group mean) who performed in the deviant direction and in similar, albeit attenuated patterns, as schizophrenia patients. Individuals identified as socially anhedonic on the basis of the RSAS display subtle working memory, WCST, sustained attention and visuoconstructive impairments; aberrant perceptual biases; smooth pursuit impairments and antisaccade task deficits and nailfold plexus visibility [159, 160, 177–182]. To date, the RSAS is one of the sole self-report anhedonia measures that have been longitudinally validated as having predictive validity for the later development of schizophrenia and schizophrenia-spectrum disorders [94, 167, 183]. Secondary analysis of the Chapmans' 10-year follow-up data [94] as well as an independent replication using a different sample from a younger cohort longitudinally followed over 5 years [167, 183] indicate that the RSAS identifies individuals at specific risk for the development of schizophrenia-spectrum disorders.

The RSAS is a rather complex measure, which assesses more than solely social anhedonia. As Reise, Horan, and Blanchard [95] demonstrated, the latent structure of RSAS data is challenging to model due to the multidimensionality of the items (i.e., the degree of introversion, schizoid indifference, and lack of close relationships are measured in addition to the experience of interpersonal pleasure) as well as the cross-loadings among some of the items. Asociality, on the other hand, seems to have a taxonic nature [184].

In summary, the data suggest that the two Chapman anhedonia scales have construct, predictive, and concurrent validity. It is therefore not surprising that both the PAS and the RSAS are two of the most widely used measures for the assessment of anhedonia. They have been translated into several languages, including French, Spanish, Chinese, and German [185]. It is also noteworthy that items from both the PAS and RSAS were used to develop other measures used for more comprehensive schizotypy assessment (e.g., the O-LIFE and the TPSQ).

Nonetheless, there are some limitations to these oft-used measures. The items in these anhedonia scales may be criticized for being somewhat obviously focused on psychopathology, rendering some individuals defensive about their replies [186]. Some investigators [40, 187] have opined that the content validity of the PAS and RSAS may be outdated. Others have criticized the PAS and RSAS due to their relatively lengthy nature. Despite these criticisms of the full Chapman anhedonia scales, they continue to be the metric against which nearly all other putative measures of anhedonia are compared. Indeed, they are consistently included when evaluating the construct validity of other instruments related to hedonic capacity.

There have been at least a few attempts to create shortened versions of the anhedonia scales, particularly for the purposes of large-scale screening and inclusion in genetic research. Under the guidance of the Chapmans, Kendler et al. [176] reduced the RSAS to 16 items for use in their Roscommon Family Study. Hay and colleagues reduced [186] the full Chapman psychosis-proneness questionnaires to a 12-item questionnaire which included two items each from the PAS and RSAS. Their abbreviated survey suggested that highly selective culling of questionnaire items may result in a scale that resembles the basic factor structure observed in the original measures. Using CTT and an IRT framework, Kwapil and colleagues have created abbreviated forms of both Chapman anhedonia scales [188]. Both of the abbreviated scales consist of 15 items each. Thus far, the preliminary psychometric data look promising, though they are based solely on college undergraduates primarily from one lab (see Table 2.2). Nonetheless, a key question is the extent to which these abbreviated scales can still identify psychometrically at-risk individuals to the same extent, i.e., with the same predictive validity, as the full-length questionnaires.

2.3.2.4 The Schizotypal Personality Questionnaire (SPQ)

The SPQ [59] is a self-report questionnaire made up of 74 items with dichotomous response format (Yes/No or True/False) designed to measure DSM-III-R [189] schizotypal personality disorder. The questionnaire consists of nine subscales, corresponding to the symptoms of schizotypal personality disorder that appear in the DSM-III-R: odd beliefs or magical thinking, unusual perceptual experiences, ideas of reference, paranoid ideation/suspiciousness, excessive social anxiety, no close friends, constricted affect, odd or eccentric behavior, and odd speech.

The factor structure of the SPQ has been a matter of investigation as well as debate [100–102, 185, 190]. Studies of community subjects resulted in Raine's three-factor model of the SPQ, which included cognitive-perceptual, social-interpersonal, and disorganization dimensions. In addition to Raine's [190] three-factor model of schizotypy and schizotypal personality disorder, Stefanis et al. [191] offered an alternative four-factor model of the SPQ. In both of these models, the interpersonal factor included the "no close friends", "excessive social anxiety", and "constricted affect" subscales. Chmielewski and Watson [102] conducted item-level structural analysis of the SPQ and concluded that Raine's three-factor solution could not be replicated. Rather, their analyses supported a five-factor solution, which included a Social Anhedonia Factor. Items from the No Close Friends and Constricted Affect subscales formed the Social Anhedonia dimension. It is noteworthy that the No Close Friends subscale contains 9 items and the Constricted Affect subscale contains 8 items; thus, less than 25 % of the entire measure contains items that are directly relevant to the assessment of anhedonia. Nonetheless, psychometric studies provide some support for use of the SPQ subscales as an indirect measure of social anhedonia. As shown in Table 2.2, levels of internal consistency for the subscales ranged from 0.57 to 0.82, and the temporal stability ranges between 0.41 and 0.70. The social-interpersonal SPQ subscales showed moderate correlations with RSAS

and PAS scores or were grouped in the same underlying factor [103, 192]. The SPQ has been widely used, and translated into French, Spanish, Italian, and German as well as Chinese [104, 191, 193–195].

Two family studies [196, 197] that used the SPQ failed to reveal significant differences between relatives and controls in terms of social-interpersonal schizotypal traits. However, in a considerably larger sample of first-degree relatives of schizophrenia probands, Calkins et al. [198] observed that the social-interpersonal schizotypal factor differentiated the relatives from the comparison subjects. Indeed, they concluded that this was the SPQ factor that best differentiated relatives from controls. Similarly, Docherty and Sponheim [199] noted that relatives of schizophrenia patients reported higher levels of social-interpersonal schizotypal traits than healthy controls. Furthermore, lack of close friends appears to have some predictive value in follow-up studies, increasing the risk of full-blown psychosis [105].

The SPQ has been criticized by some investigators because all of the items are worded so that a "true" or "yes" response contributes to a high score, thereby rendering the scale subject to an acquiescence response bias [84]. The dichotomous response format may have contributed to the somewhat lower internal consistency estimates of the SPQ, relative to other measures. Wuthrich and Bates [103] partly allayed these concerns when they adapted the SPQ to a Likert-type response format. One issue concerning the SPQ is that the social-interpersonal factor encompasses both social anxiety as well as social anhedonia; as others have noted (see, for example [200]), social anxiety is a nonspecific risk factor not specifically related to social anhedonia.

The SPQ has also been criticized due to the length of the measurement instrument. Raine and Benishay [63] developed an abbreviated version of the SPQ, the Schizotypal Personality Questionnaire-Brief (SPQ-B). The SPQ-B contains 22 items and scales for three factors, namely, the Cognitive-Perceptual Deficits, Interpersonal Deficits, and Disorganization Scales. The SPQ-B was reported to have adequate reliability and correlated well with the full measure [63]. The Interpersonal Deficits scale, which is most relevant to measuring anhedonia, contains 8 items. The SPQ-B generated considerable research interest and has been translated into Spanish [201], Turkish [202], Japanese [203], and Chinese [204]. The SPQ-B appears to have a three factor structure in adolescent psychiatric inpatient and nonpatient community samples [63, 201, 205, 206]. However, while generally showing adequate internal consistency, some investigators reported that the SPQ-B failed to conform to a three-factor solution [202, 207, 208]. Also, a Likert version of the SPQ-B has been developed [205, 209]. However, neither the total or Interpersonal subscale scores of the SPQ-B differentiated first-degree relatives of schizophrenia-spectrum probands from nonpsychiatric controls [208].

More recently, Cohen et al. [101] provided an alternative abbreviated version of the SPQ, known as the Schizotypal Personality Questionnaire-Brief-Revised (SPQ-BR). The impetus for Cohen's revision appears to have been twofold: the Interpersonal subscale of the SPQ-Brief reflected both social anxiety and social anhedonia, though these are very different and distinct constructs; and the forced choice-dichotomous response format of the full version limited the reliability and

sensitivity for the abbreviated version. The revised SPQ-B retains 32 of the original 74 items and is scored on a 5-point Likert-based response format. In the SPQ-BR, there are seven trait subscales, which result in a three or four factor higher-order structure. In the SPQ-BR, the No Close Friends/Constricted Affect subscale is separate from the Social Anxiety subscale. Moreover, the psychometric properties look encouraging. The internal consistency estimate for the No Close Friends/Constricted affect subscale is 0.81 in an undergraduate sample [101]. Although this measure is relatively new, it is being increasingly incorporated into research investigations of schizotypy [210]. It is unclear whether it will be adopted as an indirect measure of anhedonia.

2.3.2.5 The Oviedo Questionnaire for Schizotypy Assessment (ESQUIZO-Q)

Adolescence is a developmental period of special risk for schizophrenia-spectrum disorders [211]. Early detection of precursors or clinical signs in individuals at high-risk for schizophrenia spectrum disorders is necessary for preventive and/or early intervention efforts [212]. Thus, efforts have also been directed at the assessment of anhedonia (a core component of schizotypy) in this age group. A good example of these self-reports are the Junior Schizotypy Scales (JSS) [213], the Schizotypy Traits Questionnaire (STA) for children [214], Schizotypal Personality Questionnaire-Child [215], and the ESQUIZO-Q [60].

The ESQUIZO-Q [60] is a self-report composed of 51 items in a 5-point Likert-type response format, ranging from 1 (*completely disagree*) to 5 (*completely agree*) that is designed to assess schizotypal traits in adolescents. The ESQUIZO-Q is based on the diagnostic criteria proposed in the DSM-IV-TR [216] and on Meehl's schizotaxia model [11] regarding genetic predisposition to schizophrenia. The items of ESQUIZO-Q were selected on the basis of an exhaustive review of the literature on schizotypy [185]. Its construction was conducted following the proposed steps for the construction of measurement instruments [217] and the guidelines for multiple-choice item construction [218]. The ESQUIZO-Q comprises a total of 10 empirically derived subscales: Ideas of Reference, Magical Thinking, Unusual Perceptual Experiences, Odd Thinking and Language, Paranoid Ideation, Physical Anhedonia, Social Anhedonia, Odd Behavior, Lack of Close Friends and Excessive Social Anxiety. These subscales are grouped into three general dimensions: Reality Distortion, Anhedonia, and Interpersonal Disorganization. The internal consistency values for the Anhedonia dimension and subscales ranged from 0.62 to 0.77. There were no gender differences on any of the Anhedonia items. Furthermore, the Anhedonia dimension of the ESQUIZO-Q was correlated with other measures that assess emotional and behavioral problems, depressive symptoms and maladaptive personality traits [128, 219, 220]. Thus, there is good evidence of convergent validity for the Anhedonia dimension of the ESQUIZO-Q.

Although the ESQUIZO-Q is a useful tool for assessing anhedonia in the general adolescent population, it was not been developed specifically for that purpose.

One direction for future research would be to examine the relationship between ESQUIZO-Q scores with other measures of hedonic capacity in adolescent representative samples [221]. To date, the ESQUIZO-Q has only been administered to Spanish adolescents.

2.3.2.6 Temporal Experience of Pleasure Scale (TEPS)

The TEPS [19] was designed to measure individual trait dispositions in both anticipatory and consummatory experiences of pleasure. This 18-item self-report measure consists of 2 subscales: a 10-item anticipatory pleasure scale and an 8-item consummatory pleasure scale. The TEPS is scored in a 6-point Likert-type response format ranging from 1 (*very false for me*) to 6 (*very true for me*). Typically, the anticipatory and consummatory scales are scored separately and compared.

The TEPS has attracted considerable research interest since its introduction in 2006. The psychometric properties of the TEPS have been extensively studied in both clinical and nonclinical samples (see Table 2.2) [19, 44, 83, 130–136]. Research indicates that the TEPS-ANT subscale is internally consistent in schizophrenia and schizophrenia-spectrum patients (coefficient alpha's range from 0.71 to 0.79) and nonpatient controls (alpha's range from 0.64 to 0.74). Similarly, the TEPS-CON subscale appears internally consistent in both schizophrenia-spectrum patient samples (coefficient alpha's range from 0.68 to 0.78) and nonpatient controls (alpha's range from 0.64 to 0.71). The temporal stability of the TEPS-ANT and TEPS-CON subscale assessments have also been measured. In one report based upon 19 schizophrenia patients, the TEPS-CON subscale appeared to show significantly higher stability than the TEPS-ANT (ICC of 0.93 versus 0.74, respectively), and a greater sensitivity to individual differences in hedonic experience [137]. In contrast, on the basis of comparison of the test-retest scores of 51 schizophrenia-spectrum patients after a 6 month interval, Buck and Lysaker [135] observed that the TEPS-ANT showed greater temporal stability than the TEPS-CON. Clearly, there is a need for further study of the temporal stability of the TEPS-ANT and TEPS-CONS, and their relationship with various measures of clinical and psychosocial functioning.

Although factorial studies of the original version of the TEPS consistently confirmed the presence of the two factors, factor analysis of the 19-item Chinese version of the TEPS [134] revealed a four-factor structure, consisting of contextual consummatory, consummatory abstract, anticipatory context, anticipatory abstract factors. The Chinese version of the TEPS substitutes two items, thereby adding more interpersonal content to the measure. The two versions of the TEPS are otherwise similar in terms of their psychometric properties [132, 134]. There is also an 18-item French translation of the TEPS [133] that has psychometric characteristics similar to the original version developed by Gard and colleagues [19].

While there is little question that many patients with schizophrenia display a pleasure deficit, to date, findings regarding the nature of relationship between schizophrenia and anhedonia as defined by the TEPS have been mixed. Several investigations have demonstrated that the TEPS successfully discriminates patients

with schizophrenia from healthy controls in terms of anticipatory pleasure deficits but not consummatory pleasure [131, 133]. However, there have been three reports [137, 222, 223] indicating that schizophrenia patients do not show an anticipatory pleasure deficit. Interestingly, the findings of Strauss et al. indicated that schizophrenia patients differed from matched healthy controls in terms of displaying deficits in consummatory pleasure, rather than anticipatory pleasure deficits. Cassidy et al. [222] found no difference in either anticipatory or consummatory pleasure between their psychotic patient sample and controls. It is noteworthy, however, that this sample included some patients with affective psychoses in addition to schizophrenia-spectrum patients.

Supportive evidence for the convergent validity of the TEPS-ANT comes from reports of its associations with other established measures. In schizophrenia patients, TEPS-ANT scores have been associated negatively with PAS scores and RSAS scores [131, 136, 137] as well as significantly and positively associated with SANS ratings of anhedonia [131] and PANSS emotional discomfort symptom ratings [135]. Scores on the TEPS-ANT have also been found to be significantly related to scores on the Carver and White [224] Behavioral Activation Scale (BAS) [19, 131, 137] in schizophrenia patients. In controls, TEPS-ANT scores correlate negatively with the PAS [19, 136, 137] and RSAS [136], and positively with the BAS [19, 137] and the Fawcett-Clark Pleasure Scale scores [19].

There is also evidence for the validity of the TEPS-CONS. As expected, there is a somewhat different pattern of associations for the TEPS-CONS, compared to the TEPS-ANT. In schizophrenia patients, scores on the TEPS-CONS are significantly and negatively associated with the PAS [131, 136, 137] and the RSAS [136]. TEPS-CONS scores have also correlated with positive symptom ratings in schizophrenia patients [135] and BAS scores [137]. In controls, the TEPS-CONS correlates significantly and positively with the BAS [19, 137] and Fawcett-Clark Pleasure Scale [19] and significantly and negatively with the PAS [19, 34, 137]. Findings regarding the relationship between the TEPS-CON and the RSAS in nonpatient samples are mixed; there are positive reports of a negative association [34, 136] along with reports of no significant association between the two scales [19, 137].

Overall, there is considerable enthusiasm for the TEPS, because of its sound psychometric properties and its relative brevity. However, the measure has been criticized for its scant item coverage of social anhedonia [130, 137]. In summary, the major contribution of the TEPS is that it makes a clear distinction consummatory pleasure and anticipatory pleasure.

2.3.2.7 Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)

The ACIPS [33, 61] was specifically designed to measure individuals' ability to look forward to interactions with other people (anticipatory social pleasure) as well as their ability to experience pleasure about social/interpersonal interactions when they occurred (consummatory social pleasure). It is a self-report measure composed

of 17 (7 anticipatory and 10 consummatory) items that are scored on a 6-point Likert scale (ranging from *very false for me* to *very true for me*). Abnormally low scores are interpreted as indicating social anhedonia, a decreased interest or deficit in pleasure in interpersonal stimuli, interactions, and situations. Given the developers' conceptualization of social anhedonia as an individual differences trait that is distributed dimensionally throughout the population, the ACIPS was constructed for administration to nonclinical as well as clinical (at-risk, patient) populations. The measure is relatively new; empirical efforts to derive norms for various populations are ongoing. To date, research findings indicate high internal validity (coefficient alpha = 0.86) for two independent samples [33, 34]. Test-retest reliability was 0.78 for 496 subjects with an interval between testings of 5–8 weeks [33].

Scores on the ACIPS have been observed to be significantly and positively associated with reward responsiveness, as measured by the BAS [33] , and anticipatory and consummatory pleasure, as measured by the TEPS [33, 34]. Scores on the ACIPS were negatively associated with social anhedonia and physical anhedonia scales. Within a group of patients with broadly-defined schizophrenia-spectrum disorder, the anticipatory and consummatory subscales of the ACIPS were significantly and negatively associated with PANSS social withdrawal and social avoidance symptoms, respectively [138]. To date, individuals with psychometric schizotypy score lower on the ACIPS than nonschizotypal individuals. Preliminary findings indicate that individuals with broadly-defined schizophrenia-spectrum disorders reported significantly less social-interpersonal pleasure in both the anticipatory and consummatory domains, in comparison with the control group [138]. At present, factor analysis of ACIPS data from undergraduate samples did not distinguish between temporal aspects of interpersonal pleasure, though there was clear support for distinction between factors related to general versus more intimate aspects of social/interpersonal pleasure. Larger patient samples are needed to examine the factor structure of the ACIPS in clinical populations. These preliminary findings indicate that the ACIPS is a reliable and valid way to assess hedonic capacity for social interaction and interpersonal engagement in both clinical and non-clinical samples.

2.4 Conclusions and Future Directions

The construct of anhedonia, as the reduction of pleasure, has a long history in descriptive and experimental psychopathology. With the advent of neuroimaging, and advances in our understanding of affective neuroscience, the construct of anhedonia has broadened considerably. One of the advances in affective neuroscience has been the distinction between appetitive pleasure versus consummatory pleasure. Thus, anhedonia is now described not only in terms of content domains, but also in terms of its temporal components. Increasingly, measures of negative symptoms involve asking respondents to distinguish between their future-oriented (i.e., anticipated) experiences and their actual participatory (i.e., consummatory) experiences.

Issues regarding the conceptualization of anhedonia remain, which in turn, present challenges for its assessment. There are strong arguments in favor of a dimensional approach to anhedonia. Anhedonia is seen in healthy individuals, at-risk subclinical states and clinical syndromes [24]. However, it is unclear whether the anhedonia observed in patient groups is qualitatively different from that observed in individuals in the general population. Thus far, few studies have addressed this issue, and most of the available measures for assessing anhedonia have been validated for patients with schizophrenia. It is unclear whether some of the newer instruments are sufficiently sensitive to detect mild variations in anhedonia that may be present in the general population as well as in at-risk subclinical groups.

Although there appears to be empirical evidence for an association between anhedonia and schizotypy, many investigators question whether anhedonia is best thought of as an individual difference across individuals with schizophrenia, or whether anhedonia characterizes a specific subtype of schizophrenia [24, 40]. While anhedonia is not observed in all patients with schizophrenia, it is observed in a sizable proportion of them, as well as their first-degree relatives. We are intrigued by the special relationship between schizotypy and anhedonia. To that end, we have identified several research questions:

(a) Is the anhedonia experienced by individuals in the schizophrenia-spectrum qualitatively different from that experienced by individuals with other disorders, and if so, in what way(s)? That is, is there a continuum of anhedonia frequency and intensity across disorders?
(b) When in the developmental ontogeny of the schizophrenia-spectrum disorder, does anhedonia first become manifest? Do the manifestations of anhedonia change over the life-course? How can we use this knowledge about anhedonia to better inform our interventions, especially in terms of early intervention work?
(c) What is the best way to parse the anhedonia deficit experienced by many individuals in the schizophrenia-spectrum?
(d) Given the often limited experience of individuals at the more severe end of the schizophrenia spectrum, are the current measures assaying the right types of experiences? That is, how sensitive are they to the variations in patients' range of interpersonal experiences? Patients vary in terms of romantic histories, size and quality of social networks, which may or may not correlate with the age of onset of their schizophrenia-spectrum disorder.
(e) How might extant accounts for anhedonia in schizophrenia-spectrum disorders help us understand shared mechanisms with other brain disorders (e.g., major depression, bipolar disorder)?
(f) How might understanding of anhedonia in schizophrenia-spectrum disorders help elucidate the heterogeneity within the spectrum?

At present, there are several measurement instruments available for clinicians and researchers to document the presence, frequency, and severity of anhedonia symptoms and traits. The SANS is perhaps one of the best known and most widely used measures of schizophrenic symptoms. It differs from the other interview-based

measures in that it combines anhedonia and asociality into one subscale. There may be some advantages to this practice, given that anhedonia appears to be a multidimensional construct, whereas asociality seems to be taxonic in nature [184]. Moreover, the extent to which anhedonia and asociality can be differentiated in social anhedonia is unclear.

In contrast to the SANS, both the two new interview-based assessments of negative symptoms, namely, the CAINS and the BNSS, distinguish between social anhedonia and asociality. Anticipatory and consummatory aspects of pleasure are also distinguished from each other in the CAINS and BNSS. Across all three of the interview-based measures reviewed, anhedonia and avolition seem to be closely associated with each other. In the two newer interviews, anhedonia falls under the general Motivation and Pleasure factor. In the SANS, anhedonia-asociality and avolition are highly correlated with each other. It would be useful to gather evidence regarding whether the brain circuitry underlying avolition is distinction from the neural circuitry underlying the various components of hedonic experience, namely, anticipated, experienced, and remembered pleasure. One necessary future direction for this area would be to administer the newer measures to other patient populations. The CAINS and BNSS were pilot tested on schizophrenia outpatients. Nonetheless, it would be helpful to administer these measures to other patient populations, in order to determine the relative specificity of aspects of anhedonia to schizophrenia, as well as to accommodate the new conceptual framework of the RDoC [225].

The corpus of literature on the concurrent, predictive, and construct validity of the Chapman social anhedonia and physical anhedonia scales is impressive. Rather than attempt to shorten this measure which works so well empirically, it would seem prudent to take steps to improve upon its content validity by updating some of the items. This process of updating the items would be similar to what investigators have done with the MMPI. Despite its length, the MMPI [226] and the MMPI-2 [32] remain among the most widely used personality inventories clinically and in the research arena. The SPQ-BR appears to address many of the limitations of the earlier versions of the abbreviated SPQ, and may provide a quick alternative for those individuals interested in screening for schizotypal personality disorder. Fortunately, however, there appear to be other measures that appear to be more predictive assays of schizotypy and anhedonia.

The ESQUIZO-Q stands out among the extant self-report instruments as one of the sole measures of schizotypy developed for an adolescent sample. The psychometric data look promising, given the importance of early detection and the prognostic significance of anhedonia, it will be key for the developers of the measure to determine its external validity in terms of other cultural groups, as well as its relationship with other measures of hedonic capacity. Indeed, prior studies have indicated the predictive value of anhedonia during adolescence in at-risk individuals [147].

Both the TEPS and ACIPS appear to be promising measures of hedonic capacity in both clinical and nonclinical populations. The TEPS may be limited by its relative paucity of items pertaining to social pleasure. Although there is some question regarding whether the temporal aspects of pleasure can be reliably distinguished in

the ACIPS, its strength appears to be in its focus on social/interpersonal pleasure. However, given the brevity of these two measures, there may be some incremental value in administering them jointly. Together the TEPS and ACIPS form a complementary set of 35 items that could provide an assessment of both temporal aspects and content domains related to anhedonia.

Based on this review, it appears that anhedonia can be assessed in a reliable and valid manner in individuals with a schizophrenia-spectrum disorder, using either a clinical interview or a self-report questionnaire. Depending upon the measure chosen, one could describe the relative amount and severity of the self-reported anhedonia. However, it might be difficult to discern the underlying cause of the anhedonia, and to determine whether the anhedonia was primary or secondary to medication or an environmental factor. For example, an individual with a schizophrenia-spectrum disorder may have a low level of actual participatory experiences in pleasurable events due to lack of finances, lack of opportunity, lack of social skills, or lack of actual desire to engage in the pleasurable experience; only the last of these possible reasons truly constitutes consummatory anhedonia. Similarly, an individual with a schizophrenia-spectrum disorder may express reduced anticipatory pleasure due to an inability to predict future events, secondary to impaired encoding-retrieval for positive stimuli and events [21], a lack of experience with the pleasurable events, or an inability to pair positive valence with the stimulus [22]. It is not clear how one disentangles the different underlying causes for self-reported anhedonia.

Ideally, the selection of assessment instrument should be guided by one's clinical and/or research question. That is, the type of measure chosen will depend in part on the population of interest, the assessment question, and the context (e.g., clinical trial, family study or genetic study, risk screening, etc.). For the purpose of clinical trials, in order to test the effectiveness of a pharmaceutical agent or psychosocial intervention, a brief measure that is temporally reliable yet sensitive to clinical changes and includes fine-grained distinctions between various aspects of pleasure would be advantageous. On the basis of these criteria, the SANS and BNSS seem best suited for clinical trials. If one's goal is to detect heightened risk for the later development of a schizophrenia-spectrum disorder, it would seem more prudent to opt for thoroughness rather than brevity, and select a measure that assesses trait-anhedonia. It would be important to select a measure that not only reliably distinguishes between patients and nonpatient controls, but one that also has demonstrated predictive validity. Furthermore, it would be best to look for an instrument that successfully distinguishes first-degree relatives of schizophrenia probands from relatives of healthy controls. On the basis of these criteria, it appears that the PAS and RSAS are best suited for inclusions in family studies of anhedonia, as well as studies for risk prediction. The ESQUIZO-Q looks promising for use with adolescents; the Chapman scales are not appropriate for this age group.

One pressing need that this review revealed was the need for more cross-cultural research, in order to analyze the measurement invariance of anhedonia profiles across different samples. Accompanying this of course is the need for increased translation efforts; the early intervention research area would likely benefit from

developmentally-appropriate measures such as the ESQUIZO-Q. In addition to studying different ages, examination of possible gender, cultural, and/or ethnic differences may provide greater insights into how best to parse the construct of anhedonia.

Advances in new measurement models and statistical procedures, such as IRT, or computerized adaptive testing (CAT), have not yet been used to advantage in the study of individual differences in, anhedonia and the ability to experience pleasure. As a complement to classical test theory, the IRT framework could resolve some of the limitations present in the anhedonia field [227, 228]. IRT models can be useful for the interpretation of test scores and for directly comparing scores obtained by different scales or self-reports which measure the same construct (i.e. ordinal scales). Moreover, through IRT, an Item Characteristic Curve is constructed for each item. This curve, or trace line, reflects the probability of the person's response to each item and his/her level on the latent construct (e.g., anhedonia) measured by the scale. Furthermore, IRT allows us to estimate the contribution each item makes to the assessment for each level of the latent construct; this is known as the Information Function. Recent work has used the IRT framework in the assessment of anhedonia and negative symptoms [53, 188].

Another application of IRT is computerized adaptive testing (CAT) [229]. In CAT each item is dynamically selected from a pool of items until a pre-specified measurement precision is reached. CAT successively selects items in order to maximize the precision of the measurement instrument based on what is known about the person from previous items. The essential idea is that when adjusting the items to the competency (or latent trait) of the test taker, once these are calibrated according to an IRT model far fewer items are needed to assess individuals with precision in comparison to paper-and-pencil tests. Thus, items and time are saved through the use of precision and efficiency. Our research group has preliminary data which suggests that CAT can be used effectively to evaluate schizotypy in non-clinical adolescents [230]. Future research efforts should be invested in applying this IRT-based technique to the study of anhedonia.

In summary, since 2005, the schizophrenia field has been experiencing a Renaissance in terms of the assessment of negative symptoms, particularly anhedonia. Several new measures were developed which differ in potentially interesting and important ways. The CAINS and the BNSS are new interview-based measures, whereas the ESQUIZO-Q, TEPS, MAP-SR and ACIPS are recent self-report questionnaires. We are encouraged by these new developments and hope that they can be harnessed in order to lend further insights regarding the special relationship between anhedonia and schizotypy and ameliorate the lives of those affected by schizophrenia and schizophrenia-spectrum disorders.

Acknowledgments This research was funded by the Spanish Ministry of Science and Innovation (MICINN), by the *Instituto Carlos III*, *Centro de Investigación Biomédica en Red de Salud Mental* (Center for Biomedical Research in the Mental Health Network, CIBERSAM). Project references: PSI 2011–28638 and PSI 2011–23818.

The first and second authors contributed equally to this chapter.

References

1. van Os J, Kapur, S. Schizophrenia. Lancet. 2009;374:636–45.
2. Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. Schizophr Res. 2013;150:3–10. doi:pii: S0920-9964(13)00283-1. 10.1016/j.schres.2013.05.028.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
4. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67–76.
5. Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, et al. The economic burden of schizophrenia in the United States in 2002. J Clin Psychiatry. 2005;66:1122–9.
6. Mangalore R, Knapp M. Cost of schizophrenia in England. J Ment Health Policy Econ. 2007;10:23–41.
7. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007;64:1123–31.
8. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000;284:2606–10.
9. Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull. 2000;26:903–12.
10. Ritsner MS, Arbitman M, Lisker A. Anhedonia is an important factor of health-related quality-of-life deficit in schizophrenia and schizoaffective disorder. J Nerv Ment Dis. 2011;199:845–53.
11. Meehl PE. Schizotaxia, schizotypy, schizophrenia. Am Psychol. 1962;17(12):827–38.
12. Ribot TH. The psychology of emotions. London: Scott; 1987.
13. Ho N, Sommers M. Anhedonia: a concept analysis. Arch Psychiatr Nurs. 2013;27:121–9.
14. Rado S. Psychoanalysis of behavior: the collected papers of Sandor Rado. New York: Grune & Stratton; 1962.
15. Rado S. Dynamics and classification of disorder behavior. Am J Psychiatry. 1953;110: 406–16.
16. Meehl PE. Schizotaxia revisited. Arch Gen Psychiatry. 1989;46(10):935–44.
17. Chapman JP, Chapman LJ, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;87:374–82.
18. Klein D. Depression and anhedonia. In: Clark D, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1984. p. 1–34.
19. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40(6):1086–102.
20. Berridge KC, Robinson TE. Parsing reward. Trends Neurosci. 2003;26(9):507–13.
21. Cohen AS, Najolia GM, Brown LA, Minor KS. The state-trait disjunction of anhedonia in schizophrenia: potential affective, cognitive and social-based mechanisms. Clin Psychol Rev. 2011;31:440–8.
22. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull. 2008;34:835–47.
23. Kirkpatrick B, Fenton WS, Carpenter Jr WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006;32(2):214–9.
24. Kaiser S, Heekeren K, Simon JJ. The negative symptoms of schizophrenia: category or continuum? Psychopathology. 2011;44:345–53.
25. Blanchard JJ, Horan WP, Brown SA. Diagnostic differences in social anhedonia: a longitudinal study of schizophrenia and major depressive disorder. J Abnorm Psychol. 2001;110:363–71.
26. Hatzigiakoumis DS, Martinotti G, Giannantonio MD, Janiri L. Anhedonia and substance dependence: clinical correlates and treatment options. Fr Psychiatry. 2011;17(2):10.
27. Martinotti G, Nicola MD, Reina D, Andreoli S, Focà F, Cunniff A, et al. Alcohol protracted withdrawal syndrome: the role of anhedonia. Subst Use Misuse. 2008;43:271–84.

28. Gooding DC, Gjini K, Burroughs SA, Boutros NN. The association between psychosis-proneness and sensory gating in cocaine-dependent patients and healthy controls. Psychiatry Res. 2013;210:1092–100.
29. Chevallier C, Grèzes J, Molesworth C, Berthoz S, Happé F. Brief report: selective social anhedonia in high functioning autism. J Autism Dev Disord. 2012;42:1504–9.
30. Tchanturia K, Davies H, Harrison A, Fox JR, Treasure J, Schmidt U. Altered social hedonic processing in eating disorders. Int J Eat Disord. 2012;45:962–9.
31. Wechsler-Zimring A, Kearney CA. Posttraumatic stress and related symptoms among neglected and physically and sexually maltreated adolescents. J Trauma Stress. 2011;24:601–4.
32. Butcher JN, Dahlstrom WG, Graham JR, Tellegen A, Kaemmer B. The Minnesota multiphasic personality inventory-2 (MMPI-2): manual for administration and scoring. Minneapolis: MN University of Minnesota Press; 1989.
33. Gooding DC, Pflum MJ. The assessment of interpersonal pleasure: introduction of the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) and preliminary findings. Psychiatry Res. 2013. doi:10.1016/j.psychres.2013.10.012.
34. Gooding DC, Pflum MJ. The assessment of interpersonal pleasure II: further validation of the ACIPS as a measure of social hedonic experience. Psychiatry Res. 2013. doi: 10.1016/j.psychres.2013.11.009.
35. Herbener ES, Harrow M. The course of anhedonia during 10 years of schizophrenia illness. J Abnorm Psychol. 2002;111:237–48.
36. Meehl PE. Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. J Personal Disord. 1990;4(1):1–99.
37. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:22.
38. Kraepelin E. Dementia praecox and paraphrenia. New York: Robert E. Krieger; 1971.
39. Bleuler E. Dementia praecox or the group of schizophrenias. New York: International Universities Press (Trad. 1950); 1911.
40. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32:259–73.
41. Kane JM. Tools to assess negative symptoms in schizophrenia. J Clin Psychiatry. 2013;74:e12. doi:10.4088/JCP.12045tx2c.
42. Andreasen NC. The scale for the assessment of negative symptoms (SANS). Iowa City: The University of Iowa; 1983.
43. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–76.
44. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry. 2013;170:165–72.
45. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull. 2011;37(2):300–5.
46. McGlashan TH, Miller TJ, Woods SW, Rosen JL, Hoffman RE, Davidson L. Structured interview for prodromal syndromes. New Haven: PRIME Research Clinic, Yale School of Medicine; 2001.
47. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr Bull. 2006;32(2):238–45.
48. Mueser KT, Sayers SL, Schooler NR, Mance RM, Haas GL. A multisite investigation of the reliability of the scale for the assessment of negative symptoms. Am J Psychiatry. 1994;151(10):1453–62.
49. Norman RMG, Malla AK, Cortese L, Diaz F. A study of the interrelationship between and comparative interrater reliability of the SAPS, SANS and PANSS. Schizophr Res. 1996;19(1):73–85.
50. Levine SZ, Leucht S. Psychometric analysis in support of shortening the scale for the assessment of negative symptoms. Eur Neuropsychopharmacol. 2013;23:1051–6.

51. Forbes C, Blanchard JJ, Bennett M, Horan WP, Kring A, Gur R. Initial development and preliminary validation of a new negative symptom measure: the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr Res. 2010;124(1–3):36–42.
52. Barch DM. The CAINS: theoretical and practical advances in the assessment of negative symptoms in schizophrenia. Am J Psychiatry. 2013;170:133–5.
53. Horan WP, Kring AM, Gur RE, Reise SP, Blanchard JJ. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr Res. 2011;132(2–3):140–5.
54. Strauss GP, Hong LE, Gold JM, Buchanan RW, McMahon RP, Keller WR, et al. Factor structure of the brief negative symptom scale. Schizophr Res. 2012;142(1–3):96–8.
55. Strauss GP, Keller WR, Buchanan RW, Gold JM, Fischer BA, McMahon RP, et al. Next-generation negative symptom assessment for clinical trials: validation of the brief negative symptom scale. Schizophr Res. 2012;142:88–92.
56. Park SG, Llerena K, McCarthy JM, Couture SM, Bennett ME, Blanchard JJ. Screening for negative symptoms: preliminary results from the self-report version of the Clinical Assessment Interview for Negative Symptoms. Schizophr Res. 2012;135(1–3):139–43.
57. Llerena K, Park SG, McCarthy JM, Couture SM, Bennett ME, Blanchard JJ. The Motivation and Pleasure Scale-Self-Report (MAP-SR): reliability and validity of a self-report measure of negative symptoms. Compr Psychiatry. 2013;54:568–74.
58. Eckblad M, Chapman LJ, Chapman JP, Mishlove M. The revised social anhedonia scale. Unpublished manuscript. Madison: University of Wisconsin; 1982.
59. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull. 1991;17:555–64.
60. Fonseca-Pedrero E, Muñiz J, Lemos-Giráldez S, Paino M, Villazón-García U. ESQUIZO-Q: Cuestionario Oviedo para la Evaluación de la Esquizotipia [ESQUIZO-Q: Oviedo questionnaire for schizotypy assessment]. Madrid: TEA ediciones; 2010.
61. Gooding DC, Pflum MJ. Anticipatory and consummatory interpersonal pleasure scale (ACIPS). Madison: University of Wisconsin; 2011.
62. Winterstein BP, Silvia PJ, Kwapil T, Kaufmann JC, Reiter-Palmon R, Wigert B. Brief assessment of schizotypy: developing short forms of the Wisconsin schizotypy scales. Personal Individ Differ. 2011;51:920–4.
63. Raine A, Benishay D. The SPQ-B: a brief screening instrument for schizotypal personality disorder. J Personal Disord. 1995;9:346–55.
64. Mason O, Claridge G, Jackson M. New scales for the assessment of schizotypy. Personal Individ Differ. 1995;18(1):7–13.
65. Mason O, Claridge G. The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): further description and extended norms. Schizophr Res. 2006;82(2):203–11.
66. Stefanis NC, Hanssen M, Smirnis NK, Avramopoulos DA, Evdokimidis IK, Stefanis CN, et al. Evidence that three dimensions of psychosis have a distribution in the general population. Psychol Med. 2002;32(2):347–58.
67. Linscott RJ, Knight RG. Potentiated automatic memory in schizotypy. Personal Individ Differ. 2004;37(7):1503–17.
68. Ritsner MS, Mar M, Arbitman M, Grinshpoon A. Symptom severity scale of the DSM5 for schizophrenia, and other psychotic disorders: diagnostic validity and clinical feasibility. Psychiatry Res. 2013;208:1–8.
69. Reininghaus U, Priebe S, Bentall RP. Testing the psychopathology of psychosis: evidence for a general psychosis dimension. Schizophr Bull. 2013;38:884–95. doi:10.1093/schbul/sbr182.
70. Peralta V, Cuesta MJ. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry Res. 1994;53:31–40.
71. Rodriguez-Jimenez R, Bagney A, Mezquita L, Martinez-Gras I, Sanchez-Morla EM, Mesa N, et al. Cognition and the five-factor model of the positive and negative syndrome scale in schizophrenia. Schizophr Res. 2013;143:77–83.
72. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. Schizophr Res. 2012;137:246–50.

73. Comparelli A, Savoja V, Kotzalidis GD, Woods SW, Mosticoni S, Vassallo F, et al. Factor-structure of the Italian version of the Scale of Prodromal Symptoms (SOPS): a comparison with the English version. Epidemiol Psychiatr Sci. 2011;20:45–54.
74. Lemos-Giráldez S, Vallina O, Fernández P, Ortega JA, García P, Gutiérrez A, et al. Validez predictiva de la escala de síntomas prodrómicos (SOPS) [Predictive validity of the Scale of Prodromal Symptoms (SOPS)]. Actas Esp Psiquiatr. 2006;34:216–33.
75. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Ventura J, McFarlane W, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003;29(4):703–15.
76. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, et al. Validity of the prodromal risk syndrome for first psychosis: findings from the north American prodrome longitudinal study. Schizophr Bull. 2009;35(5):894–908.
77. Hawkins KA, McGlashan TH, Quinlan D, Miller TJ, Perkins DO, Zipursky RB, et al. Factorial structure of the scale of prodromal symptoms. Schizophr Res. 2004;68(2–3):339–47.
78. Lencz T, Smith CW, Auther A, Correll CU, Cornblatt B. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. Schizophr Res. 2004;68:37–48.
79. Piskulic D, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, et al. Negative symptoms in individuals at clinical high risk of psychosis. Psychiatry Res. 2012;196:220–4.
80. Horan WP, Reise SP, Subotnik KL, Ventura J, Nuechterlein KH. The validity of psychosis proneness scales as vulnerability indicators in recent-onset schizophrenia patients. Schizophr Res. 2008;100:224–36.
81. Fonseca-Pedrero E, Paino M, Lemos-Giraldez S, Garcia-Cueto E, Villazon-Garcia U, Bobes J, et al. Psychometric properties of the revised physical and social anhedonia scales in non-clinical young adults. Span J Psychol. 2009;12(2):815–22.
82. Kwapil TR, Barrantes Vidal N, Silvia PJ. The dimensional structure of the Wisconsin schizotypy scales: factor identification and construct validity. Schizophr Bull. 2008;34:444–57.
83. Strauss GP, Horan WP, Kirkpatrick B, Fischer BA, Keller WR, Miski P, et al. Deconstructing negative symptoms of schizophrenia: avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. J Psychiatr Res. 2013;47:783–90.
84. Chapman JP, Chapman LJ, Kwapil TR. Scales for the measurement of schizotypy. In: Raine A, Lencz T, Mednick SA, editors. Schizotypal personality. New York: Cambridge University Press; 1995. p. 79–106.
85. Miettunen J, Veijola J, Isohanni M, Paunio T, Freimer N, Jääskeläinen E, et al. Identifying schizophrenia and other psychoses with psychological scales in the general population. J Nerv Ment Dis. 2011;199:230–8.
86. Meyer AD, Hautzinger M. Two-year stability of psychosis proneness scales and their relations to personality disorder traits. J Pers Assess. 1999;72:472–88.
87. Pope CA, Kwapil TR. Dissociative experiences in hypothetically psychosis-prone college students. J Nerv Ment Dis. 2000;188(8):530–6.
88. Ross SR, Lutz CJ, Bailley SE. Positive and negative symptoms of schizotypy and the five-factor model: a domain and facet level analysis. J Pers Assess. 2002;79(1):53–72.
89. Kwapil TR, Crump RA, Pickup DR. Assessment of psychosis proneness in African-American college students. J Clin Psychol. 2002;58(12):1601–14.
90. Lewandowski KE, Barrantes-Vidal N, Nelson-Gray RO, Clancy C, Kepley HO, Kwapil TR. Anxiety and depression symptoms in psychometrically identified schizotypy. Schizophr Res. 2006;83(2):225–35.
91. Gross GM, Silvia PJ, Barrantes-Vidal N, Kwapil TR. Psychometric properties and validity of short forms of the Wisconsin schizotypy scales in two large samples. Schizophr Res. 2012;134:267–72.
92. Kwapil TR, Brown LH, Silvia PJ, Myin-Germeys I, Barrantes-Vidal N. The expression of positive and negative schizotypy in daily life: an experience sampling study. Psychol Med. 2012;42:2555–66.

93. Chan RC, Wang Y, Yan C, Zhao Q, McGrath J, Hsi X, et al. A study of trait anhedonia in non-clinical Chinese samples: evidence from the Chapman scales for physical and social anhedonia. PLoS One. 2012;7:e34275.
94. Kwapil TR. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. J Abnorm Psychol. 1998;107(4):558–65.
95. Reise SP, Horan WP, Blanchard JJ. The challenges of fitting an item response theory model to the social anhedonia scale. J Pers Assess. 2011;93:213–24.
96. Graves RE, Weinstein S. A Rasch analysis of three of the Wisconsin scales of psychosis proneness: measurement of schizotypy. J Appl Meas. 2004;5(5):160–71.
97. Horan WP, Brown SA, Blanchard JJ. Social anhedonia and schizotypy: the contribution of individual differences in affective traits, stress, and coping. Psychiatry Res. 2007;149(1–3):147–56.
98. Rawlings D, Williams B, Haslam N, Claridge G. Taxonometric analysis support a dimensional latent structure for schizotypy. Pers Individ Differ. 2008;44(8);1640–51.
99. Blanchard JJ, Collins LM, Aghevli M, Leung WW, Cohen AS. Social anhedonia and schizotypy in a community sample: the Maryland longitudinal study of schizotypy. Schizophr Bull. 2011;37:587–602.
100. Compton MT, Goulding SM, Bakeman R, McClure-Tone EB. Confirmation of a four-factor structure of the schizotypal personality questionnaire among undergraduate students. Schizophr Res. 2009;111:46–52.
101. Cohen AS, Matthews RA, Najolia GM, Brown LA. Toward a more psychometrically sound brief measure of schizotypal traits: introducing the SPQ-brief revised. J Personal Disord. 2010;24:516–37.
102. Chmielewski M, Watson D. The heterogeneous structure of schizotypal personality disorder: item-level factors of the schizotypal personality questionnaire and their associations with obsessive-compulsive disorder symptoms, dissociative tendencies, and normal personality. J Abnorm Psychol. 2008;117:364–76.
103. Wuthrich VM, Bates TC. Confirmatory factor analysis of the three-factor structure of the schizotypal personality questionnaire and Chapman schizotypy scales. J Pers Assess. 2006;87(3):292–304.
104. Fossati A, Raine A, Carretta I, Leonardi B, Maffei C. The three-factor model of schizotypal personality: invariance across age and gender. Personal Individ Differ. 2003;35:1007–19.
105. Salokangas RK, Dingemans P, Heinimaa M, Svirskis T, Luutonen S, Hietala J, et al. Prediction of psychosis in clinical high-risk patients by the schizotypal personality questionnaire. Results of the EPOS project. Eur Psychiatry. 2013;28:469–75.
106. Stefanis NC, Vitoratou S, Ntzoufras I, Smyrnis N, Evdokimidis I, Stefanis CN. Psychometric properties of the Greek version of the Schizotypal Personality Questionnaire (SPQ) in young male obligatory conscripts: a two years test-retest study. Personal Individ Differ. 2006;41(7):1275–86.
107. Debbané M, Badoud D, Balanzin D, Eliez S. Broadly defined risk mental states during adolescence: disorganization mediates positive schizotypal expression. Schizophr Res. 2013;147:153–6.
108. Morrison AP, French P, Lewis S, Roberts M, Raja S, Neil S, et al. Psychological factors in people at ultra-high risk of psychosis: comparison with non-patients and associations with symptoms. Psychol Med. 2006;36:1395–404.
109. Lin A, Wigman JT, Nelson B, Wood SJ, Vollebergh WA, van Os J, et al. Follow-up factor structure of schizotypy and its clinical associations in a help-seeking sample meeting ultra-high risk for psychosis criteria at baseline. Compr Psychiatry. 2013;54:173–80.
110. Cella M, Serra M, Lai A, Mason OJ, Sisti D, Rocchi MB, et al. Schizotypal traits in adolescents: links to family history of psychosis and psychological distress. Eur Psychiatry. 2013;28:247–53.
111. Barrantes-Vidal N, Gómez-de-Regil L, Navarro B, Vicens-Vilanova J, Obiols J, Kwapil T. Psychotic-like symptoms and positive schizotypy are associated with mixed and ambiguous handedness in an adolescent community sample. Psychiatry Res. 2013;206:188–94.

112. Corcoran R, Devan K, Durrant S, Liddle P. The relationship between schizotypal ideation and subjective cognition reflects more than just cognitive disorganisation: introducing the brief cognitive schizotypy index. Cognit Neuropsychiatry. 2013;18:491–514. doi:10.1080/13546805.2012.747431.
113. Kocsis-Bogár K, Miklósi M, Forintos DP. Impact of adverse life events on individuals with low and high schizotypy in a nonpatient sample. J Nerv Ment Dis. 2013;201:208–15.
114. Cochrane M, Petch I, Pickering AD. Do measures of schizotypal personality provide non-clinical analogues of schizophrenic symptomatology? Psychiatry Res. 2010;176:150–4.
115. Grant P, Kuepper Y, Mueller EA, Wielpuetz C, Mason O, Hennig J. Dopaminergic foundations of schizotypy as measured by the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)-a suitable endophenotype of schizophrenia. Front Hum Neurosci. 2013;7:1–11. doi:10.3389/fnhum.2013.00001.
116. Álvarez-Moya EM, Barrantes-Vidal N, Navarro JB, Subira S, Obiols JE. Exophenotypical profile of adolescents with sustained attention deficit: a 10-year follow-up study. Psychiatry Res. 2007;153(2):119–30.
117. Konings M, Bak M, Hanssen M, van Os J, Krabbendam L. Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatr Scand. 2006;114:55–61.
118. Fonseca-Pedrero E, Paino M, Lemos-Giráldez S, Muñiz J. Validation of the Community Assessment Psychic Experiences -42 (CAPE-42) in Spanish college students and patients with psychosis. Actas Esp Psiquiatr. 2012;40:169–76.
119. Barragan M, Laurens KR, Navarro JB, Obiols JE. Psychotic-like experiences and depressive symptoms in a community sample of adolescents. Eur Psychiatry. 2011;26:396–401.
120. Yung AR, Nelson B, Baker K, Buckby JA, Baksheev G, Cosgrave EM. Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia. Aust N Z J Psychiatry. 2009;43:118–28.
121. Hanssen M, Krabbendam L, Vollema M, Delespaul P, Van Os J. Evidence for instrument and family-specific variation of subclinical psychosis dimensions in the general population. J Abnorm Psychol. 2006;115(1):5–14.
122. Mossaheb N, Becker J, Schaefer MR, Klier CM, Schloegelhofer M, Papageorgiou K, et al. The Community Assessment of Psychic Experience (CAPE) questionnaire as a screening-instrument in the detection of individuals at ultra-high risk for psychosis. Schizophr Res. 2012;141:210–4.
123. Pfeifer S, van Os J, Hanssen M, Delespaul P, Krabbendam L. Subjective experience of cognitive failures as possible risk factor for negative symptoms of psychosis in the general population. Schizophr Bull. 2009;35:766–74.
124. Linscott RJ. The latent structure and coincidence of hyphedonia and schizotypy and their validity as indices of psychometric risk for schizophrenia. J Personal Disord. 2007;21:225–42.
125. Fonseca-Pedrero E, Linscott RJ, Lemos-Giráldez S, Paino M, Muñiz J. Psychometric properties of two measures for the assessment of schizotypy in adolescents. Psychiatry Res. 2010;179:165–70.
126. Fonseca-Pedrero E, Paino M, Lemos-Giráldez S, Villazón-García U, García-Cueto E, Bobes J, et al. Versión reducida del Cuestionario TPSQ de Estilos Perceptuales y de Pensamiento [A reduced version of Thinking and Perceptual Style Questionnaire (TPSQ)]. Psicothema. 2009;21:499–505.
127. Paino MM, Fonseca-Pedrero E, Lemos-Giráldez S, Muñiz J. Dimensionality of schizotypy in young people according to sex and age. Personal Individ Differ. 2008;45:132–8.
128. Fonseca-Pedrero E, Lemos-Giráldez S, Paino M, Muñiz J. Schizotypy, emotional-behavioural problems and personality disorder traits in a non-clinical adolescent population. Psychiatry Res. 2011;190:316–21.
129. Fonseca-Pedrero E, Lemos-Giráldez S, Paino M, Santarén-Rosell M, Sierra-Baigrie S, Muñiz J. Reliability and sources of validity evidence of the Oviedo schizotypy assessment questionnaire-abbreviated (ESQUIZO-Q-A). Span J Psychol. 2012;15:840–9.

130. Gooding DC, Pflum MJ. The nature of diminished pleasure in individuals at risk for or affected by schizophrenia. Psychiatry Res. 2012;198:172–3.
131. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93(1–3):253–60.
132. Chan RCK, Wang Y, Huang J, Shi Y, Hong X, Ma Z, et al. Anticipatory and consummatory components of the experience of pleasure in schizophrenia: cross-cultural validation and extension. Psychiatry Res. 2010;175(1–2):181–3.
133. Favrod J, Ernst F, Giuliani F, Bonsack C. Validation of the temporal experience of pleasure scale (TEPS) in a French-speaking environment. Encéphale. 2009;35:241–8.
134. Chan RC, Shi YF, Lai MK, Wang YN, Wang Y, Kring AM. The Temporal Experience of Pleasure Scale (TEPS): exploration and confirmation of factor structure in a healthy Chinese sample. PLoS One. 2012;7:e35352.
135. Buck B, Lysaker PH. Consummatory and anticipatory anhedonia in schizophrenia: stability, and associations with emotional distress and social function over six months. Psychiatry Res. 2013;205:30–5.
136. Loas G, Monestes J-L, Ameller A, Bubrovskzky M, Yon V, Wallier J, et al. Psychometric properties of the French version of the Temporal Experience of Pleasure Scale (TEPS): study on 125 university students and on 162 psychiatric subjects. Ann Med Psychol. 2009;167:641–8.
137. Strauss GP, Wilbur RC, Warren KR, August SM, Gold JM. Anticipatory vs. consummatory pleasure: what is the nature of hedonic deficits in schizophrenia? Psychiatry Res. 2011;187(1–2):36–41.
138. Trachik BJ, Gooding DC, Chan CC, Kadison L, Puentes C, Bedwell JS. Subtypes of anhedonia in broadly defined schizophrenia spectrum disorders. Schizophr Bull. 2013;39:S25.
139. Pflum MJ, Gooding DC. The ACIPS: a scale to assess interpersonal pleasure. Poster presentation at the 22nd annual meeting of the Society for Research in Psychopathology. Ann Arbor, MI, USA; 2008.
140. Chapman LJ, Chapman JP. Revised physical anhedonia scale (Available from L. J. Chapman). Madison: Department of Psychology, University of Wisconsin; 1978.
141. Burbridge JA, Barch DM. Anhedonia and the experience of emotion in individuals with schizophrenia. J Abnorm Psychol. 2007;116:30–42.
142. Kontaxakis VP, Kollias CT, Havaki-Kontaxaki BJ, Margariti MM, Stamouli SS, Petridou E, et al. Physical anhedonia in the acute phase of schizophrenia. Ann Gen Psychiatry. 2006;5:1–5.
143. Schürhoff F, Szöke A, Bellivier F, Turcas C, Villermur M, Tigmol J, et al. Anhedonia in schizophrenia: a distinct familial subtype? Schizophr Res. 2003;61:59–66.
144. Horan WP, Green MF, Kring AM, Nuechterlein KH. Does anhedonia in schizophrenia reflect faulty memory for subjectively experienced Emotions? J Abnorm Psychol. 2006;115:496–508.
145. Katsanis J, Iacono WG, Beiser M. Anhedonia and perceptual aberration in first episode psychotic patients and their relatives. J Abnorm Psychol. 1990;99:202–6.
146. Blanchard JJ, Horan WP, Collins LM. Examining the latent structure of negative symptoms: is there a distinct subtype of negative symptom schizophrenia? Schizophr Res. 2005;77(2–3):151–65.
147. Freedman LR, Rock D, Roberts SA, Cornblatt BA, Erlenmeyer-Kimling L. The New York high-risk project: attention, anhedonia and social outcome. Schizophr Res. 1998;30(1):1–9.
148. Franke P, Maier W, Hardt J, Hain C. Cognitive functioning and anhedonia in subjects at risk for schizophrenia. Schizophr Res. 1993;10(1):77–84.
149. Clementz BA, Grove WM, Katsanis J, Iacono WG. Psychometric detection of schizotypy: perceptual aberration and physical anhedonia in relatives of schizophrenics. J Abnorm Psychol. 1991;100(4):607–12.
150. Grove WM, Lebow BS, Clementz BA, Cerri A. Familial prevalence and coaggregation of schizotypy indicators: a multitrait family study. J Abnorm Psychol. 1991;100(2):115–21.

151. Glatt SJ, Stone WS, Faraone SV, Seidman LJ, Tsuang MT. Psychopathology, personality traits and social development of young first-degree relatives of patients with schizophrenia. Br J Psychiatry. 2006;189:337–45.
152. Kuha A, Suvisaari JM, Perala J, Eerola M, Saarni S, Partonen T, et al. Associations of anhedonia and cognition in persons with schizophrenia spectrum disorders, their siblings, and controls. J Nerv Ment Dis. 2011;199:30–7.
153. Fanous A, Gardner C, Walsh D, Kendler KS. Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. Arch Gen Psychiatry. 2001;58:669–73.
154. Blanchard C, Mueser KT, Bellack AS. Anhedonia, positive and negative affect, and social functioning in schizophrenia. Schizophr Bull. 1998;24:413–24.
155. Herbener ES, Harrow M, Hill SK. Change in the relationship between anhedonia and functional deficits over 20-year period in individuals with schizophrenia. Schizophr Res. 2005;75:97–105.
156. Loas G, Noisette C, Legrand A, Boyer P. Is anhedonia a specific dimension in chronic schizophrenia? Schizophr Bull. 2000;26(2):495–506.
157. Meyer TD, Keller F. Exploring the latent structure of the perceptual aberration, magical ideation, and physical anhedonia scales in a German sample. J Personal Disord. 2001;15(6):521–35.
158. Gooding DC, Miller MD. Nailfold capillary plexus visibility in relation to schizotypy. Schizophr Res. 1998;32(3):207–12.
159. Gooding DC. Antisaccade task performance in questionnaire-identified schizotypes. Schizophr Res. 1999;35(2):157–66.
160. Gooding DC, Miller MD, Kwapil TR. Smooth pursuit eye tracking and visual fixation in psychosis-prone individuals. Psychiatry Res. 2000;93(1):41–54.
161. Soliman A, O'Driscoll GA, Pruessner J, Holahan AL, Boileau I, Gagnon D, et al. Stress-induced dopamine release in humans at risk of psychosis: a [11C] raclopride PET study. Neuropsychopharmacology. 2008;33:2033–41.
162. Harvey P-O, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry. 2007;12:767–75.
163. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. PLoS One. 2012;7(5):e35622.
164. Brown LH, Silvia PJ, Myins-Germeys I, Lewandowski KE, Kwapil TR. The relationship of social anxiety and social anhedonia to psychometrically identified schizotypy. J Soc Clin Psychol. 2008;27(2):127–49.
165. Cohen AS, Matthews RA. Primary and secondary negative schizotypal traits in a large non-clinical sample. Personal Individ Differ. 2010;49(5):419–24.
166. Gooding DC, Davidson RJ, Putnam KM, Tallent KA. Normative emotion-modulated startle response in individuals at risk for schizophrenia-spectrum disorders. Schizophr Res. 2002;57(1):109–20.
167. Gooding DC, Tallent KA, Matts CW. Clinical status of at-risk individuals 5 years later: further validation of the psychometric high-risk strategy. J Abnorm Psychol. 2005;114(1):170–5.
168. Kerns JG. Schizotypy facets, cognitive control, and emotion. J Abnorm Psychol. 2006;115(3):418–27.
169. Baslet G, Termini L, Herbener E. Deficits in emotional awareness in schizophrenia and their relationship with measures of functioning. J Nerv Ment Dis. 2009;197:655–60.
170. Zhornitsky S, Rizkallah E, Pampoulova T, Chiasson JP, Lipp O, Stip E, et al. Sensation-seeking, social anhedonia, and impulsivity in substance use disorder patients with and without schizophrenia and in non-abusing schizophrenia patients. Psychiatry Res. 2012;200:237–41.
171. Kollias CT, Kontaxakis VP, Havaki-Kontaxaki BJ, Stamouli S, Margarit M, Petridou E. Association of physical and social anhedonia with depression in the acute phase of schizophrenia. Psychopathology. 2008;41:365–70.

172. Bailey B, West KY, Widiger TA, Freiman K. The convergent and discriminant validity of the Chapman scales. J Pers Assess. 1993;61(1):121–35.
173. Carver JC, Pogue-Geile MF. Familial liability to schizophrenia: a sibling study of negative symptoms. Schizophr Bull. 1999;25:827–39.
174. Mishlove M, Chapman LJ. Social anhedonia in prediction of psychosis proneness. J Abnorm Psychol. 1985;94:384–96.
175. Camisa KM, Bockbrader MA, Lysaker PH, Rae LL, Brenner CA, O'Donnell BF. Personality traits in schizophrenia and related personality disorders. Psychiatry Res. 2005;133(1):23–33.
176. Kendler KS, Thacker L, Walsh D. Self-report measures of schizotypy as indices of familial vulnerability to schizophrenia. Schizophr Bull. 1996;22(3):511–20.
177. Gooding DC, Kwapil TR, Tallent KA. Wisconsin card sorting test deficits in schizotypic individuals. Schizophr Res. 1999;40(3):201–9.
178. Gooding DC, Tallent KA. Spatial, object, and affective working memory in social anhedonia: an exploratory study. Schizophr Res. 2003;63:247–60.
179. Gooding DC, Braun JG. Visuoconstructive performance, implicit hemispatial inattention, and schizotypy. Schizophr Res. 2004;68(2):261–9.
180. Gooding DC, Shea HB, Matts CW. Saccadic performance in questionnaire-identified schizotypes over time. Psychiatry Res. 2005;133:173–86.
181. Daly MP, Gooding DC, Jessen HM, Auger AP. Indicators of developmental deviance in individuals at risk for schizophrenia. Schizophr Res. 2008;101:152–60.
182. Gooding DC, Matts CW, Rollmann EA. Sustained attention deficits in relation to psychometrically identified schizotypy: evaluating a potential endophenotypic marker. Schizophr Res. 2006;82:27–37.
183. Gooding DC, Tallent KA, Matts CW. Rates of avoidant, schizotypal, schizoid and paranoid personality disorders in psychometric high-risk groups at 5-year follow-up. Schizophr Res. 2007;94:273–4.
184. Horan WP, Blanchard JJ, Gangestad SW, Kwapil TR. The psychometric detection of schizotypy: do putative schizotypy indicators identify the same latent class? J Abnorm Psychol. 2004;113(3):339–57.
185. Fonseca-Pedrero E, Paino M, Lemos-Giráldez S, García-Cueto E, Campillo-Álvarez A, Villazón-García U, et al. Schizotypy assessment: state of the art and future prospects. Int J Clin Health Psychol. 2008;8:577–93.
186. Hay DA, Martin NG, Foley D, Treloar SA, Kirk KM, Heath AC. Phenotypic and genetic analyses of a short measure of psychosis-proneness in a large-scale Australian twin study. Twin Res. 2011;4:30–40.
187. Miettunen J, Vijola J, Freimer N, Lichtermann D, Peltonen L, Paunio T, et al. Data on schizotypy and affective scales are gender and education dependent: study in the Northern Finland 1966 birth cohort. Psychiatry Res. 2010;178:408–13.
188. Winterstein BP, Ackerman TA, Silvia PJ, Kwapil TR. Psychometric properties of the Wisconsin schizotypy scales: classical test theory, item response theory, and differential item functioning. J Psychophatol Behav Assess. 2011;33:480–90.
189. American Psychiatric Association. Diagnostic and statistical manual of mental disorder. 3rd. ed. revised. Washington, DC: American Psychiatric Association; 1987.
190. Raine A, Reynolds C, Lencz T, Scerbo A, Triphon N, Kim D. Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. Schizophr Bull. 1994;20:191–201.
191. Stefanis NC, Smyrnis N, Avramopoulos D, Evdokimidis I, Ntzoufras I, Stefanis CN. Factorial composition of self-rated schizotypal traits among young males undergoing military training. Schizophr Bull. 2004;30:335–50.
192. Tackett JL, Silberschmidt AL, Krueger RF, Sponheim SR. A dimensional model of personality disorder: incorporating DSM cluster A characteristics. J Abnorm Psychol. 2008;117:454–9.
193. Chen WJ, Hsiao CK, Lin CCH. Schizotypy in community samples: the three-factor structure and correlation with sustained attention. J Abnorm Psychol. 1997;106(4):649–54.

194. Badoud D, Chanal J, Eliez S, Van Der Linden M, Debbané M. Validation study of the French schizotypal personality questionnaire in an sample of adolescents; a confirmatory factor analysis. L'Encéphale. 2011;37:299–307.
195. Fonseca-Pedrero E, Fumero A, Paino M, de Miguel A, Ortuño-Sierra J, Lemos Giraldez S, et al. Schizotypal personality questionnaire: new sources of validity evidence in college students. Manuscript under review.
196. Kremen WS, Faraone SV, Toomey R, Seidman LJ, Tsuang MT. Sex differences in self-reported schizotypal traits in relatives of schizophrenic probands. Schizophr Res. 1998;34(1):27–37.
197. Yaralian PS, Raine A, Lencz T, Hooley JM, Bihrle SE, Mills S, et al. Elevated levels of cognitive-perceptual deficits in individuals with a family history of schizophrenia spectrum disorders. Schizophr Res. 2000;46(1):57–63.
198. Calkins ME, Curtis CE, Grove WM, Iacono WG. Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. Schizophr Bull. 2004;30(2):317–25.
199. Docherty AR, Sponheim SR. Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. J Abnorm Psychol. 2008;117:788–98.
200. Siever LJ, Silverman JM, Bernstein D. Schizotypal personality disorder: a review of its currents status. J Personal Disord. 1991;5:178–93.
201. Fonseca-Pedrero E, Lemos-Giráldez S, Paino M, Villazón-García U, Muñiz J. Validation of the schizotypal personality questionnaire brief form in adolescents. Schizophr Res. 2009;111:53–60.
202. Aycicegi A, Dinn WM, Harris CL. Validation of Turkish and English versions of the schizotypal personality questionnaire-B. Eur J Psychol Assess. 2005;21(1):34–43.
203. Ito S, Okumura Y, Sakamoto S. Sex differences in the schizotypal personality questionnaire brief among Japanese employees and undergraduates: a cross-sectional study. Personal Individ Differ. 2010;48:40–3.
204. Ma WF, Wu PL, Yang SJ, Cheng KF, Chiu HT, Lane HY. Sensitivity and specificity of the Chinese version of the Schizotypal Personality Questionnaire-Brief for identifying undergraduate students susceptible to psychosis. Int J Nurs Stud. 2010;47:1535–44.
205. Fonseca-Pedrero E, Paíno M, Lemos-Giráldez S, Sierra-Baigrie S, Muñiz J. Measurement invariance of the Schizotypal Personality Questionnaire-Brief across gender and age. Psychiatry Res. 2011;190:309–15.
206. Axelrod SR, Grilo MC, Sanislow C, McGlashan TH. Schizotypal Personality Questionnaire-Brief: factor structure and convergent validity in inpatient adolescent. J Personal Disord. 2001;15(2):168–79.
207. Compton MT, Goulding SM, Bakeman R, McClure-Tone EB. An examination of the factorial structure of the Schizotypal Personality Questionnaire-Brief (SPQ-B) among undergraduate students. Schizophr Res. 2009;115:286–9.
208. Compton MT, Chien VH, Bollini A. Psychometric properties of the Brief version of the Schizotypal Personality Questionnaire in relatives with schizophrenia-spectrum disorders and non-psychotic control. Schizophr Res. 2007;91:122–31.
209. Fonseca-Pedrero E, Lemos-Giráldez S, Paíno-Piñeiro M, Villazón-García U, Muñiz J. Schizotypal traits, obsessive-compulsive symptoms, and social functioning in adolescents. Compr Psychiatry. 2010;51:71–7.
210. Leach EL, Hurd PL, Crespi BJ. Schizotypy, cognitive performance, and genetic risk for schizophrenia in a non-clinical population. Personal Individ Differ. 2013;55:334–8.
211. Walker E, Bollini A. Pubertal neurodevelopmental and the emergence of psychotic symptoms. Schizophr Res. 2002;54:17–23.
212. Addington J, Heinssen R. Prediction and prevention of psychosis in youth at clinical high risk. Annu Rev Clin Psychol. 2012;8:269–89.
213. Rawlings D, MacFarlane C. A multidimensional schizotypal traits questionnaire for young adolescents. Personal Individ Differ. 1994;17(4):489–96.
214. Cyhlarova E, Claridge G. Development of a version of the Schizotypy Traits Questionnaire (STA) for screening children. Schizophr Res. 2005;80(2–3):253–61.

215. Raine A, Fung AL, Lam BY. Peer victimization partially mediates the schizotypy-aggression relationship in children and adolescents. Schizophr Bull. 2011;37:937–45.
216. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed revised. Washington, DC: American Psychiatric Association; 2000.
217. Schmeiser CB, Welch C. Test development. In: Brennan RL, editor. Educational measurement. 4th ed. Westport: American Council on Education/Praeger; 2006. p. 307–53.
218. Moreno R, Martínez R, Muñiz J. New guidelines for developing multiple-choice items. Methodology. 2006;2:65–72.
219. Fonseca-Pedrero E, Paino M, Lemos-Girádez S, Sierra-Baigrie S, Ordóñez N, Muñiz J. Early psychopathological features in Spanish adolescents. Psicothema. 2011;23:87–93.
220. Fonseca-Pedrero E, Lemos-Giráldez S, Paíno M, Sierra-Baigrie S, Santarén-Rosell M, Muñiz J. Internal structure and reliability of the Oviedo Schizotypy Assessment Questionnaire (ESQUIZO-Q). Int J Clin Health Psychol. 2011;11:385–402.
221. Fonseca-Pedrero E, Lemos-Giráldez S, Paino M, Sierra-Baigrie S, Muñiz J. Phenotypic expression of schizotypal traits in an adolescent population. J Personal Disord. 2012;26:539–50.
222. Cassidy CM, Lepage M, Harvey P-O, Malla A. Cannabis use and anticipatory pleasure as reported by subjects with early psychosis and community controls. Schizophr Res. 2012;137:39–44.
223. Trémeau F, Antonius D, Cacioppo JT, Ziwich R, Butler P, Malaspina D, et al. Anticipated, on-line and remembered positive experience in schizophrenia. Schizophr Res. 2010;122:199–205.
224. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol. 1994;67(2):319–33.
225. Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, et al. Developing constructs for psychopathology research: research domain criteria. J Abnorm Psychol. 2010;119:631–9.
226. Hathaway SR, McKinley JC. A multiphasic personality schedule (Minnesota): I. Construction of the schedule. J Psychol. 1940;10:249–54.
227. De Ayala RJ. The theory and practice of item response theory. New York: The Guilford Press; 2009.
228. Hambleton RK, Swaminathan H, Rogers HJ. Fundamentals of item response theory. Beverly Hills: Sage; 1991.
229. Bartram D, Hambleton R. Computer-based testing and the internet. Issues and advances. England: Wiley; 2006.
230. Fonseca-Pedrero E, Menéndez LF, Paino M, Lemos-Girádez S, Muñiz J. Development of a computerized adaptive test for schizotypy assessment. PLoS One. 2013;8:e73201.

Chapter 3
Hedonic Capacity and Related Factors in Schizophrenia and Schizoaffective Disorder

Michael S. Ritsner

Abstract Anhedonia describes the feeling of decreased capacity to experience pleasure, for example, when activities that an individual once found pleasurable are no longer enjoyable. The present chapter outlines the attribution of multidimensional independent variables to the levels of physical and social anhedonia in 87 patients with schizophrenia (SZ), and schizoaffective (SA) disorder. No significant differences between SZ and SA patients were revealed in the Revised Physical and Social Anhedonia Scale scores. There are two groups of independent variables with alternative associations with hedonic capacity dimensions: increasing and enhancing severity of anhedonia. The correlations of anhedonia scales with both negative and depressive symptoms were the loss significance after controlling for general quality of life, self-esteem, self-efficacy, and coping styles. A well-fitting factor model provides support for the dimensional structure of 25 independent variables with physical and social anhedonia scales that differentially associated into three domains: psychopathology and functioning, anhedonia and personality features, distress and unmet needs. Hedonic capacity deficit did not associate with the following variables: severity of illness and, PANSS positive factor, activation factor, dysphoric mood and autistic preoccupations, somatization, emotion oriented coping, general, sexual, social and occupational functioning, violence risk, alcohol, drug and substance use, antipsychotic agents, gender, and marital status. Further research is needed to clarify the factor structure of the anhedonia scales. Thus, the hedonic capacity of patients with SZ/SA is attributed to a number of personality related traits that uniquely contributed to the relationship of anhedonia levels with severity of negative and depressive symptoms. These findings might be of therapeutic relevance and enable better understanding of the multifactorial nature of anhedonia.

M.S. Ritsner, M.D., Ph.D. (✉)
Department of Psychiatry, Rappaport Faculty of Medicine Technion,
Technion – Israel Institute of Technology, Haifa, Israel
e-mail: ritsnerm@gmail.com

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_3,

Keywords Schizophrenia • Anhedonia • Symptoms • Emotional distress • Self-efficacy • Self-esteem • Coping styles • Social support • Functioning • Care needs • Alcohol • Substance use • Side effects • Ciolence risk • Sexual functioning

Abbreviations

ASEX	Arizona Sexual Experience Scale
AUS	Alcohol Use Scale
BSI-S	Brief Symptom Inventory Scale-Somatization
CANSAS-P	Camberwell Assessment of Need scale patient-rated
CDSS	Calgary Depression Scale for Schizophrenia
CISS	Coping Inventory for Stressful Situations
CGI-S	Clinical Global Impression Scale
CT	combined therapy (a combination of FGAs and SGAs)
DSAS	Distress Scale for Adverse Symptoms
DUS	Drug Use Scale
GSES	General Self-Efficacy Scale
GAF	Global Assessment of Functioning scale
FGAs	First-generation antipsychotic agents
MCAS	Multnomah Community Ability Scale
MSPSS	Multidimensional Scale of Perceived Social Support
PANSS	Positive and Negative Syndromes Scale
PAS	Revised Physical Anhedonia Scale
PAS/SAS	All PAS and SAS items together
RAQ	Risk Assessment Questionnaire
RSES	Rosenberg Self-Esteem Scale
SA	Schizoaffective disorder
SAS	Revised Social Anhedonia Scale
SATS	Substance Abuse Treatment Scales
SGAs	Second-generation antipsychotics
SZ	Schizophrenia
SZ/SA	Schizophrenia and schizoaffective disorder together
SOFAS	Social and Occupational Functioning Assessment Scale
TBDI	Talbieh Brief Distress Inventory
Q-LES-Q	Quality of Life Enjoyment and Life Satisfaction Questionnaire

3.1 Introduction

Anhedonia (diminished interest, pleasure or deficits) describes a feeling of decreased capacity to experience pleasure, where activities that an individual once found pleasurable are no longer enjoyable [1, 2]. The concept of anhedonia was introduced by

Ribot [3] and recently discussed by Ho, and Sommers [4]. In addition to an array of psychotic, negative, affective, cognitive, and behavioral consequences, research suggests that there is a distinct pattern of *hedonic functioning or capacity* in schizophrenia (SZ) that may contribute to some of the most intractable symptoms and outcomes of the disorder. Although anhedonia is a prominent feature of many psychiatric disorders ("state marker") like schizophrenia, schizoaffective (SA), mood and substance use disorders, it is also observed dimensionally in healthy individuals ("trait marker") in college and community populations, schizophrenia patients' unaffected relatives, in patients with Ultra High Risk for psychosis in comparison to patients who did not develop psychosis [5–8].

Anhedonia remains poorly understood. There seems to be a multidimensionality and multifactorial construct [9] associated with a dysfunction of the mesolimbic dopaminergic reward system [10]. Studies in humans and non-human animal models indicate that dysfunction of central dopaminergic neurotransmission interferes with the process of motivation rather than with the ability to experience pleasure; the latter may be mediated by opioidergic and serotonergic neurotransmissions [11, 12]. Although behavioral neuroscience has expanded our understanding of reward-related processes, the concept of anhedonia has remained relatively unchanged over the past three decades [13–15]. Overall, anhedonia has been considered [9, 16–18] both a *hallmark symptom of clinical state*, and *a trait-like or a vulnerability marker*.

There is confusion regarding the nature of anhedonia in schizophrenia stemming from contradictory findings in the empirical literature, which have been called the "emotion paradox" [19]. Patients report levels of positive emotion similar to those of healthy comparison subjects when reporting their current feelings, but they report less pleasure compared to control subjects when reporting their noncurrent feelings [20]. Basic science points to the importance of distinguishing between anticipatory and consummatory (or in-the-moment) pleasure experiences and this distinction may help to reconcile the mixed findings on anhedonia in schizophrenia.

Findings from both animal studies and affective neuroscience suggest that hedonic capacity is not a monolithic phenomenon but can be parsed into distinct subcomponents including consummatory (or liking) and anticipatory pleasure (or wanting) [18, 19, 21]. Gard et al. [22] found evidence for an anticipatory but not a consummatory pleasure deficit in schizophrenia. A meta-analysis showed that people with schizophrenia did not report hedonic impairments in response to laboratory stimuli, but they did report higher levels of negative emotion in response to positive and neutral stimuli compared with people without schizophrenia [20]. Taken together, these findings suggest that patients with schizophrenia are not anhedonic in their "in the moment" experience of pleasure, and the absence of an association between objective and subjective ratings of hedonic experience [23]. Consummatory pleasure is more closely linked to satiation, or a resolution of desire, an "in the moment" experience of pleasure, whereas anticipatory or appetitive pleasure is more closely linked to motivation, goal-directed behavior and the experience of "wanting" [18].

Chan et al. [24] examined anticipatory and consummatory pleasure in schizophrenia patients with and without negative symptoms. There is evidence that at a behavioral level, the implicit and explicit processing of emotional prosody can be dissociated [25]. These aspects of anhedonia are widely presented in other chapters of this book. Deficits in anticipatory pleasure, but not in consummatory pleasure, were significantly associated with increased clinical risk for schizophrenia. However, this relation was found exclusively among women in the sample, whereas men did not show a significant relation between anticipatory pleasure deficits and clinical high-risk [26].

Herbener and Harrow [27], using prospectively collected longitudinal data covering a 10-year span for 127 individuals with schizophrenia, found that (a) physical, but not depressive, *anhedonia is a stable characteristic over a 10-year period*; (b) physical anhedonia does not show strong and consistent relationships with psychotic, negative, or depressive symptoms; and (c) the relationship between some premorbid characteristics and physical anhedonia are significant even 10 years into the course of illness. Furthermore, the longitudinal study suggested increasing convergence of impairments in emotional, adaptive, and cognitive capacities over a 20-year period. Physical anhedonia was associated with poorer outcome in a sample of 61 individuals with schizophrenia [28].

The association of hedonic capacity with psychopathological and personality-related factors in SZ/SA disorder remains controversial. In the present chapter we discuss the attribution of multidimensional illness-, personality- , and environmental-related variables, functioning and care needs to the levels of hedonic capacity in patients with chronic SZ/SA disorder.

3.2 Dependent Variables

3.2.1 Hedonic Capacity Dimensions

Chapman and Raulin [29] defined two subtypes of hedonic deficit, *physical anhedonia* that represents an inability to feel physical pleasures and *social anhedonia* that represents lack of capacity to experience interpersonal pleasure.

Among measurement scales, the most commonly used are the Snaith-Hamilton Pleasure Scale, the Scale for the Assessment of Negative Symptoms, the Bech-Rafaelsen Melancholia Scale, the Fawcett-Clark Pleasure Scale, and the Revised Physical and Social Anhedonia Scales [30].

Physical anhedonia is usually assessed with the Revised Physical Anhedonia Scale (PAS) [31]. The PAS assesses a self-reported deficit in the ability to experience pleasure from typically pleasurable physical stimuli such as food, sex, and settings. The PAS contains *61 true-false items* that yield scores ranging from 0 to 61. High scores indicate more severe physical anhedonia.

Social anhedonia was assessed with the Revised Social Anhedonia Scale (SAS) [32], which showed adequate psychometric characteristics [33]. The SAS assesses deficits in the ability to experience pleasure from non-physical stimuli such as other people, talking or exchanging expressions of feelings. *Forty* true-false items constitute the SAS, and higher score on the SAS indicates less pleasure from social interactions.

In addition, all PAS and SAS items were calculated together (*PAS/SAS, 101 items*) on the present sample SZ/SA patients, mean score = 36.6 ± 12.6 (SD) scores. Internal consistency reliability (Chronbach's α coefficient) indicated good internal consistency: for the PAS (α = 0.92), the SAS (α = 0.90), and the PAS/SAS (α = 0.90).

An elevated score on the PAS, SAS, and PAS/SAS reflects increased *anhedonia* or *hedonic capacity deficit*. The PAS (≥ 18) and SAS (≥ 12) cut-off scores used for categorization each patient as 'hypohedonics' (the subject had to reach PAS or SAS cut-off), or 'double anhedonics' (the subject had to reach both PAS and SAS cut-off at the same time), or 'normal hedonics' (the subject does not reach PAS and SAS cut-off) [34, 35].

Following dependent variables were used in the present analyses:

(a) raw scores of the physical anhedonia (total PAS scores),
(b) raw scores of the social anhedonia (total SAS scores),
(c) raw scores of the both anhedonia scales (PAS/SAS scores),
(d) hedonic capacity level: 'normal hedonics', 'hypohedonics', 'double anhedonics', and
(e) frequency of the PAS and SAS items in the studied sample.

3.3 Participants

The study sample was drawn from a database of patients who participated in the 10-year follow-up stage of an ongoing naturalistic prospective investigation of patients with major psychiatric disorders that was initiated in 1998 (Fig. 3.1). A detailed description of the design, data collection, measures and findings was reported elsewhere [36–41]. Briefly, the initial sample was systematically selected from the hospital case register according to the following inclusion criteria: (i) fulfilment of DSM-IV criteria for major psychiatric disorders [42], (ii) age 18–65, and (iii) inpatient status in closed, open or rehabilitation hospital departments of a university hospital. Patients with mental retardation, organic brain disease, severe physical disorders, drug/alcohol abuse, and those with low comprehension skills were not enrolled. Patients that met the inclusion criteria were assessed three times: prior to discharge from hospital (initial assessment), about 2 and 10 years later. The Sha'ar Menashe Internal Review Board and the Israel Ministry of Health approved the study. All participants provided written informed consent for participation in the study, after receiving a comprehensive explanation of study procedures.

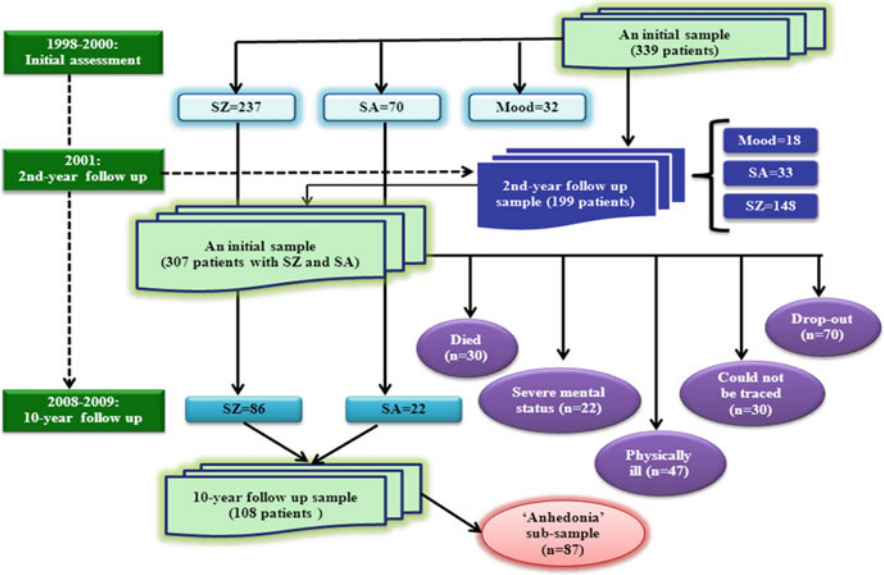

Fig. 3.1 A flow diagram of the study population in framework of the Sha'ar Menashe Quality of Life Project [40] (© M. S. Ritsner (2014) and used by permission)

3.3.1 Sample Characteristics

The patient sample included 87 subjects, 66 (75.9 %) men, mean age 47.8 ± 9.4 years (range: 30–69), 54 people (62.13 %) were single, 22 (25.3 %) were married, and the rest 11 (12.6 %) were divorced, separated or widowed (see Table 3.1). Mean extent of education was 10.7 ± 2.6 years. Mean (± SD) age of application for psychiatric care was 23.2 ± 7.8 years, and mean duration of disorder was 25.0 ± 9.2 years (range: 11–49). None of the participants had exacerbation of their mental state or physical disorders at the assessment. Patients were treated with first-generation antipsychotic agents (FGAs, 51 patients), 16 – with second-generation antipsychotics (SGAs, 16 patients) and with a combination of FGAs and SGAs (20 patients).

3.3.2 Hedonic Capacity

The sample included 68 patients with SZ and 19 patients with SA disorder. Consistent with published findings [43], ANOVA showed no significant differences between SZ and SA patients in the physical anhedonia (PAS; $F_{1.87}=2.1$, $p=0.15$) and social anhedonia (SAS; $F_{1.87}=0.1$, $p=0.95$) scale scores. Therefore, in all analyses we used the entire sample of 87 subjects. The PAS (22.0 ± 8.6) and the SAS (17.0 ± 8.4) scores for

Table 3.1 Demographic and background characteristics of the sample

Characteristics	N	%
Sex		
Male	66	75.9
Female	21	24.1
Marital status		
Never married	54	62.1
Married	22	25.3
Divorced, separated, widowed	11	12.6
Living alone	10	11.5
Living with husband/wife/partner and children	17	19.5
Living with parents	14	16.1
Living with others	14	16.1
Hostel	32	36.8
Employment:		
Paid or self-employment	7	8.0
Sheltered employment	24	27.6
Unemployed	56	64.4
Number of suicide attempts:		
0	66	75.9
1	13	14.9
2–4	8	9.2
Diagnosis (DSM-IV)		
Schizophrenia, paranoid type (295.3)	48	55.2
Schizoaffective disorder (295.7)	19	21.8
Schizophrenia, residual type (295.6)	18	20.7
Schizophrenia, disorganized type (295.1)	1	1.1
Schizophrenia, undifferentiated type (295.9)	1	1.1
	Mean	SD
Education (year)	10.7	2.6
Age (year)	47.8	9.4
Age of onset (year)	23.2	7.8
Duration of illness (year)	25.0	9.2

the entire sample were elevated compared to normative data (15.0 ± 7.0, and 9.4 ± 5.5, respectively [44]. Hedonic capacity of our sample scores were consistent with those reported by Pelizza and Ferrari [35] who also demonstrated elevated scores on the PAS and SAS (20.9 ± 8.0 and 15.9 ± 6.4, respectively) in a schizophrenia sample.

ANOVAs did not indicate significant associations of both PAS and SAS scores with sex ($F_{1.87} = 0.1$, $p = 0.96$, and $F_{1.87} = 1.1$, $p = 0.30$, respectively), marital status ($F_{2,87} = 0.8$, $p = 0.46$, and $F_{2,87} = 0.2$, respectively), and with type of antipsychotic therapy (FGAs, SGAs, CT; $F_{2,87} = 2.7$, $p = 0.051$, and $F_{2,87} = 1.1$, $p = 0.34$, respectively). Men showed significantly higher levels of physical ($F = 5.1$, $p < 0.001$) and social ($F = 4.4$, $p < 0.005$) anhedonia than women [45].

3.4 Independent Variables

Figure 3.2 shows dependent and four blocks of independent variables: the illness-, personality-, environmental-related, functioning and care needs. All rating scales and questionnaires used for assessment of these variables are presented in Table 3.2.

3.4.1 Illness-Related Dimensions (Variables)

Diagnosis of SZ/SA was based on DSM-IV criteria [42], medical records, and consensus between two senior psychiatrists after a face-to-face interview. Illness severity was assessed using *the Clinical Global Impression Scale* (CGI-S) [46]. Severity of psychopathology was assessed using *the Positive and Negative Syndromes Scale* (PANSS) [47], and *the Calgary Depression Scale* (CDSS). Five factors PANSS model including scores of negative factor, positive factor, activation, dysphoric mood and autistic preoccupations were evaluated [48]. The CDSS is a nine-item structured interview scale developed by Addington et al. [49] to assess depression among individuals with schizophrenia. *An increase in CGI-S, PANSS, and/or CDSS scores reflect greater severity of illness and relevant symptoms*.

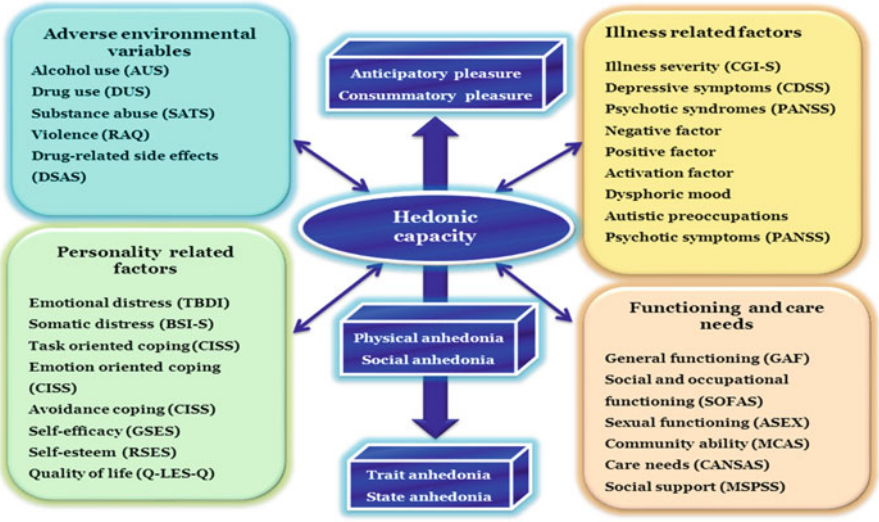

Fig. 3.2 Four blocks of independent variables possible related to hedonic capacity in schizophrenia (© M. S. Ritsner (2014) and used by permission)

Table 3.2 Instruments used for assessment dependent and independent variables

Variables		Scale	References
Dependent variables			
1. Physical anhedonia	PAS	Revised Physical Anhedonia Scale	[31]
2. Social anhedonia	SAS	Revised Social Anhedonia Scale	[32]
Independent variables			
3. Illness severity	CGI-S	Clinical Global Impression Scale	[46]
4. Depressive symptoms	CDSS	Calgary Depression Scale for Schizophrenia	[49]
5. Psychotic syndromes	PANSS	Positive and Negative Syndromes Scale	[47]
6. Emotional distress	TBDI	Talbieh Brief Distress Inventory	[53, 54]
7. Somatic distress	BSI-S	Brief Symptom Inventory Scale-Somatization	[51]
8. Coping abilities	CISS	Coping Inventory for Stressful Situations	[61]
9. Self-efficacy	GSES	General Self-Efficacy Scale	[66]
10. Self-esteem	RSES	Rosenberg Self-Esteem Scale	[67]
11. Perceived quality of life	Q-LES-Q	Quality of Life Enjoyment and Life Satisfaction Questionnaire	[77]
12. General functioning	GAF	Global Assessment of Functioning scale	[42]
13. Social and Occupational	SOFAS	Social and Occupational Functioning Assessment Scale	[42, 94]
14. Sexual Functioning	ASEX	Arizona Sexual Experience Scale	[95]
15. Community ability	MCAS	Multnomah Community Ability Scale	[97]
16. Care needs	CANSAS-P	Camberwell Assessment of Need scale, patient-rated	[98, 99]
17. Social support	MSPSS	Multidimensional Scale of Perceived Social Support	[101]
18. Alcohol use	AUS	Alcohol Use Scale	[82, 83]
19. Drug use	DUS	Drug Use Scale	
20. Substance Abuse	SATS	Substance Abuse Treatment Scales	
21. Violence risk	RAQ	Risk Assessment Questionnaire	[87]
22. Drug-related side effects	DSAS	Distress Scale for Adverse Symptoms	[36]

3.4.2 Personality Related Dimensions (Variables)

Personality is a broad concept involving both basic neurophysiologic and potentially genetically determined traits (i.e. temperament) and developmental aspects of personality (i.e. self-related factors). Six personality related dimensions were assessed in the present study: emotional and somatic distress (or somatization), coping styles, self-efficacy, self-esteem, and perceived quality of life (Table 3.2).

3.4.2.1 Emotional Distress

Emotional distress is described as the reaction of an individual to external and internal stressors and is characterized by a mixture of sub-threshold distress

symptoms, such as obsessiveness, depression, hostility, sensitivity, anxiety, and paranoid ideation [37, 50–52].

Emotional distress symptoms were assessed using *the Talbieh Brief Distress Inventory* (TBDI). The TBDI is a 24-item self-report instrument that measures subjective discomfort from psychiatric symptoms [53, 54]. These items were drawn from the Psychiatric Epidemiology Research Interview Demoralization Scale [50] and the Brief Symptom Inventory Scale (BSI) [51]. Responses are 0 to 4- with higher scores indicating greater intensity of six distress symptoms: obsessiveness, hostility, sensitivity, depression, anxiety, and paranoid ideation. TBDI demonstrated high reliability (Cronbach's α for TBDI symptoms ranged from 0.76 to 0.91).

3.4.2.2 Somatic Distress (Somatization)

The definition of somatization as the presentation of five or more somatic symptoms, which cannot be accounted for by detectable somatic illness, has shown good validity in various populations [55, 56]. Somatization has often been viewed as a continuum on which increasing degrees of somatic symptoms indicate increasing distress, a defence against underlying unconscious conflict, disability, and maladaptive illness behavior [57].

Somatization or somatic distress was assessed using *the Somatization Scale* (BSI-S) that was derived from the BSI [51]. The BSI-S has demonstrated high reliability (Cronbach's $\alpha = 0.85$).

Schizophrenia patients have a higher risk for somatization than the general population since: (1) they experience significantly more emotional distress (associated with psychopathological symptoms) when compared with healthy controls [58], and (2) the impact of antipsychotic drug therapy and adverse effects, is not restricted to motor symptoms, but also affects cognition and emotion. On the other hand, patients with somatization disorder have increased psychotic, manic, depressive, and anxiety symptoms [59]. The frequency of somatization among the SZ/SA inpatients was observed in 27–30 % of the patients [59]. Thus, somatization is a prevalent problem among schizophrenia patients and is associated with emotional distress attributed to psychopathology, side effects of antipsychotic agents and family member's attitudes towards schizophrenia patients.

3.4.2.3 Coping Abilities

Coping with stressful situations and adverse life events including mental disorders is an important personality resource and a measure of one's adaptability. According to the cognitive-transactional theory of stress [60], coping has been defined as one's cognitive and behavioral effort to manage the internal and external demands of a person-environment transaction that is considered taxing or exceeding one's resources. Three main coping strategies are engaged in an individual's response to stressful situations including mental illness [61]. First, *emotion-oriented coping strategy* involves emotional responses, self-preoccupation, and fantasizing reactions to stress. Second, *task related*

coping style is used to solve a problem, reconceptualize it (cognitively), or minimize its effects. Third, *avoidance coping strategy* involves both task and person orientation; a person may avoid a stressful situation by choosing to be with other people (via social diversion) or by engaging in a substitute task (via distraction).

Endler and Parker [61] developed the *Coping Inventory for Stressful Situations* (CISS). The CISS is a 48-item inventory that assesses ways people react to various difficulties and stressful or upsetting situations. Responses are scored on a five-point scale ranging from 'not at all' to 'very much' with higher scores indicating greater coping abilities. Three basic coping styles are evaluated (each by 16 items): task-oriented, emotion-oriented and avoidance-oriented coping [62]. For the present sample, internal consistency of the CISS dimensions was high: Cronbach's coefficient α for task, emotion-oriented and avoidance oriented coping strategies was 0.84, 0.86, and 0.91, respectively.

Research has indicated that schizophrenia patients are not flexible in their use of coping strategies or styles [63], tend to use maladaptive or emotion-oriented coping styles [64], and rely more on passive avoidant strategies and less on active problem solving [65].

3.4.2.4 Self-efficacy and Self-esteem

General self-efficacy is the belief in one's competence to cope with a broad range of stressful or challenging demands, whereas specific self-efficacy is constrained to a particular task at hand. Perceived general self-efficacy is measured by means of *the General Self-Efficacy Scale* (GSES). It is a 10-item psychometric scale that is designed to assess a sense of personal competence in stressful situations, optimistic self-beliefs to cope with a variety of difficult demands in life. Responses are 0–4- with higher scores indicating greater self-efficacy. The scale was originally developed in Germany in 1981 and has been used in many studies with hundreds of thousands of participants [66].

Self-esteem was measured using *the Rosenberg Self-Esteem Scale* (RSES) [67]. The RSES is a well-known 10-item self-report questionnaire for measuring self-esteem and self-regard; a decreased score reflects increased self-esteem. The RSES measures global self-esteem and personal worthiness. It includes 10 general statements that assess the degree to which respondents are satisfied with their lives and feel good about themselves. *A decreased score reflects increased self-esteem*. It is the most widely used scale to measure global self-esteem in research studies. For the present sample, internal consistency of the GSES and RSES was quite satisfactory (Cronbach's $\alpha = 0.87$ and 82, respectively).

3.4.2.5 Perceived Quality of Life

Conceptualization and measurement of quality of life (QOL) has been the subject of many publications (see book [68]). Dissatisfaction with life quality of SZ/SA patients is associated with distressing factors, including depressive and negative symptoms [69, 70], antipsychotic-induced side-effects [37, 71], and high levels of

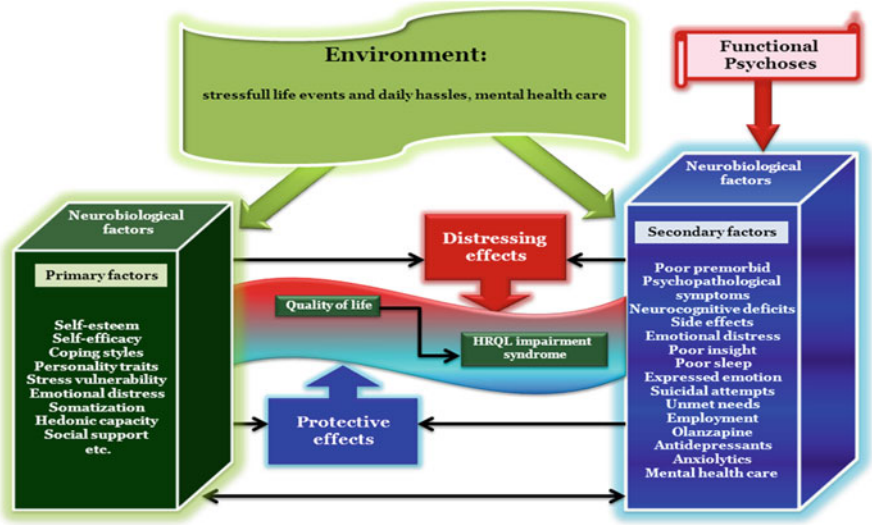

Fig. 3.3 Distress/Protection Vulnerability model of health-related quality of life impairment in functional psychoses (© M. S. Ritsner [38] and used by permission)

emotional distress [36, 72, 73]. Research findings also highlighted the importance of addressing some personality related psychosocial factors with protective effects of QOL levels [36, 74–76]. Empiric findings may be understood in the framework of the Distress/Protection Vulnerability model that postulated that (1) dissatisfaction with QOL is a syndrome observed in severe mental disorders; (2) it is an outcome of the interaction of distressing factors and putative stress process related protective factors; (3) dissatisfaction with quality of life increases if distressing factors overweigh protective factors, and vice versa; and (4) *primary or vulnerability* QOL related factors are considered inborn or personal characteristics, while *secondary factors* are related to illness and environment (Fig. 3.3) [36, 38].

Quality of Life Enjoyment and Life Satisfaction Questionnaire (Q-LES-Q) [77], a self-report instrument, was used to assess subjective quality of life. Responses are scored on a 1–5-point scale (1 = 'not at all or never' to 5 = 'frequently or all the time'), with higher scores indicating better enjoyment and satisfaction with specific life domains. Mean scores of seven domains and the general quality of life (measured with Q-LES-Q_{index}) are presented as an average of the scores of the items [36]. Internal consistency of these seven domains as measured by Cronbach's α coefficient ranged from 0.82 to 0.91. Mean scores of seven domains and the general quality of life measured with Q-LES-Q_{index} are presented as an average of the scores of the items. Internal consistency of Q-LES-Q measures ranged from 0.82 to 0.91 (Cronbach's α coefficient).

Figure 3.4 depicts decreased satisfaction with quality of life among SZ/SA patients compared to mentally healthy subjects. These differences remained after a 10-year follow-up. However, when paired or individual longitudinal analysis of

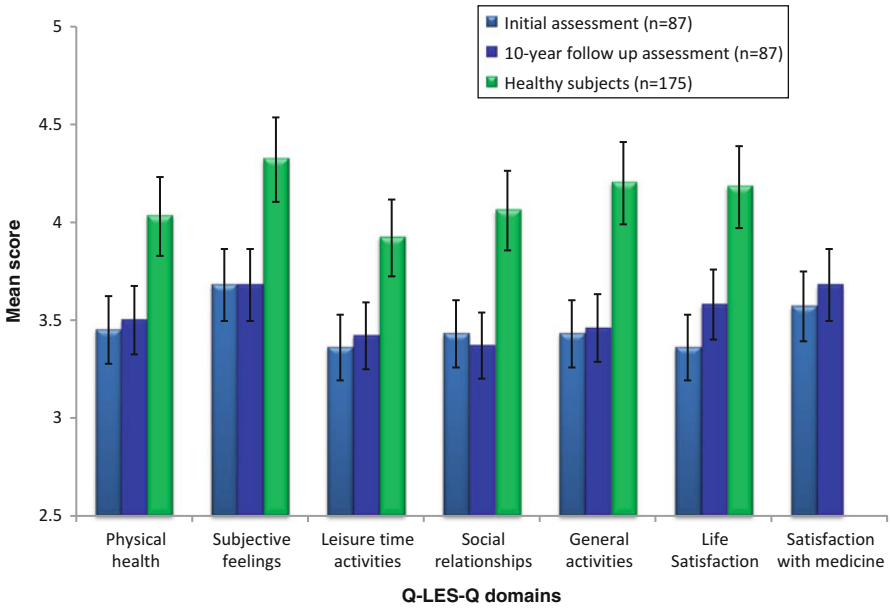

Fig. 3.4 Quality of life domain scores of healthy subjects and patients with schizophrenia and schizoaffective disorders at the initial assessment and 10-year later. (© M. S. Ritsner (2014) and used by permission)

general quality of life (Q-LES-Q_{index} score) was conducted, four distinct patient subgroups were identified: (a) 53 of 87 patients (60.9 %) were permanently dissatisfied, and (b) 10 patients (11.5 %) became more dissatisfied in general life quality over time, whereas (c) 8 patients (9.2 %) were permanently satisfied, and (d) 16 patients (18.4 % improved over the follow up period) [40].

3.4.3 Adverse Environmental Variables

A large body of evidence indicates that risk and course of schizophrenia is associated with a number of adverse environmental factors, including alcohol use, drug use, substance abuse, violence risk and drug-related side effects [78, 79].

3.4.3.1 Drug-Related Side Effects

Antipsychotic drugs are the medications most commonly used to treat schizophrenia. The first-generation antipsychotic drugs (FGAs) are associated with motor side effects such as tremor and other involuntary movements. The newer (second-generation)

antipsychotic drugs (SGAs) are relatively safe in this regard, but side effects include drug-induced metabolic syndrome, weight gain and its complications [80]. Antipsychotics act primarily by blocking dopamine ("the pleasure molecule") which can cause sedation, depression, and anhedonia.

The presence and severity of adverse effects of medication as well as psychological responses to them were measured with *the Distress Scale for Adverse Symptoms* [36]. The DSAS is a clinician administered rating scale with a checklist of the 22 most frequently observed side effects and discomfort associated with antipsychotic treatment. *Responses are on a 5-point scale, with higher scores indicating higher adverse symptom severity and greater distress*. The global DSAS index was computed as the average of adverse symptoms, mental and somatic distress scores (Cronbach's $\alpha = 0.88$).

3.4.3.2 Alcohol, Drug and Substance Use

For detection of alcohol, drug and substance use three scales were applied: *the Alcohol Use Scale* (AUS) and *the Drug Use Scale* (DUS) [81], and *the Substance Abuse Treatment Scale* (SATS) [82]. The AUS and DUS are five-point scales based on DSM-III-R criteria for severity of disorder: (1) abstinence, (2) use without impairment, (3) abuse, (4) dependence, and (5) severe dependence. A time frame of 6 months for the ratings is recommended [83]. The SATS is an 8-point scale that indicates progressive involvement in treatment and movement toward long-term remission from a substance use disorder according to the Osher and Kofoed [84] model of treatment and recovery: 1–2 = early and late stages of engagement, 3–4 = stages of persuasion, 5–6 = stages of active treatment, and 7–8 = stages of relapse prevention and recovery.

3.4.3.3 Violence Risk

Schizophrenia and other psychoses are associated with violence and violent offending [85]. Aggression in schizophrenia patients may be associated with psychotic disorganization, co-morbid personality disorder, alcohol and drug abuse or reasons not related to psychiatric impairment [86]. *The Risk Assessment Questionnaire* (RAQ) [87, 88] was used to assess violent behavior.

Personality factors rather than symptoms and neuropsychological function might be important in understanding in-patient violence in forensic patients with schizophrenia [89]. Fanning et al. [90] determined social anhedonia in a nonclinical sample of 120 undergraduates using a multi-modal approach to assess aggression. They found that SAS scores predicted aggressive behavior over and above the effects of gender, anger and hostility. The results suggest that social anhedonia and possibly low positive affect more broadly, may be associated with an increased risk of aggression in response to provocation.

3.4.4 Functioning and Care Needs

This block of variables included general functioning, social and occupational functioning, sexual functioning, community ability, care needs, and perceived social support.

3.4.4.1 General Functioning

The Global Assessment of Functioning scale (GAF) is one of the most widely used measures of impairment and functioning in clinical and research settings [91]. Clinicians rate clients on a 1–100 scale in terms of their psychological, social, and occupational functioning [42]. The scale includes 10 sets of anchor descriptions spaced at 10-point intervals. Anchors allow clinicians to consider both symptom severity and social/occupational functioning in their ratings. The GAF measures of symptom severity and the degree of impairment in psychological, social, and occupational functioning. Scores above 65 are considered within the functionally recovered range [92, 93].

3.4.4.2 Social and Occupational Functioning

The Social and Occupational Functioning Assessment Scale (SOFAS) is designed to assess an individual's level of social and occupational functioning not directly influenced by the overall severity of psychiatric symptoms (DSM-IV Axis V) [42, 94]. This scale also considers the effects of the individual's general medical condition in the evaluation of social and occupational functioning. The SOFAS is a scale that differs from the GAF in that it focuses exclusively on the individual's level of social and occupational functioning and is not directly influenced by the overall severity of the individual's psychological symptoms. Also in contrast to the GAF Scale, any impairment in social and occupational functioning that is due to general medical conditions is considered in the SOFAS rating. The SOFAS was used to assess current functioning.

3.4.4.3 Sexual Functioning

The Arizona Sexual Experience Scale (ASEX) was developed by McGahuey et al. [95] at the University of Arizona in response to the need to evaluate psychotropic drug-induced sexual dysfunction. Initially, the scale was tested to assess sexual dysfunction among selective serotonin reuptake inhibitor (SSRI)-treated subjects. The ASEX is a brief 5-item questionnaire designed to measure sexual functioning in the following domains: sexual drive, arousal, penile erection/vaginal lubrification, ability to reach orgasm, and satisfaction with orgasm over the past week [95].

The scale was self-administered. The scale is applicable to patients regardless of the availability of a sexual partner. Male and female patients are assessed separately. Items are rated on a 6-point scale ranging from 1(hyperfunction) through to 6 (hypofunction), providing a total score range between 5 and 30 with a higher score indicating greater – patient sexual dysfunction. A total score > 18, or a score ≥ 5 (very difficult) on any single item or any three items with individual scores ≥ 4 is indicative of clinically significant sexual dysfunction. Byerly et al. [96] tested the psychometric properties of ASEX in patients with schizophrenia and schizoaffective disorder and demonstrated that ASEX represents an easy-to-administer tool for assessing sexual dysfunction in this population.

3.4.4.4 Community Ability

The Multnomah Community Ability Scale (MCAS; 17-items) [97] was used to measure the psychosocial functioning of participants. It is an informant questionnaire and is commonly completed by mental health clinicians or staff with a broad knowledge of the individual's functioning gained by regularly working with the individual over a period of time. Scores of items range from 1 to 5 with higher numbers indicating better functioning. The instrument contains questions such as "How successfully does the client manage his/her money and control expenditures?" There are five possible responses, ranging from 1, "almost never manages money successfully," through 3, "sometimes manages money successfully," to 5, "almost always manages money successfully." The MCAS addresses four areas:

- interference with functioning,
- adjustment to living in the community,
- social competence, and
- behavioral problems.

3.4.4.5 Care Needs

Needs were assessed using the Camberwell Assessment of Need scale [98], patient-rated short form (CANSAS-P) [99]. The CANSAS-P assesses needs over the past month in 22 health and social items. The need rating for each item is 0 = 'no need' (no problems at all in the domain), 1 = 'met need' (no or moderate problems in the domain because of help received), or 2 = 'unmet need' (a serious problem, regardless of help provided). For this sample, Cronbach's α coefficient was 0.83.

The mean number of met and unmet needs together identified per patient was 7.29 ± 4.8; among them unmet needs was 3.39 ± 2.9. The most common areas of unmet needs were psychological distress (33.7 %) and psychotic symptoms (25.3 %), sexual expression (33.7 %), intimate relationships (31.9 %), company (31.6 %), physical health (26.3 %), daytime activities (24.2 %), information on conditions and treatment (21.1 %), accommodations (21.1 %), and money (20 %) (Fig. 3.5) [100].

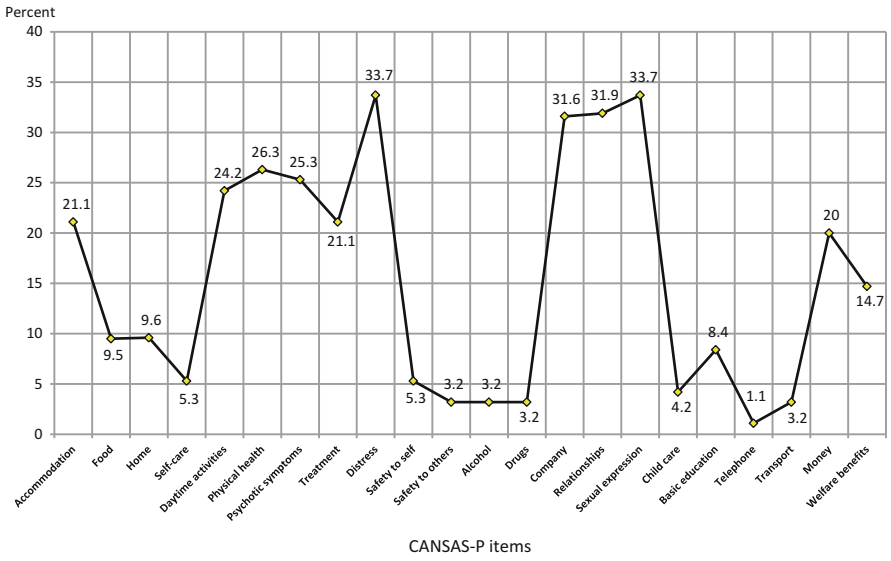

Fig. 3.5 Profile of unmet needs of 95 patients with schizophrenia and schizoaffective disorder

CANSAS-P subscales (or domains). Exploratory factor analysis revealed a four-factor model that explains 50.4 % of the total variance of the 20 CANSAS-P items [100]:

- The first factor or subscale, labelled "*Social disability*', generally captures difficulties in basic social needs, and covers many everyday social and practical skills in patients' independent living.
- The second factor is generally defined as any difficulty linked to 'basic education', 'telephone', 'transportation', and 'welfare benefits'. It is reasonable to assume that unmet needs in these areas might relate to cognitive or information processing impairment, therefore, it is called '*Information processing disability'* that contributes significantly to functional impairments.
- The third factor, '*Emotional processing disability*', consists of lack of assistance with 'daytime activities', 'psychotic symptoms', 'psychological distress', 'company', 'intimate relationships', and 'sexual expression' item scores, that reflects deficits in the treatment processing of negative emotional information.
- '*Coping disability'*, the fourth factor was constructed using 'self-care', 'safety to self', 'safety to others', 'drugs', 'child care' scores. This factor relates to lacking protective behavior and skills, to decreased self-esteem, self-efficacy, and coping abilities in the context of feeling safe.

Higher scores of specific subscales indicate increased unmet needs. CANSAS-P subscales (or domains) showed acceptable internal consistency (Cronbach's α coefficient 0.67–0.77).

3.4.4.6 Perceived Social Support

The Multidimensional Scale of Perceived Social Support (MSPSS) was used to measure social support as perceived by the individual [101]. The MSPSS is a 12-item questionnaire, each item is scored 1–7, *and higher scores indicate higher levels of perceived support*. The MSPSS assess both perceived availability and adequacy of emotional and instrumental social support, across three factors that relate to the source of support (i.e., *family, friends or significant others*). MSPSS gives a total score and three subscale scores (Cronbach's $\alpha = 0.84–0.90$). The confirmatory factor analysis supports the factor structure of the MSPSS [102].

3.5 Correlation Analysis

Statistical analysis was performed using the *Number Cruncher Statistical Systems* (NCSS) [103]. Mean values with standard deviation (SD) are presented. Differences in the frequency of categorical variables were examined with the χ^2 test. Analysis of variance (ANOVA) was applied to examine between-group differences. For all analyses, the level of statistical significance was defined as $p < 0.05$.

3.5.1 Pearson's Correlations

Correlation coefficient between PAS and SAS scores was 0.51 ($p < 0.001$). The exploration of the relationships of physical and social anhedonia measures (PAS, SAS and PAS/SAS scores) with multidimensional independent variables depicted in Tables 3.3, 3.4, and 3.5.

As can be seen, *two groups of variables* significantly correlated with physical and social hedonic capacity: *positively* and *negatively associated with* PAS and SAS mean scores [41].

1. *Physical hedonic capacity (PAS) scores positively correlated* with scores of depressive symptoms (CDSS), PANSS Negative factor, emotional distress and symptoms (TBDI total, 0bsessiveness, sensitivity, depression), and information processing disability (CANSAS-P) (r ranges from 0.22 to 0.29). In addition, four PANSS items correlated with PAS scores: poor rapport (N3; $r = 0.26$, $p = 0.012$), lack of spontaneity (N6; $r = 0.28$, $p = 0.008$), preoccupation (G15; $r = 0.22$, $p = 0.045$), active social avoidance (G16; $r = 0.22$, $p = 0.036$).
2. *Social hedonic capacity (SAS) scores* also *positively correlated* with scores of depressive symptoms (CDSS), PANSS Negative factor, emotional distress (TBDI total, sensitivity, depression), and information and emotional processing disability (CANSAS-P) (r ranges from 0.22 to 0.40). Six PANSS items showed

Table 3.3 Pearson correlation coefficients of anhedonia scores with illness related variables of 87 patients with schizophrenia and schizoaffective disorders

			Correlation coefficients		
Variables	Mean	SD	Physical anhedonia	Social anhedonia	PASSAS scale
Physical anhedonia (PAS)	22.0	8.6	–	0.51***	0.88***
Social anhedonia (SAS)	16.8	8.5	–	–	0.87***
Illness severity (CGI-S)	4.0	1.0	0.17	0.08	0.14
Depressive symptoms (CDSS)	3.3	3.8	0.24*	0.29**	0.27**
Psychotic syndromes (PANSS)	76.2	17.6	0.19	0.23*	0.22*
Negative factor	25.9	6.4	0.23*	0.26*	0.31***
Positive factor	10.8	3.6	0.09	0.07	0.07
Activation factor	13.4	3.3	0.13	0.19	0.23*
Dysphoric mood	11.0	3.0	0.02	0.10	0.10
Autistic preoccupations	16.1	4.4	0.15	0.21	0.16
Psychotic symptoms (PANSS items):					
N3 – Poor rapport	2.35	1.16	0.26*	0.34***	0.19
N4 – Apathetic social withdrawal	3.18	1.16	0.19	0.40***	0.15
N6 – Lack of spontaneity	2.75	1.38	0.28**	0.24*	0.16
G2 – Anxiety	2.24	1.02	0.02	0.22*	0.02
G15 – Preoccupation	2.78	0.97	0.22*	0.22*	0.22*
G16 – Active social avoidance	2.79	1.09	0.22*	0.41***	0.22*

Significance: *p<0.05; **p<0.01; ***p<0.001

Table 3.4 Pearson correlation coefficients of anhedonia scores with personality related variables of 87 patients with schizophrenia and schizoaffective disorders

				Correlation coefficients		
Variables	Tools	Mean	SD	Physical anhedonia	Social anhedonia	PASSAS scale
Perceived emotional distress	TBDI	1.16	0.85	0.24*	0.27*	0.27**
Obsessiveness		1.31	1.10	0.29**	0.18	0.28**
Hostility		0.88	0.96	0.01	0.16	0.10
Sensitivity		1.12	0.93	0.25*	0.22*	0.27**
Depression		1.23	1.10	0.23*	0.23*	0.26*
Anxiety		1.06	1.20	0.09	0.13	0.13
Paranoid ideation		1.37	1.11	0.17	0.17	0.20
Perceived somatic distress	BSI-S	0.90	0.87	0.12	0.20	0.16
Coping styles:						
Task oriented coping	CISS	55.5	16.0	−0.47***	−0.29**	−0.41***
Emotion oriented coping		42.7	13.0	0.03	0.05	0.06
Avoidance coping		48.5	13.5	−0.43***	−0.24*	−0.37***
Self-efficacy	GSES	27.6	7.4	−0.39***	−0.17	−0.32***
Self-esteem	RSES	22.4	4.0	−0.27**	0.13	0.28***
General quality of life	Q-LES-Q	3.5	0.76	−0.50***	−0.35**	0.44***

Significance: *p<0.05; **p<0.01; ***p<0.001

Table 3.5 Pearson correlation coefficients of anhedonia scores with dimensions of functioning and care needs of 87 patients with schizophrenia and schizoaffective disorders

				Correlation coefficients		
Variables	Tools	Mean	SD	Physical anhedonia	Social anhedonia	PASSAS scale
General functioning	GAF	60.9	11.0	–0.14	–0.10	–0.16
Social and Occupational Scale	SOFAS	58.0	12.2	–0.12	–0.07	–0.12
Arizona Sexual Experience Scale	ASEX	20.2	7.3	0.22	0.12	0.16
Community ability	MCAS	25.3	6.1	–0.28*	–0.38***	–0.33***
Care needs (sub-scales):						
Social disability	CANSAS-P	3.5	2.5	0.12	0.09	0.11
Information processing disability		1.0	1.5	0.28**	0.23*	0.27**
Emotional processing disability		4.5	3.6	0.18	0.23*	0.23*
Coping disability		1.0	1.6	0.07	0.08	0.13
Number needs		7.3	4.8	0.22*	0.24*	0.26**
Perceived social support, total	MSPSS	55.7	18.8	–0.42***	–0.40***	–0.47***
Family support		19.9	6.8	–0.24*	–0.24*	–0.39***
Friend support		15.5	8.1	–0.36***	–0.34**	–0.41***
Other significant support		20.2	7.5	–0.44***	–0.41***	–0.50***
Drug-related side effects[a]	DSAS	0.57	0.4	0.03	0.06	0.02

Significance: *p<0.05; **p<0.01; ***p<0.001

[a]Alcohol use (AUS), Drug use (DUS), Substance Abuse (SATS), and Violence risk (RAQ) do not correlate with anhedonia scales (PAS, SAS, and PAS/SAS)

positive correlations with SAS scores: poor rapport (N3; $r=0.34$, $p<0.001$), lack of spontaneity (N6; $r=0.24$, $p=0.024$), preoccupation (G15; $r=0.22$, $p=0.042$), active social avoidance (G16; $r=0.41$, $p<0.001$), apathetic social withdrawal (N4; $r=0.40$, $p<0.001$), and anxiety (G2; $r=0.22$, $p=0.040$). The present study also indicates that PAS scores correlated with CDSS items (hopelessness, morning depression, suicide, and observed depression; r ranged from 0.21 to 0.25, $p<0.005$), while SAS correlated only with depression ($r=0.24$, $p<0.05$), morning and observed depression items ($r=0.33$, $p<0.01$).

3. *PAS scores* were significantly and *negatively correlated* with scores of task oriented and avoidance coping styles (CISS), self-efficacy (GSES) and self-esteem (RSES), general quality of life (Q-LES-Q $_{\text{index}}$), community ability (MCAS) items: social acceptability, interest, effectiveness and network), social support (MSPSS; family and friend support, and other significant support) (r ranges from –0.22 to –0.50).

4. *SAS scores* were significantly and *negatively correlated* with the same variables (r ranges from −0.24 to −0.41) excepting self-efficacy and self-esteem scores.

Age at examination (r = 0.28, p = 0.007), and illness duration (r = 0.24, p = 0.026) were slightly significantly associated with PAS scores, but not with SAS scores (r = 0.04–0.04, p > 0.05).

No significant correlations with illness severity (CGI-S), other PANSS factors (positive, activation factors, dysphoric mood and autistic preoccupations), distress symptoms (somatization, hostility, anxiety, paranoid ideation), emotion oriented coping, general functioning (GAF), social and occupational functioning (SOFAS), sexual functioning (ASEX), care needs like social and coping disabilities (CANSAS-P sub-scales), and all adverse environment variable scores were detected. In addition, PAS and SAS scores were not significantly associated with sex, marital status, DSM-IV SZ/SA sub-types, and types of antipsychotic agents (FGAs, SGAs, combined therapy) (all p's >0.05).

3.5.2 Partial Correlations

Partial correlation analysis was applied in order to test effect of nine independent variables on Pearson's correlations of anhedonia scales (PAS, SAS, and PAS/SAS) with PANSS negative factor and depressive symptoms (CDSS).

The partial correlations of *anhedonia scales with depressive symptoms* do not remain significant when the effect of the PANSS Negative factor, self-esteem, self-efficacy, task oriented coping, somatization (for PAS only), and emotional distress were partialled-out (Table 3.6). However, correlations of anhedonia scales with PANSS Negative factor remain significant when the CDSS, self-esteem, self-efficacy and task oriented coping (except PAS), emotional distress, somatization, and social support were used as a partial variables. Correlation coefficients of anhedonia scales with both negative and depressive symptoms do not remain significant after adjustment for general quality of life scores. The correlation coefficient (r) of general quality of life with PAS score was – 0.49 (p < 0.001) and SAS was – 0.31 (p < 0.001).

The negative relationship remained significant when the effect of both the PANSS negative and Calgary Depression Scale scores was removed from the correlation matrix:

(a) Q-LES-L_{index} – PAS = − 0.46 (p < 0.001) and SAS was – 0.26 (p < 0.05) after adjusting for PANSS negative factor ratings;
(b) Q-LES-L_{index} – PAS = − 0.45 (p < 0.001) and SAS was – 0.21 (p < 0.05) after adjusting for CDSS depressive ratings.

Finally, controlling for three personality related variables together (GSAS, RSAS, and CISS), analysis revealed the loss of significance of partial correlations of anhedonia with negative and depressive symptoms.

Table 3.6 Partial Pearson's correlations of anhedonia scales with negative and depressive symptoms

Variables		PANSS negative factor			Calgary depression scale		
		PAS	SAS	PASSAS	PAS	SAS	PASSAS
Pearson's correlations	Tools	0.27**	0.28**	0.31**	0.23*	0.26*	0.27**
Partial variables[a]:		*Partial correlations*					
PANSS Negative factor	PANSS	–	–	–	0.16	0.19	0.20
Calgary Depression Scale	CDSS	0.21	0.22*	0.25*	–	–	–
Self-efficacy	GSES	0.17	0.24*	0.24*	0.11	0.20	0.18
Self-esteem	RSES	0.24*	0.26**	0.29**	0.07	0.20	0.16
Task oriented coping	CISS	0.16	0.22*	0.22*	0.12	0.19	0.18
Emotional distress index		0.23*	0.24*	0.28**	0.11	0.15	0.14
Emotional distress, total	TBDI	0.20	0.21	0.24*	0.10	0.13	0.13
Somatization	BSI-S	0.25*	0.25*	0.28**	0.20	0.21*	0.24*
Social support	MSPSS	0.33***	0.34***	0.40***	0.25*	0.28**	0.31**
General quality of life	Q-LES-Q	0.14	0.20	0.20	–0.06	0.10	0.03
GSES, RSES, and CISS		0.10	0.14	0.14	–0.01	0.12	0.07

Significance: *p<0.05; **p<0.01; ***p<0.001

[a]*Partial variables.* The influence of these variables is removed by sweeping them from the remaining variables

3.6 Hedonic Capacity Levels

When the PAS and SAS cut-offs were used, 59 of 87 patients reached PAS cut-off scores (67.8 %; *physical anhedonics*), 62 patients reached SAS cut-off score (71.3 %; *social anhedonics*), 29 patients had to reach PAS or SAS cut-off (*33.3 %; hypohedonics*), while 46 of 87 patients reached both PAS/SAS cut-offs (*52.9 %; double anhedonics*), and 12 (14 %) did not reach the PAS or SAS cut-off. Consequently, 32.2 % (PAS) and 28.7 % (SAS) of patients scored within the normal range (*normal hedonics*), consistent with published findings [34, 35].

Figure 3.6 compares independent variables between three subgroups of patients stratified by levels of hedonic capacity (ANOVA, df=2,78). The comparison revealed that 'double anhedonics' had increased scores on PANSS Negative factor (F=4.6, p=0.013), depressive symptoms (CDSS; F=5.1, p=0.008), emotional distress symptoms (TBDI total score, F=3.8, p=0.027; obsessiveness, F=5.0, p=0.009; sensitivity, F=4.3, p=0.016; paranoid ideation, F=3.2, p=0.047), and information processing disability (CANSAS, F=3.9, p0.023) compared to 'normal hedonics'. At the same time, 'double anhedonics' had lower levels of task oriented (F=7.2, p<0.001) and avoidance coping (F=5.5, p=0.006), self-efficacy (F=4.1, p=0.021), community ability (MCAS, F=6.3, p=0.003), perceived social support (MSPSS total scores; F=9.7, p<0.001), family support (F=4.3, p=0.017), friend support (F=6.0, p=0.004), and other significant support (F=9.4, p<0.001) compared to 'normal hedonics' and/or 'hypohedonics' (Tukey-Kramer multiple-comparison test, p<0.05).

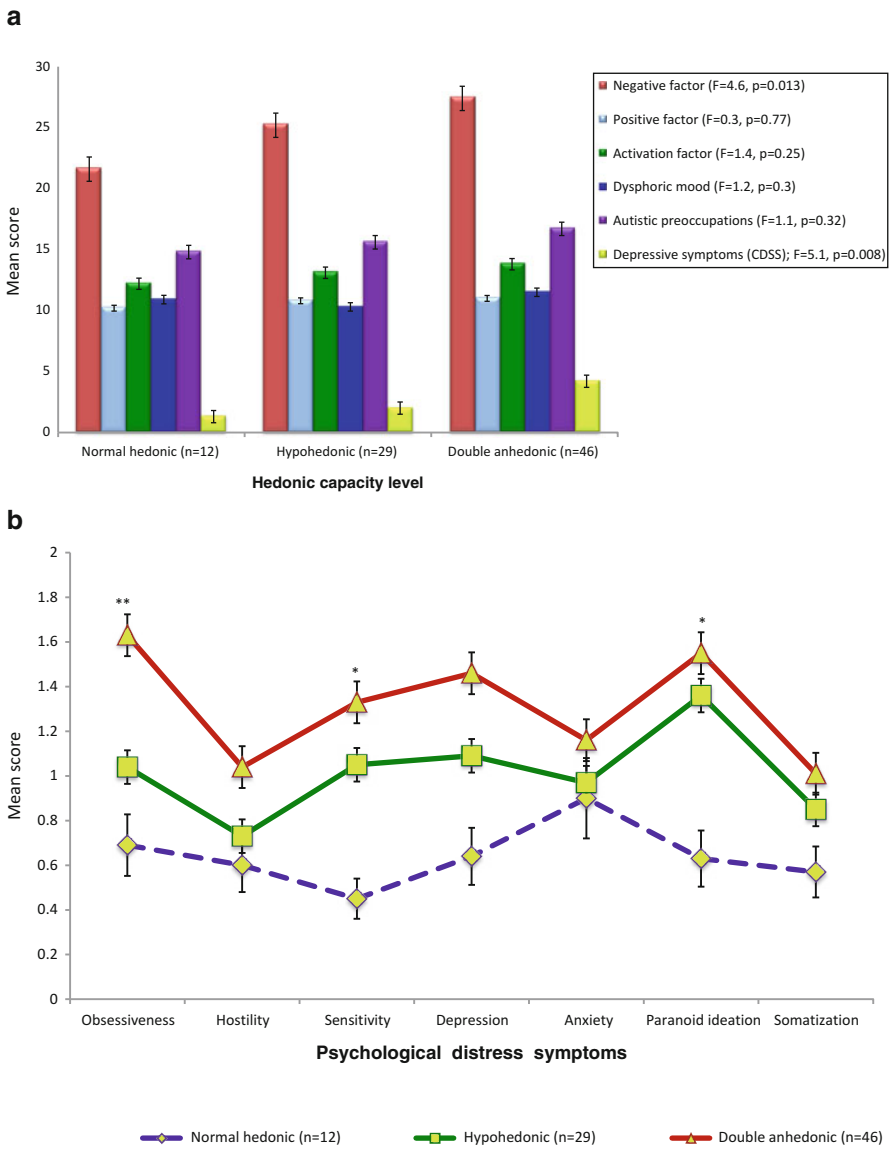

Fig. 3.6 Mean scores of independent variables by hedonic capacity levels of 87 patients with schizophrenia and schizoaffective disorders. (© M. S. Ritsner (2014) and used by permission). (**a**) Mean PANSS factor and CDSS scores (± SE). SE – Standard error. (**b**) Mean distress symptom scores (± SE). (**c**) Mean coping style scores (± SE). (**d**) Mean self-constructs and social support scores (± SE)

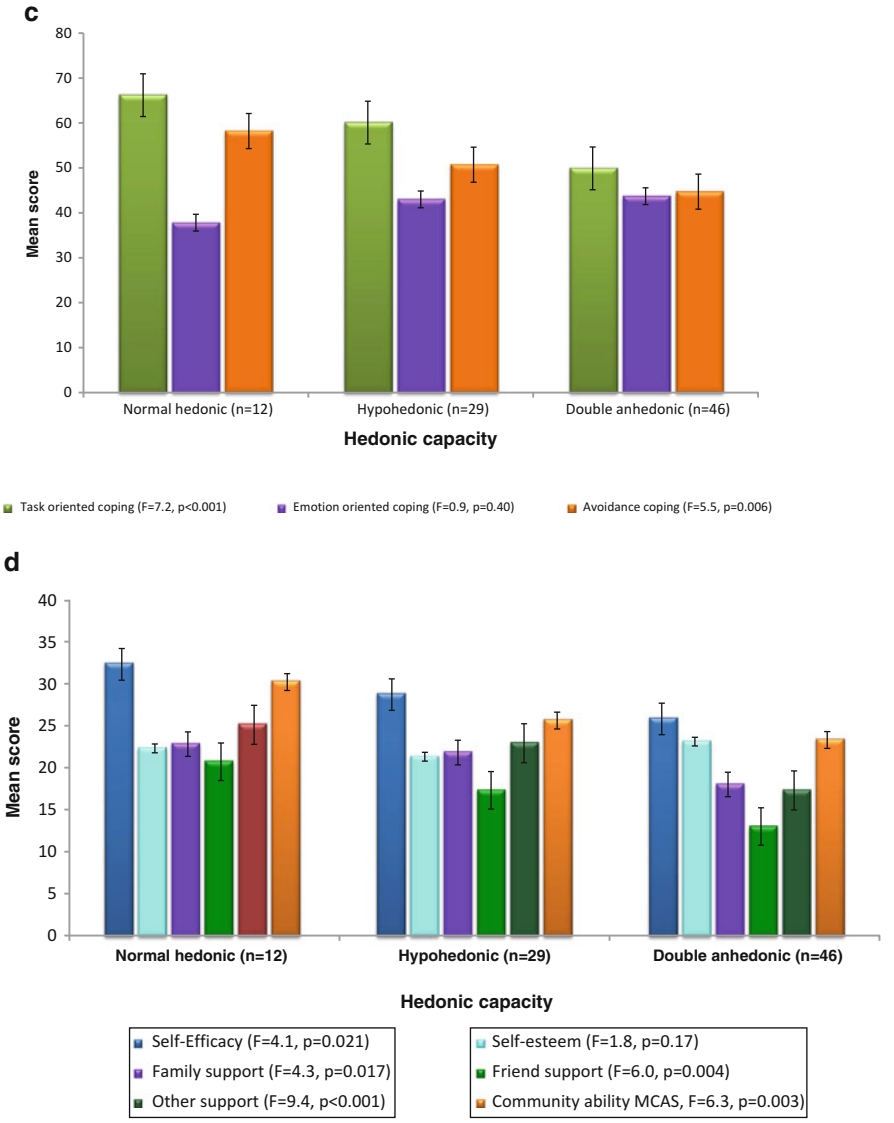

Fig. 3.6 (continued)

Figure 3.7 presents the relationship between satisfaction with quality of life and hedonic capacity. 'Double anhedonics' had poorer satisfaction with all quality of life domains compared to 'normal hedonics', and in social relationships, general activities, life satisfaction, and satisfaction with medicine compared to 'hypohedonics' (Tukey-Kramer multiple-comparison test, $p < 0.05$). However,

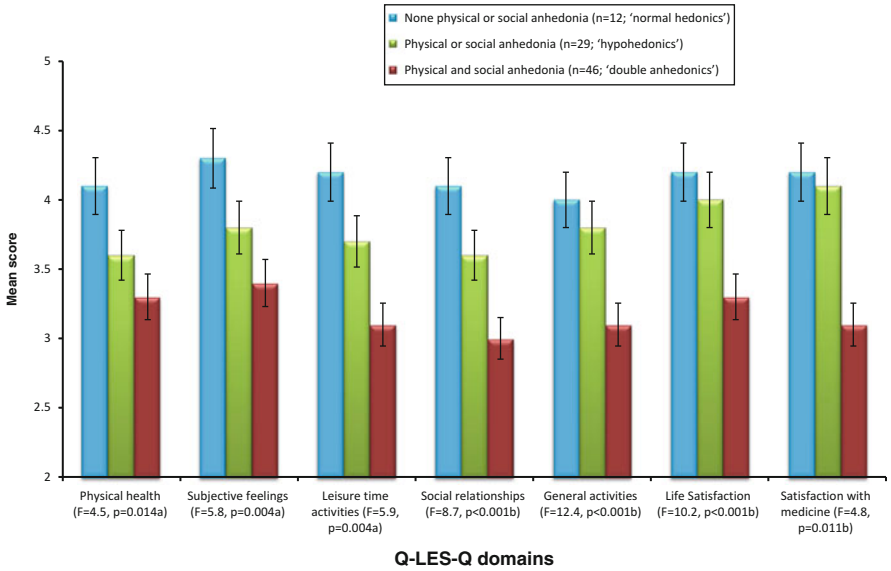

Fig. 3.7 Mean scores of domain-specific quality of life by severity of hedonic deficit of patients with schizophrenia and schizoaffective disorder (© M. S. Ritsner (2014) and used by permission)

no significant differences in Q-LES-Q domains were found between 'normal hedonics' and 'hypohedonics' ($p > 0.05$) [104].

Figure 3.8 compares four distinct patient subgroups with different courses of general quality of life over 10 years by hedonic capacity levels. ANOVAs showed significant between-group differences for the PAS ($F_{3,87} = 9.5$, $p < 0.001$) and SAS ($F_{3,87} = 4.3$, $p = 0.007$) scores. Specifically, patients who were permanently dissatisfied, and revealed worsened general quality of life over time had significantly higher hedonic deficits (PAS/SAS scores) than patients who were permanently satisfied, and improved over the follow up period.

No significant differences between hedonic capacity levels and illness severity (CGI-S; $F = 0.9$, $p = 0.41$), other symptoms: PANSS total score ($F = 3.0$, $p = 0.055$), positive factor ($F = 0.3$, $p = 0.77$), activation factor ($F = 1.4$, $p = 0.25$), dysphoric mood ($F = 1.2$, $p = 0.30$), autistic preoccupations ($F = 1.1$, $p = 0.32$), side effects (DSAS; $F = 0.9$, $p = 0.37$); general functioning (GAF; $F = 1.0$, $p = 0.35$), social and occupational functioning (SOFAS; $F = 1.2$, $p = 0.29$), and sexual functioning (AXES; $F = 1.1$, $p = 0.33$) scores, emotional distress symptoms (TBDI): hostility ($F = 1.4$, $p = 0.24$), depression ($F = 2.8$, $p = 0.066$), anxiety ($F = 0.3$, $p = 0.72$), and somatization (BSI-S; $F = 1.2$, $p = 0.30$), emotion oriented coping (CISS; $F = 0.9$, $p = 0.40$), and self-esteem (RSES; $F = 1.8$, $p = 0.17$) scores were observed. Furthermore, no significant differences were detected between hedonic capacity subgroups in terms of gender, age, education, duration of illness, type and dosage of medication.

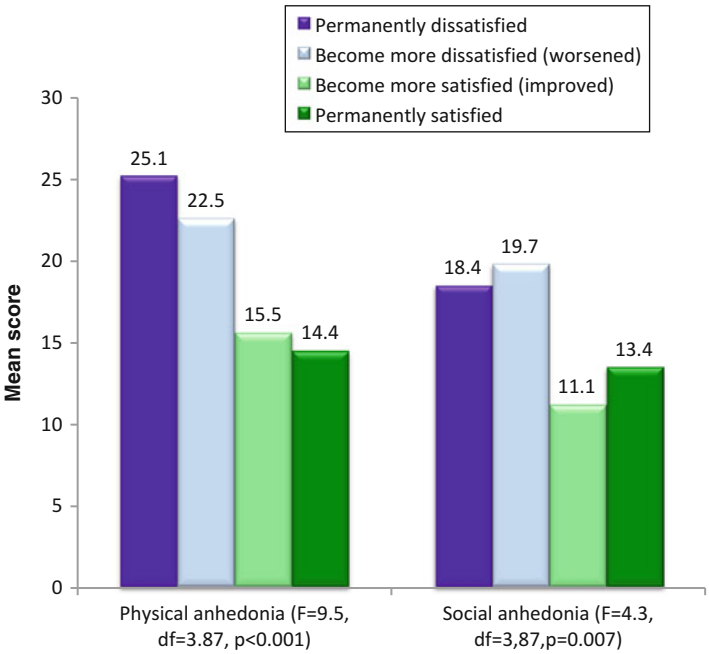

Fig. 3.8 Mean physical and social anhedonia scores of schizophrenia and schizoaffective disorder patients with different course of general quality of life over 10 years (© M. S. Ritsner (2014) and used by permission)

3.7 PAS and SAS Items

On the physical anhedonia scale items, more than 40 % of the patients with SZ/SA reported that they had an anhedonia experience (items 8, 10, 11, 14, 15, 23, 31, 32, 40–42, and 50):

- item 8 ("*I have had very little fun from physical activities like walking, swimming, or sports*"),
- item 10 ("*On hearing a good song, I have seldom wanted to sing along with it*"),
- item 11 ("*I have always hated the feeling of exhaustion that comes from vigorous activity*"),
- item 14 ("*Sunbathing isn't really more fun than lying down indoors*"),
- item 15 ("*There just are not many things that I have ever really enjoyed doing*"),
- item 23 ("*When I have seen a statue, I have had the urge to feel it"*),
- item 31 ("*I have often felt uncomfortable when my friends touch me"*),
- item 32 ("*I have never found a thunderstorm exhilarating*"),
- item 40 ("*Sex is okay, but not as much fun as most people claim it is"*),
- item 41 ("*I have sometimes danced by myself just to feel my body move with the music"*),
- item 42 ("*I have seldom cared to sing in the shower"*), and

- item 50 ("*I have usually finished my bath or shower as quickly as possible just to get it over with*").

At the same time, on the social anhedonia scale items, more than 40 % of the participants reported that they have the anhedonia experience (items 2, 3, 8, 13, 15, 29, 30, 32, 34, 38, and 39):

- item 2 *("I attach very little importance to having close friends"),*
- item 3 ("*I prefer watching television to going out with other people*"*),*
- item 8 ("*Although there are things that I enjoy doing by myself, I usually seem to have more fun when I do things with other people*", *reverse item*),
- item 13 ("*My emotional responses seem very different from those of other people*"),
- item 15 *("Just being with friends can make me feel really good"*, *reverse item),*
- item 29 *("There are few things more tiring than to have a long, personal discussion with someone"),*
- item 30 *("It made me sad to see all my high school friends go their separate ways when high school was over",* reverse item*),*
- item 32 *("Making new friends isn't worth the energy it takes"),*
- item 34 *("People who try to get to know me better usually give up after awhile"),*
- item 38 *("I don't really feel very close to my friends"),* and
- item 39 *("My relationships with other people never get very intense").*

SZ/SA patients had higher frequency of mentioned above PAS and SAS items than those healthy Chinese sample [45] (Fig. 3.9).

3.8 Factor Analysis

3.8.1 Factor Structure of Dependent and Independent Variables

An exploratory factor analysis was performed to identify the underlying factors (subsets of variables) associated with the PAS and SAS scores and independent variables. The principle axis method of factor analysis with varimax rotated factor matrix was performed. The eigenvalues are used to determine how many factors to retain. One rule-of-thumb is to retain those factors whose eigenvalues are greater than one. Variables with an absolute loading greater than the amount set in the minimum loading option ($\geq$0.4) were selected.

Three factors were identified on the highest eigenvalues (4.35, 4.05, and 4.77, respectively; see Table 3.7).

1. The first factor, labelled *'Illness & Function Ability'*, generally captures severity of illness, symptoms, and difficulties in functioning (general, social and occupational).
2. The second factor, labelled '*Anhedonia & Personality*', included negative loadings physical anhedonia (PAS) scores together with positive loading self-efficacy,

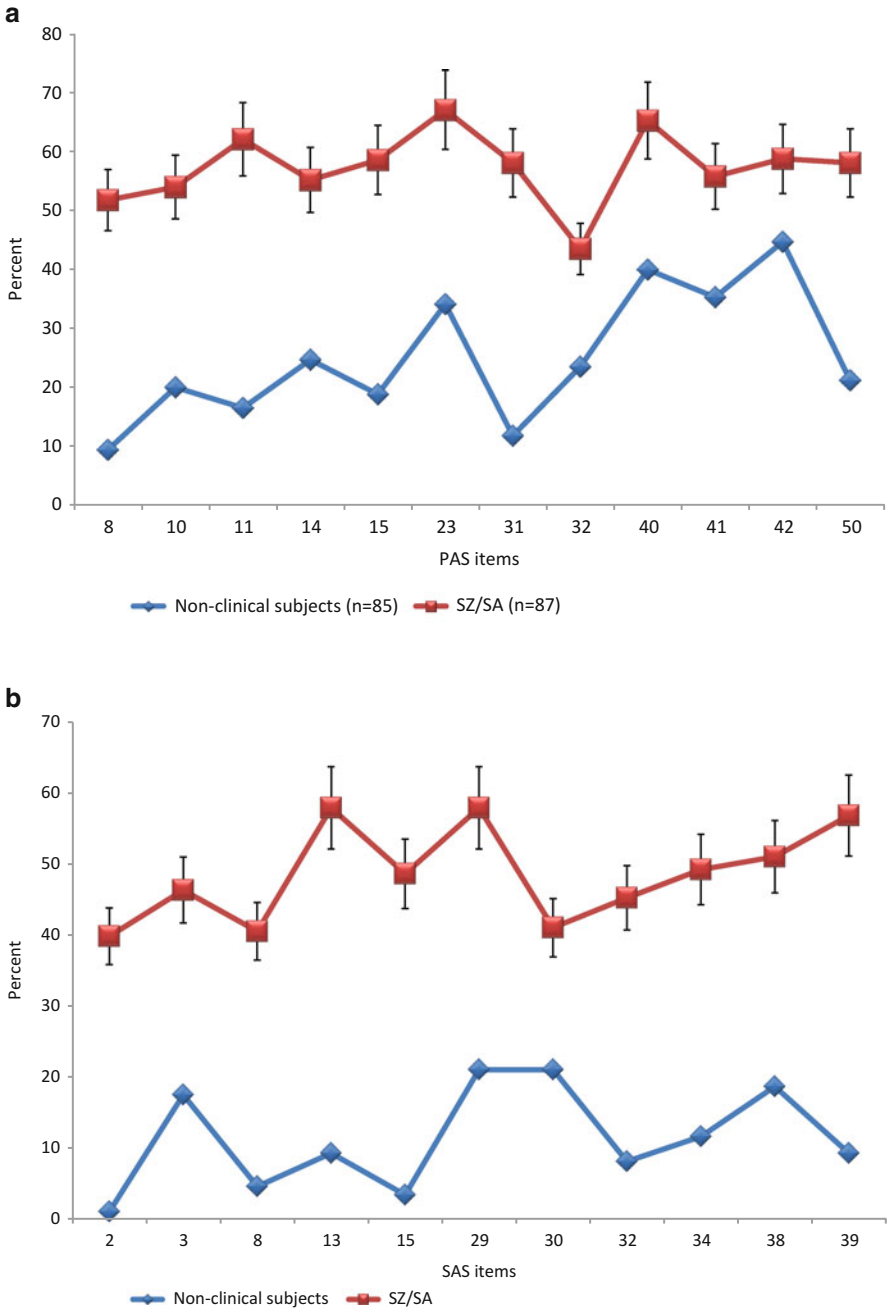

Fig. 3.9 Schizophrenia and schizoaffective (SZ/SA) patients compared to sample of non-clinical people [45] (© M. S. Ritsner (2014) and used by permission). (**a**) Physical Anhedonia Scale. (**b**) Social Anhedonia Scale

Table 3.7 Factor loadings and communalities after varimax rotation of variable values among 87 patients with SZ/SA disorders[a]

		Factor 1 (Eigenvalue = 4.35)		Factor 2 (Eigenvalue = 4.05)		Factor 3 (Eigenvalue = 4.77)	
		'Illness & Function Ability'		*'Anhedonia & Personality'*		*'Distress & Unmet Needs'*	
Variables	Tools	Factor loading	Communalities	Factor loading	Communalities	Factor loading	Communalities
Physical anhedonia	PAS	–0.1774	0.0315	–0.5821	0.3389	–0.0222	0.0004
Social anhedonia	SAS	–0.2916	0.0850	–0.3440	0.1183	0.0697	0.0048
Illness severity	CGI-S	–0.7603	0.5781	–0.0219	0.0004	0.2727	0.0743
Calgary Depression Scale	CDSS	–0.0878	0.0077	–0.2606	0.0679	0.6278	0.3941
Psychotic syndromes							
Negative factor	PANSS	–0.7690	0.5914	–0.1636	0.0267	0.1427	0.0203
Positive factor		–0.5632	0.3172	0.1633	0.0266	0.4292	0.1842
Activation factor		–0.6834	0.4671	0.0039	0.0000	0.0206	0.0004
Autistic preoccupations		–0.1169	0.0136	0.1645	0.0270	0.7356	0.5412
Dysphoric mood		–0.8011	0.6418	0.1267	0.0160	0.1881	0.0354
General functioning	GAF	0.7340	0.5387	0.2431	0.0591	–0.1436	0.0206
Social and Occupational Scale	SOFAS	0.6986	0.4881	0.2612	0.0682	–0.1257	0.0158
Multnomach Community Ability Scale	MCAS	0.5288	0.2796	0.2205	0.0486	–0.3146	0.0990
Sexual Functioning	ASEX	–0.0412	0.0017	–0.2099	0.0440	0.4345	0.1888
Care needs:							
Social disability	CANSAS-P	–0.1323	0.0175	–0.0839	0.0070	0.4213	0.1775
Information processing disability		–0.1672	0.0279	–0.2144	0.0459	0.3691	0.1362
Emotional processing disability		–0.1975	0.0390	–0.3210	0.1030	0.4793	0.2297
Coping disability		–0.1163	0.0135	–0.0324	0.0010	0.4769	0.2275
Social support	MSPSS	0.2273	0.0516	0.6584	0.4335	–0.1989	0.0395
Side effects, total score	DSAS	–0.1646	0.0271	0.0786	0.0061	0.6669	0.4448

(continued)

Table 3.7 (continued)

Variables	Tools	Factor 1 (Eigenvalue = 4.35) *'Illness & Function Ability'*		Factor 2 (Eigenvalue = 4.05) *'Anhedonia & Personality'*		Factor 3 (Eigenvalue = 4.77) *'Distress & Unmet Needs'*	
		Factor loading	Communalities	Factor loading	Communalities	Factor loading	Communalities
Emotional distress index	TBDI	–0.1722	0.0296	–0.2289	0.0524	0.8216	0.6751
Somatization	BSI-S	–0.2013	0.0405	–0.0744	0.0055	0.6968	0.4856
Coping styles:							
Task oriented coping	CISS	0.0614	0.0037	0.8148	0.6639	–0.1189	0.0141
Emotion oriented coping		–0.0665	0.0044	0.0255	0.0006	0.5364	0.2877
Avoidance coping		–0.1169	0.0136	0.6997	0.4896	0.0957	0.0091
Self-efficacy	GSES	0.0495	0.0024	0.7550	0.5701	–0.0450	0.0020
Self-esteem[b]	RSES	0.1178	0.0138	–0.5969[b]	0.3563	0.4486	0.2012
General quality of life	Q-LES-Q $_{index}$	0.1483	0.0220	0.6854	0.4698	–0.5114	0.2615
Factors' contribution (%)		31.7	–	29.5	–	34.8	–

[a]Variables with an absolute loading greater than the amount set in the minimum loading option (≥0.40) were selected
[b]A decreased score reflects increased self-esteem

self-esteem, task oriented coping, avoidance coping, general quality of life, and perceived social support.

3. The *third factor*, called *'Distress & Unmet Needs'*, includes positive loading depressive and positive symptoms, autistic preoccupations, emotional distress index, somatization, and emotion oriented coping style, sexual functioning, side effects, self-esteem, care needs, and negative loading general quality of life.

Correspondingly, these factors accounted for 31.7, 29.5, and 34.8 % of the total variance of the 27 measures. Social anhedonia (SAS) and information processing disability (CANSAS-P) did not reach the minimum loading option (0.4).

Although there are many studies that used the PAS and SAS to evaluate anhedonia in schizophrenia, depression and other disorders, there have been some concerns regarding the construct validity of these scales [105]. For example, Leventhal et al. [106] compared the psychometric properties of three self-report scales: the Snaith-Hamilton Pleasure Scale [107], Fawcett-Clark Pleasure Capacity Scale [108], and the PAS using a sample of college students (n = 157). Confirmatory factor analysis revealed a *Hedonic Capacity factor* that was not significantly related to the PAS. Our preliminary exploratory factor analysis with 101 raw scores of the PAS/SAS yielded two and three-factor solutions [unpublished]. The two-factor solution yielded 36 and 17 items from the PAS/SAS. Each factor included items from both the PAS and SAS that contradict the conclusion that PAS and SAS are different mono-dimensional scales [29]. The three-factor solution accounted for 10.5, 18.3, and 26.8 % of the total variance of the 56 items. Forty-five of 101 PAS/SAS items did not reach the minimum loading option (≥0.4).

- *Factor 1* (n = 21 items; eigenvalue = 10.6) included items 1, 3, 34, 48, 60 from the PAS; and items 5, 7, 9, 11, 15, 19–22, 24, 25, 30–32, 38, 39 from the SAS.
- *Factor 2* (n = 16 items; eigenvalue = 7.9) included items 19, 25, 28, 31, 44 from the PAS, and items 1, 3, 10, 13, 14, 17, 27–29, 35, 37 from the SAS.
- *Factor 3* (n = 19 items; eigenvalue = 8.5) included items 2, 7, 14, 20, 24, 26, 29, 30, 33, 36, 38, 39, 46, 52, 58, 59, 61 from the PAS, and items 4 and 18 from the SAS.

Additional limitations of the PAS and SAS measures should be mentioned. These tools assess physical and social hedonic capacity based on whether an individual enjoys certain activities, for instance, being around people, looking at stars at night, playing with puppies and kittens, should be pleasurable. Although this may be the case for most people, some people may not enjoy the activities described by the assessment tool. If an individual currently does not enjoy those particular activities and never enjoyed them in the past, they do not have anhedonia [4]. Thus, further research is needed to clarify the factor structure of the PAS and SAS scales [see more in this book: Eduardo Fonseca-Pedrero et al., "Measuring anhedonia in schizophrenia-spectrum disorders: a selective update"].

3.9 Conclusions and Future Directions

The principle results from the study indicated the following. The PAS (22.0 ± 8.6) and the SAS (17.0 ± 8.4) scores for the entire sample were elevated compared to normative data (15.0 ± 7.0, and 9.4 ± 5.5, respectively [44].

1. *The hedonic capacity scores, measured with PAS (22.0 ± 8.6) and SAS (17.0 ± 8.4), for the entire sample were elevated compared to normative data; consistent with previously reported findings in schizophrenia and schizoaffective disorder. Physical anhedonia was observed among 67.8 % of the patients, social anhedonia found among 71.3 %, while 'double anhedonia' was indicated among 52.9 % of the patients and 14 % were defined as 'normal hedonics'. Correlation coefficient between the PAS and SAS scores was 0.51 ($p < 0.001$).*
2. *More than 40 % of the patients with SZ/SA reported that they had an anhedonia experience on 12 PAS items (8, 10, 11, 14, 15, 23, 31, 32, 40–42, and 50) and on 11 SAS items (2, 3, 8, 13, 15, 29, 30, 32, 34, 38, and 39). On these items SZ/SA patients had higher physical and social anhedonia than healthy Chinese subjects* [45].
3. *Two groups of independent variables significantly correlated with PAS and SAS scores: with positive and negative association (Table 3.8). Negative and depressive symptoms, emotional distress and unmet needs positively associated with elevated the PAS and SAS scores or hedonic capacity deficit (first group), while higher task oriented and avoidance coping styles, self-efficacy, self-esteem, community ability, general quality of life, and social support scores correlated with lower anhedonia scale scores indicating better hedonic capacity levels of the patients (second group).*
4. *Partial correlation of PAS and SAS scores with the PANSS Negative and CDSS scores, after controlling for general quality of life, did not remain significant. No significant partial correlation was found between the CDSS and anhedonia scales when the effect of the PANSS Negative factor, self-esteem, self-efficacy, task oriented coping, and emotional distress scores were controlled. At the same time, correlations of anhedonia scales with the PANSS Negative factor remained significant when the CDSS, self-esteem, self-efficacy, and emotional distress, somatization, and social support scores were used as partial variables. Finally, controlling for three personality related variables together (GSES, RSES, and CISS), analysis revealed loss of significance of partial correlations of anhedonia scales with both negative and depressive symptoms.*
5. *Factor analysis with anhedonia (PAS and SAS mean scores) and 25 independent variables revealed a three-factor solution ('Illness & Function Ability', 'Anhedonia & Personality', and 'Distress & Unmet Needs'). Only one of them ('Anhedonia & Personality') included physical anhedonia (negative loadings; PAS) together with positive loading self-efficacy, self-esteem, task oriented coping, avoidance coping, general quality of life, and perceived social support. Social anhedonia (SAS) did not*

Table 3.8 Summary of correlation analysis

Low hedonic capacity		High hedonic capacity	
Physical hedonic capacity (*r* ranges from 0.22 to 0.29)	Social hedonic capacity (*r* ranges from 0.22 to 0.40)	Physical hedonic capacity (*r* ranges from –0.22 to –0.50)	Social hedonic capacity (*r* ranges from –0.24 to –0.41)
Depressive symptoms (CDSS)	Depressive symptoms (CDSS)	Task oriented coping (CISS)	Task oriented coping (CISS)
Negative symptoms (PANSS)	Negative symptoms (PANSS)	Avoidance coping (CISS)	Avoidance coping (CISS)
PANSS items:	PANSS items:	Quality of life (Q-LES-Q $_{index}$)	Quality of life (Q-LES-Q $_{index}$)
Poor rapport (N3)	Poor rapport (N3)	Community ability (MCAS)	Community ability (MCAS)
Lack of spontaneity (N6)	Lack of spontaneity (N6)	Social acceptability	Social acceptability
Preoccupation (G15)	Preoccupation (G15)	Social interest	Social interest
Active social avoidance (G16)	Active social avoidance (G16)	Social effectiveness	Social effectiveness
	Anxiety (G2)	Social network	Social network
	Apathetic social withdrawal (N4)	Social support (MSPSS)	Social support (MSPSS)
Emotional distress (TBDI)	Emotional distress (TBDI)	Self-efficacy (GSES)	
Depression, Sensitivity	Depression, Sensitivity	Self-esteem (RSES)	
Obsessiveness			
Information processing disability (CANSAS-P)	Information processing disability (CANSAS-P) ANSAS-P)		
	Emotional processing disability (CANSAS-P)		

reach the minimum loading option (0.4). Thus, well-fitting 3-factor model provides support for dimensional structure of 25 items that differentially associated into three domains: psychopathology and functioning, anhedonia and personality features, distress and care needs related variables. However, this model should be interpreted with caution owing to the limitations of this study.

6. *Hedonic capacity deficit did not associate with some of the following variables: illness severity (CGI-S), PANSS positive, activation factors, dysphoric mood and autistic preoccupations, somatization, emotion oriented coping (CISS), general functioning (GAF), social and occupational functioning (SOFAS), sexual functioning (ASEX), violence risk, alcohol, drug and substance use (RAQ, AUS, DUS, SATS), DSM-IV SZ/SA sub-types, types of antipsychotic agents (FGAs, SGAs, combined therapy), gender, and marital status.*

3.10 Comments

3.10.1 Hedonic Capacity

The descriptive findings indicated that our sample included individuals with a reasonable level of variance of key variables. In this study no significant differences between SZ and SA patients were found on both the physical anhedonia and social anhedonia scores, consistent with previously published findings [43]. The mean PAS (22.0 ± 8.6) and the SAS (17.0 ± 8.4) scores for the entire sample (SZ/SA) were consistent with those reported by Pelizza and Ferrari [35]: 20.9 ± 8.0 and 15.9 ± 6.4, respectively. These findings indicate elevated scores on PAS and SAS compared to normative data (15.0 ± 7.0, and 9.4 ± 5.5, respectively [44]. Men showed significantly higher levels of physical and social anhedonia than women [45]. Distribution of our sample by hedonic levels is also consistent with published findings [34, 35].

Table 3.9 summarized the main significant associations between dependent and independent variables.

3.10.2 Illness-Related Dimensions (CGI-S, PANSS, CDSS)

Anhedonia was found to be elevated in community populations [5, 6], in schizophrenia probands' unaffected relatives [7, 109], and in patients at ultra-high risk for psychosis in comparison with patients who did not develop psychosis [8]. Anhedonia has long been presented as a negative symptom of schizophrenia, and in depressive episodes. DSM-IV suggests that anhedonia is a core symptom of Major Depression Disorder (MDD), but no study to date has adequately addressed the sensitivity or specificity of this symptom for MDD [110]. Although several studies indicated the relationship of anhedonia with negative symptoms of schizophrenia [35, 111], other studies have reported that anhedonia levels are not associated with negative or depressive symptoms [16, 112, 113].

In the present study a slight correlation was indicated between PAS, SAS, PANSS negative factor and CDSS scores (r ranged from 0.23 to 0.29, $p < 0.05$). Only six of 30 items of PANSS were significantly correlated with anhedonia measures (N3 – poor rapport, N4 – apathetic social withdrawal, N6 – lack of spontaneity, G2 – anxiety, G15 – preoccupation, G16 – active social avoidance). The results further suggest that these correlations of anhedonia scales with both negative and/or depressive symptoms do not remain significant after controlling for general quality of life, self-esteem, self-efficacy, and task oriented coping (see Table 3.6). In addition, factor analysis indicated association of psychopathological symptoms with two other factors: *'Illness & Function Ability'* factor with severity of illness, PANSS negative, positive, activation, and dysphoric mood, and *'Distress & Unmet Needs' factor with the* CDSS, PANSS positive factor, and autistic preoccupations). Both these main factors did not associate with anhedonia measures.

Table 3.9 Summary of the main associations between variables

Variables	Tools	Double anhedonics versus normal hedonics	Correlations with PAS or SAS			Factor analysis		
			*Elevated a*nhedonia level	Lowered anhedonia level	Partial correlation	Illness & Function Ability	Anhedonia & Personality	Distress & Unmet Needs
Physical anhedonia	PAS						+	
Social anhedonia	SAS							
Illness severity	CGI-S					+		
Depressive symptoms	CDSS	+	+					+
Negative factor	PANSS	+	+		+	+		
Positive factor								+
Autistic preoccupations	PANSS							+
Emotional distress	TBDI	+	+		+			
Somatic distress	BSI-S				+			+
Coping styles	CISS	+		+	+			+
Self-efficacy	GSES	+		+	+		+	
Self-esteem	RSES			+	+		+	
Perceived quality of life	Q-LES-Q			+	+		+	
General functioning	GAF					+		
Social and Occupational functioning	SOFAS					+		
Sexual Functioning	ASEX							+
Community ability	MCAS	+		+		+		
Information & emotional processing disabilities	CANSAS	+	+					+
Social support	MSPSS	+		+			+	
Drug-related side effects	DSAS							+

The influence of these variables (+) on partial Pearson's correlations of anhedonia scales with negative and depressive symptoms
Alcohol use (AUS), Drug use (DUS), Substance Abuse (SATS), and Violence risk (RAQ) do not associate with dependent and other independent variables

Thus, obtained findings suggest that hedonic capacity deficit (anhedonia) is not significantly associated with negative or depressive symptoms.

3.10.3 Personality Related Dimensions

The 'Anhedonia & Personality' main factor presents an association of physical anhedonia with coping styles (task oriented and avoidance coping), self-efficacy, self-esteem, social support, and general quality of life. According to a factor loading, better hedonic capacity is related to the better coping strategies, self-constructs, and perceived social support and quality of life (Table 3.7).

3.10.3.1 Emotional and Somatic Distress (TBDI, BSI-S)

Self-reported emotional distress experienced by schizophrenia patients is associated with symptom expression [54, 114–116], and side effects of antipsychotic agents [117, 118], with temperament types, emotion-oriented coping, and weak self-constructs [119], and psychosocial functioning [120]. *S*omatization is associated with elevated emotional distress [36, 121], severity of depressive symptoms [114] and anxiety [122], with gender (women) [55], age (being aged 45–64), marital status (being separated, widowed, or divorced), and/or with low educational and economic levels [58]. Anhedonia might possibly accompany stress because the loss of the pleasure of aiming for a goal and achieving it could lead to immobility [123].

The present study revealed that emotional distress (obsessiveness, sensitivity, depression) slightly correlated with PAS and SAS scores, and was significantly elevated in the 'double anhedonics' group, while somatisation scores did not associate with hedonic capacity scores.

3.10.3.2 Coping Abilities (CISS)

There is evidence indicating a significant relationship between coping strategies and both severity of symptoms and emotional distress in SZ/SA patients [124–126]. Experienced emotional distress, self-efficacy, and social support predicted coping strategies used by schizophrenia patients [127]. Two coping strategies (task oriented and avoidance) demonstrated significant associations with PAS and SAS scores in this study (Table 3.4). Emotion oriented coping was related to the third main factor (*'Distress & Unmet Needs'*).

3.10.3.3 Self-efficacy and Self-esteem (GSES, RSES)

The self-concept is a factual description of how you perceive yourself. The construct of self-efficacy was introduced by Albert Bandura and represents one core

aspect of his social-cognitive theory [128, 129]. The self-efficacy theory suggests that although some individuals may have the capacity to perform functional behaviors, they may or may not have confidence that they can successfully perform these behaviors in real-world settings. According to this concept self-efficacy makes a difference in how people feel, think and act. For example, people with a weak sense of self-efficacy avoid challenging tasks, believe that difficulties in life are beyond their control, and quickly lose confidence in themselves when falling short or failing.People who have high self-esteem are more likely to have higher self-efficacy traits than those with low self-esteem.

This study showed that increased self-constructs, measured with GSES and RSES, might improve physical, but not social anhedonia as confirmed by factor analysis.

Few studies have assessed the association of self-efficacy with personality- and illness-related variables. For instance, the GSES scores strongly correlate with other self-evaluation constructs, including self-esteem, locus of control, and neuroticism [130].

Self-efficacy strongly related to negative symptoms and moderately associated with social and general functioning [131, 132]. Patients with negative symptoms reported low self-efficacy estimates for everyday tasks, which they performed less frequently than the controls. Overall, the findings suggest that low self-efficacy is characteristic of negative symptom patients, but the causal status of such beliefs remains unclear [133].

Self-esteem, a global and complex concept, is the degree of value a person considers for himself. It is comprised of both appraisal of self-worth based on personal achievements and anticipation of evaluation by others [134]. Some models of global self-esteem suggest that it is both a trait and a state measure [135].

The nature of the relationship between reduced self-esteem and psychiatric disorders remain uncertain. It is not yet clear if reduced self-esteem that occurs in a few psychiatric conditions is relatively specific to them, or if it is simply representative of poor psychological health regardless of the diagnosis.

A number of previous studies have reported lower self-esteem in psychiatric patients compared to normal controls. Low self-esteem is associated with presentations of mental disorders [136], appears to increase the risk of psychiatric disorders such as depression, eating disorders and substance abuse [137]. In psychotic disorders, low self-esteem has been implicated in both the development of delusions [138] and the maintenance of psychotic symptoms [139].

Low self-esteem significantly correlated with various factors, including schizophrenia [140, 141], premorbid adjustment, PANSS positive (items P3, and P6) and negative symptoms (N3, N7) [142], depression, eating disorders, anxiety disorders, and alcohol and drug abuse [143–145]. Self-esteem fully mediated the relationship between role functioning and psychiatric symptoms of individuals with severe mental illness [146].

Patients with schizophrenia and low self-esteem are expected to have a compromised quality of life [36]. Recently, Chinese researchers examined 133 people with

schizophrenia and 50 healthy controls and indicated that compared to the controls people with schizophrenia showed lower self-esteem, higher levels of dysfunctional beliefs and negative coping styles [147].

3.10.3.4 Perceived Quality of Life (Q-LES-Q)

The concept of quality of life has both objective (social functioning and environment) and subjective (well-being, life satisfaction or happiness) components [148]. Quality of life scales are based on assessment of human needs [149–151] using the *hedonic approach*, which focuses on happiness and wellbeing [152]. The term health-related quality of life refers to the physical, psychological, and social domains of health.

The relationship between satisfaction with quality of life among patients with SZ/SA and hedonic deficits may be understood in the framework of the Distress/Protection Vulnerability model (Fig. 3.3) [36, 38]. In this model hedonic deficit might be defined as a primary factor with harmful effects on satisfaction with general and domain-specific quality of life. Primary factors such as harm avoidance, high levels of neuroticism, poor coping skills, elevated emotional distress, emotion-oriented coping, and weak self-constructs [119, 153, 154] might lower the vulnerability threshold, and, consequently, result in severe QOL impairment.

This chapter demonstrates a strong association between quality of life and anhedonia scales ($r = -0.35$–0.50) with conformation by factor and partial correlation analyses. One interpretation is likely related to the close neurobiological alterations in hedonic and QOL deficits that could include alterations, in emotion perception and reward processing. Animal data and functional neuroimaging studies in humans indicate that emotion perception may be dependent upon the functioning of: a ventral system, including the amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and prefrontal cortex [56, 155]. It has been hypothesized that hedonic deficit (anhedonia) is associated with dysfunction of the dopaminergic reward system [10], and the activity of the ventral striatum and orbitofrontal cortex [156, 157]. Thus, it seems that hedonic and quality of life deficits are likely related to the similar neurobiological alterations that could include changes in the signaling, information encoding, plasticity, and neurochemical properties of neurons or glia. Integration of hedonic and quality of life deficits into neurobiological investigations may provide new vistas for these impairments in mental disorders.

3.10.4 Adverse Environmental Variables

3.10.4.1 Drug-Related Side Effects (DSAS)

First-generation antipsychotic drugs (FGAs) are associated with motor side effects like tremor and other involuntary movements. The newer (second-generation)

antipsychotic drugs (SGAs) are relatively safe in this regard, but side effects include drug-induced metabolic syndrome, weight gain and its complications [80]. Antipsychotics act primarily by blocking dopamine ("the pleasure molecule") which can cause sedation, depression, and anhedonia. However, side effects (DSAS score) did not correlate with anhedonia scales and did not load with PAS and SAS scores in the common main factor.

3.10.4.2 Violence Risk, Alcohol, Drug and Substance Use (RAQ, AUS, DUS, SATS)

In the present study correlations of anhedonia scales with *RAQ, AUS, DUS, SATS* scale scores did not reach significant levels. Likewise, in the factor analysis these scales did not reach the minimum loading option (0.4).

3.10.5 Functioning and Care Needs

This block of variables included general functioning, social and occupational functioning, sexual functioning, community ability, care needs, and perceived social support.

3.10.5.1 General, Social and Occupational Functioning (GAF, SOFAS)

An association of greater physical and social anhedonia with poor social functioning in the schizophrenia group was observed [158]; but we did not find significant association of the severity of anhedonia with general, social and occupational functioning as measured by the GAF and SOFAS. Furthermore, these scales loaded with some symptom severity to the first *main factor ('Illness & Function Ability').*

3.10.5.2 Sexual Functioning (ASEX)

Sexual dysfunctions have been described as common in schizophrenia patients; it is estimated to affect 30–80 % of patients with schizophrenia. The pathophysiology behind their development remains unclear. They can be secondary to the disease itself or an adverse event of antipsychotic medication. It is well documented that antipsychotic agents and elevated serum prolactin levels have an impact on sexual experiences and sexual self-perception in mental health patients [159, 160]. No significant correlations were found in the present analysis: between PAS and SAS scores and ASEX scores. Factor analysis shows loading ASEX scores to the third main factor ('Distress & Unmet Needs').

3.10.5.3 Community Ability (MCAS)

The MCAS was found associated with planning skills during meal preparation among 82 individuals with schizophrenia living in the community [161].

In the present study Multnomah Community Ability Scale significantly correlated with anhedonia dimensions, but was not associated with PAS and SAS scale scores in the factor analysis.

3.10.5.4 Care Needs (CANSAS-P)

The CANSAS-P subscale scores positively correlated with severity of symptoms snf distress (r ranged from 0.34 to 0.45), and negatively associated with general functioning (r = –0.34), friend (r = –0.46) and family support (r = – 0.41), satisfaction with medicine (r = – 0.35), general activities (r = – 0.40), and general QOL (r = – 0.35) (*all P's < 0.001*) [162].

In this study the number needs slightly positively correlated with PAS and SAS scores due to information and emotional processing disabilities. Factor analysis shows positive loading of three CANSAS-P domains (coping, information and emotional processing disabilities) with a third factor ('Distress & Unmet Needs').

3.10.5.5 Perceived Social Support (MSPSS)

Perceived support is essentially the belief or faith that support is available from network members, whereas actual support is its mobilization and expression. Taking into account this distinction, Cohen et al. [163] defined social support as "the social resources that persons perceive to be available or that are actually provided to them by nonprofessionals in the context of both formal support groups and informal helping relationships" (p. 4). Depending on study aims, investigators may be interested in assessing perceived or received support from the perspective of the provider, the recipient, or both [164]. There is evidence regarding the concurrent influence of social (mostly family) support on adherence but this effect does not persist over time. Changes in the degree of social support may have a complex effect on changes in adherence [165].

We found that better friend, family and other significant social support correlated with lower hedonic capacity deficit that conformed by factor 2 ('Anhedonia & Personality'; see Table 3.7).

3.11 Limitations and Summary

The present findings and conclusions should be interpreted in light of potential *limitations*: (a) acute psychotic patients were unable or refused to participate in the study; (b) the reliability of self-report methodology in research involving severely

ill psychiatric patients; (c) the results of the present study might apply only to adult (30–69 years old) individuals with chronic schizophrenia and schizoaffective disorder (illness duration: 11–49 years) who tend to be more treatment compliant and more cooperative patients; (d) the cross-sectional design of this study cannot establish the direction of causality among the variables assessed.

In summary, despite these limitations, the present study suggests that

1. there are no significant differences between SZ and SA patients in the physical anhedonia and social anhedonia scale scores;
2. there are two groups of independent variables with alternative associations with hedonic capacity dimensions: increasing and enhancing severity of anhedonia;
3. controlling for general quality of life, self-esteem, self-efficacy, and coping styles revealed a loss of significance of partial correlations of anhedonia scales with both negative and depressive symptoms that uniquely contributed to the relationship of hedonic capacity levels with severity of negative and depressive symptoms among SZ/SA patients. These findings, at least partly, help explain an overestimation of the correlation between anhedonia dimensions and psychopathological symptoms in previously published studies;
4. a well-fitting three-factor model provides support for a dimensional structure of 25 independent variables that differentially associated into three domains: psychopathology and functioning, anhedonia and personality features, distress and unmet needs related variables.
5. hedonic capacity deficit did not associate with some of the following variables: illness severity, PANSS positive, activation factors, dysphoric mood and autistic preoccupations, somatization, emotion oriented coping, general functioning, social and occupational functioning, sexual functioning, violence risk, alcohol, drug and substance use, DSM-IV sub-types, types of antipsychotic agents, gender, and marital status;
6. further research is needed to clarify the factor structure of the PAS and SAS scales.

Thus, the hedonic capacity of patients with SZ/SA is attributed to a number of personality related characteristics rather than to current clinical state. These findings might be of therapeutic relevance and enable better understanding of the multifactorial nature of anhedonia.

Acknowledgements Special *thanks* R. Kurs, B.A. *for editing this manuscript.*

References

1. Agrawal A, Nelson EC, Littlefield AK, et al. Cannabinoid receptor genotype moderation of the effects of childhood physical abuse on anhedonia and depression. Arch Gen Psychiatry. 2012;69(7):732–40.
2. Rubin DH. Joy returns last: anhedonia and treatment resistance in depressed adolescents. J Am Acad Child Adolesc Psychiatry. 2012;51(4):353–5.
3. Ribot TL. Psychologie Des sentiments. Paris: Felix Alcan; 1896.

4. Ho N, Sommers M. Anhedonia: a concept analysis. Arch Psychiatr Nurs. 2013;27:121–9.
5. Chapman LJ, Chapman JP, Kwapil TR, Eckblad M, Zinser MC. Putatively psychosis-prone subjects 10 years later. J Abnorm Psychol. 1994;103:171–83.
6. Kwapil TR. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorder. J Abnorm Psychol. 1998;107:558–65.
7. Laurent A, Biloa-Tang M, Bougerol T, et al. Executive/attentional performance and measures of schizotypy in patients with schizophrenia and in their nonpsychotic first-degree relatives. Schizophr Res. 2000;46:269–83.
8. Velthorst E, Nieman DH, Becker HE, et al. Baseline differences in clinical symptomatology between ultrahigh risk subjects with and without a transition to psychosis. Schizophr Res. 2009;109:60–5.
9. Wolf DH. Anhedonia in schizophrenia. Curr Psychiatry Rep. 2006;8:322–8.
10. Wise RA. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox Res. 2008;14:169–83.
11. Juckel G, Sass L, Heinz AA. Anhedonia, self-experience in schizophrenia, and implications for treatment. Pharmacopsychiatry. 2003;36 Suppl 3:S176–80.
12. Kranz GS, Kasper S, Lanzenberger R. Reward and the serotonergic system. Neuroscience. 2010;166(4):1023–35. doi:10.1016/j.neuroscience.2010.01.036.
13. Loas G, Pierson A. Anhedonia in psychiatry: a review. Ann Med Psychol (Paris). 1989;147:705–17.
14. Horan WP, Blanchard JJ, Clark LA, Green MF. Affective traits in schizophrenia and schizotypy. Schizophr Bull. 2008;34:856–74.
15. Kuha A, Suvisaari J, Perälä J, et al. Associations of anhedonia and cognition in persons with schizophrenia spectrum disorders, their siblings, and controls. J Nerv Ment Dis. 1991;2011:30–7.
16. Loas G, Noisette C, Legrand A, Boyer P. Anhedonia, depression and the deficit syndrome of schizophrenia. Acta Psychiatr Scand. 1996;94:477–9.
17. Blanchard JJ, Horan WP, Brown SA. Diagnostic differences in social anhedonia: a longitudinal study of schizophrenia and major depressive disorder. J Abnorm Psychol. 2001;110:363–71.
18. Klein D. Depression and anhedonia. In: Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1987. p. 1–34.
19. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169:364–73. doi:10.1176/appi.ajp.2011.11030447.
20. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36:143–50.
21. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008;199:457–80.
22. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93(1–3):253–60.
23. Burbridge JA, Barch DM. Anhedonia and the experience of emotion in individuals with schizophrenia. J Abnorm Psychol. 2007;116(1):30–42.
24. Chan RC, Wang Y, Huang J, et al. Anticipatory and consummatory components of the experience of pleasure in schizophrenia: cross-cultural validation and extension. Psychiatry Res. 2010;175(1–2):181–3.
25. Roux P, Christophe A, Passerieux C. The emotional paradox: dissociation between explicit and implicit processing of emotional prosody in schizophrenia. Neuropsychologia. 2010;48(12):3642–9.
26. Sandt AR. Hedonic functioning and subthreshold psychotic symptoms (9781267634016) [Doctoral dissertation]. Temple University; 2013.
27. Herbener ES, Harrow M. The course of anhedonia during 10 years of schizophrenic illness. J Abnorm Psychol. 2002;111(2):237–48.
28. Herbener ES, Harrow M, et al. Change in the relationship between anhedonia and functional deficits over a 20-year period in individuals with schizophrenia. Schizophr Res. 2005;75(1):97–105.

29. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374–82.
30. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32(2):259–73.
31. Chapman LJ, Chapman JP. Revised physical anhedonia scale. Unpublished test. Madison, WI: University of Wisconsin; 1978.
32. Eckblad ML, Chapman LJ, Chapman JP, Mishlove M. The revised social anhedonia scale. Unpublished test. Madison: University of Wisconsin; 1982.
33. Fonseca-Pedrero E, Paino M, Lemos-Giráldez S, et al. Psychometric properties of the revised physical and social anhedonia scales in non-clinical young adults. Span J Psychol. 2009;12:815–22.
34. Assouly-Besse FS, Dollfus S, Petit M. French translation of the Chapman social and physical anhedonia questionnaire: validation of the French translation in controls and schizophrenic patients. Encéphale. 1995;21:273–84.
35. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:22.
36. Ritsner M, Modai I, Endicott J, et al. Differences in quality of life domains, psychopathological and psychosocial factors in psychiatric patients. J Clin Psychiatry. 2000;61:880–9.
37. Ritsner MS, Gibel A. Quality of life impairment syndrome in schizophrenia. In: Ritsner MS, Awad AG, editors. Quality of life impairment in schizophrenia, mood and anxiety disorders. New perspectives on research and treatment. Dordrecht: Springer; 2007. p. 173–226.
38. Ritsner MS. The distress/protection vulnerability model of the quality of life impairment syndrome: current evidence and new directions for research. In: Ritsner MS, Awad AG, editors. Quality of life impairment in schizophrenia, mood and anxiety disorders. New perspectives on research and treatment. Dordrecht: Springer; 2007. p. 3–19.
39. Ritsner MS, Arbitman M, Lisker A, Ponizovsky AM. Ten-year quality of life outcomes among patients with schizophrenia and schizoaffective disorder II. Predictive value of psychosocial factors. Qual Life Res. 2012;21(6):1075–84. doi:10.1007/s11136-011-0015-4.
40. Ritsner MS, Lisker A, Arbitman M. Ten-year quality of life outcomes among patients with schizophrenia and schizoaffective disorders: I. Predictive value of disorder-related factors. Qual Life Res. 2011;21(5):837–47. doi:10.1007/s11136-011-9988-2.
41. Ritsner MS. Anhedonia of patients with schizophrenia and schizoaffective disorder is attributed to personality-related factors rather than to state-dependent clinical symptoms. Clin Schizophr Relat Psychoses. 2013;21:1–32.
42. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
43. Blanchard JJ, Bellack AS, Mueser KT. Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. J Abnorm Psychol. 1994;103:719–28.
44. Miettunen J, Veijola J, Freimer N, Lichtermann D, Peltonen L, Paunio T, Isohanni M, Joukamaa M, Ekelund J. Data on schizotypy and affective scales are gender and education dependent–study in the Northern Finland 1966 Birth Cohort. Psychiatry Res. 2010;178(2):408–13. doi:10.1016/j.psychres.2008.07.022.
45. Chan RCK, Wang Y, Yan C, Zhao Q, McGrath J, et al. A study of trait anhedonia in non-clinical Chinese samples: evidence from the Chapman scales for physical and social anhedonia. PLoS ONE. 2012;7(4):e34275. doi:10.1371/journal.pone.0034275.
46. Guy W. ECDEU assessment manual for psychopharmacology. Revised ed. Washington, DC: US Department of Health, Education and Welfare; 1976.
47. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–76.
48. White L, Harvey PD, Opler L, Lindenmayer JP. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. Psychopathology. 1997;30:263–74.

49. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophr Res. 1990;3:247–51.
50. Dohrenwend BP, Shrout PE, Egri G, Mendelsohn FS. Nonspecific psychological distress and other dimensions of psychopathology. Measures for use in the general population. Arch Gen Psychiatry. 1980;37:1229–36.
51. Derogatis LR, Spencer PM. The Brief Symptom Inventory (BSI): administration, scoring and procedures manual. Baltimore: Johns Hopkins University, School of Medicine; 1982.
52. Derogatis LR, Coons HL. Self-report measures of stress. In: Goldberger L, Breznittz S, editors. Handbook of stress: theoretical and clinical aspects. 2nd ed. New York: The Free Press; 1993. p. 200–33.
53. Ritsner M, Rabinowitz J, Slyuzberg M. The Talbieh Brief Distress inventory: a brief instrument to measure psychological distress among immigrants. Compr Psychiatry. 1995;36:1–367.
54. Ritsner M, Modai I, Ponizovsky A. The Talbieh Brief Distress inventory: validation for use with psychiatric patients. Compr Psychiatry. 2002;2:144–63.
55. Portegijs PJ, van der Horst FG, Proot IM, Kraan HF, et al. Somatization in frequent attenders of general practice. Soc Psychiatry Psychiatr Epidemiol. 1996;31:29–37.
56. Phillips KA (ed). Somatoform and factitious disorders (Review of psychiatry series, Volume 20, Number 3; Oldham JM and Riba MB, series eds). Washington, DC: American Psychiatric Publishing; 2001.
57. Kirmayer LJ. Cultural variations in the clinical presentation of depression and anxiety: implications for diagnosis and treatment. J Clin Psychiatry. 2001;62 Suppl 13:22–8. discussion 29–30.
58. Escobar JL, Ribio-Stipec M, Canino G, Karno M. Somatic Symptom Index (SSI). a new and abridged somatization construct. J Nerv Ment Dis. 1989;177:140–6.
59. Ritsner M. The attribution of somatization in schizophrenia patients: a naturalistic follow-up study. J Clin Psychiatry. 2003;64(11):1370–8.
60. Lazarus R, Folkman S. Coping and adaptation. In: Gentry WD, editor. Handbook of behavioral medicine. New York: Guilford Press; 1984.
61. Endler NS, Parker JD. Multidimensional assessment of coping: a critical evaluation. J Pers Soc Psychol. 1990;58:844–54.
62. Parker JD, Endler NS. Coping with coping assessment: a critical review. Eur J Pers. 1992;6:321–44.
63. Wilder-Willis KE, Shear PK, Steffen JJ, Borkin J. The relationship between cognitive dysfunction and coping abilities in schizophrenia. Schizophr Res. 2002;55:259–67.
64. Van Den Bosch RJ, Van Asma MJO, Rombouts R, Louwerens JW. Coping style and cognitive dysfunction in schizophrenic patients. Br J Psychiatry. 1992;161 Suppl 18:123–8.
65. Lysaker PH, Bryson GJ, Marks K, Greig TC, Bell MD. Coping style in schizophrenia: associations with neurocognitive deficits and personality. Schizophr Bull. 2004;30:113–21.
66. Jerusalem M, Schwarzer R. Self-efficacy as a resource factor in stress appraisal processes. In: Schwarzer R, editor. Self-efficacy: thought control of action. Washington, DC: Hemisphere; 1992. p. 195–213.
67. Rosenberg M. Society and the adolescent self-image. Revised ed. Middletown, CT: Wesleyan University Press; 1989.
68. Ritsner MS, Awad AG, editors. Quality of life impairment in schizophrenia, mood and anxiety disorders. New perspectives on research and treatment. Dordrecht: Springer; 2007. 388 pp.
69. Fitzgerald PB, Williams CL, Corteling N. Subject and observer-rated quality of life in schizophrenia. Acta Psychiatr Scand. 2001;103:387–92.
70. Bechdolf A, Klosterkotter J, Hambrecht M, Knost B, Kuntermann C, Schiller S, Pukrop R. Determinants of subjective quality of life in post- acute patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2003;253:228–35.
71. Young AS, Sullivan G, Burnam MA. Measuring the quality of outpatient treatment for schizophrenia. Arch Gen Psychiatry. 1998;28:1221–30.

72. Ritsner M, Gibel A, Ratner Y. Determinants of changes in perceived quality of life in the course of schizophrenia. Qual Life Res. 2006;15:515–26.
73. Lasalvia A, Ruggeri M, Santolini N. Subjective quality of life: its relationship with clinician-rated and patient-rated psychopathology. The South-Verona outcome project 6. Psychother Psychosom. 2002;71:275–84.
74. Hansson L, Middelboe T, Merinder L, et al. Predictors of subjective quality of life in schizophrenic patients living in the community. A Nordic multicentre study. Int J Soc Psychiatry. 1999;45:247–58.
75. Ritsner M, Ben-Avi I, Ponizovsky A, Timinsky I, Modai I. Quality of life and coping with schizophrenia symptoms. Qual Life Res. 2003;12:1–9.
76. Eklund M, Backstrom M, Hansson L. Personality and self-variables: important determinants of subjective quality of life in schizophrenia out-patients. Acta Psychiatr Scand. 2003;108:134–43.
77. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of life enjoyment and satisfaction questionnaire: a new measure. Psychopharmacol Bull. 1993;29:321–6.
78. Westermeyer J. Comorbid schizophrenia and substance abuse: a review of epidemiology and course. Am J Addict. 2006;15(5):345–55.
79. Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. PLoS Med. 2009;6(8):e1000120. doi:10.1371/journal.pmed.1000120.
80. Meyer JM, Stahl SM. The metabolic syndrome and schizophrenia. Acta Psychiatr Scand. 2009;119:4–14.
81. Drake RE, Osher FC, Noordsy DL. Diagnosis of alcohol use disorders in schizophrenia. Schizophr Bull. 1990;16:57–67.
82. McHugo GJ, Drake RE, Burton HL, Ackerson TH. A scale for assessing the stage of substance abuse treatment in persons with severe mental illness. J Nerv Ment Dis. 1995;183:762–7.
83. Drake RE, Mueser KT, McHugo GJ. Clinician rating scales: Alcohol Use Scale (AUS), Drug Use Scale (DUS), and Substance Abuse Treatment Scale (SATS). In: Sederer LI, Dickey B, editors. Outcomes assessment in clinical practice. Baltimore: Williams and Wilkins; 1996. p. 113–6.
84. Osher FC, Kofoed LL. Treatment of patients with psychiatric and psychoactive substance use disorders. Hosp Community Psychiatry. 1989;40:1025–30.
85. Walsh E, Buchanan A, Fahy T. Violence and schizophrenia: examining the evidence. Br J Psychiatry. 2002;180:490–5.
86. Binder RLL, McNiel DE. The relationship of gender to violent behavior in acutely disturbed psychiatric patients. J Clin Psychiatry. 1990;51:110–4.
87. Borum R, Swartz M, Swanson J. Assessing and managing violence risk in clinical practice. J Pract Psychiatry Behav Health. 1996;4:205–15.
88. Borum R. Improving the clinical practice of violence risk assessment. Technology, guidelines, and training. Am Psychol. 1996;51(9):945–56.
89. Fullam RS, Dolan MC. Executive function and in-patient violence in forensic patients with schizophrenia. Br J Psychiatry. 2008;193(3):247–53. doi:10.1192/bjp.bp.107.040345.
90. Fanning JR, Berman ME, Guillot CR. Social anhedonia and aggressive behavior. Personal Individ Differ. 2012;53(7):868–73.
91. Basco MR, Krebaum SR, Rush AJ. Outcome measures of depression. In: Strupp HH, Horowitz LM, Lambert MJ, editors. Measuring patient changes in mood, anxiety, and personality disorders: toward a core battery. Washington, DC: American Psychological Association; 1997. p. 191–245.
92. Torgalsbøen AK. Full recovery from schizophrenia: the prognostic role of premorbid adjustment, symptoms at first admission, precipitating events and gender. Psychiatry Res. 1999;88(2):143–52.
93. Torgalsbøen AK, Rund BR. Maintenance of recovery from schizophrenia at 20-year follow-up: what happened? Psychiatry. 2010;73(1):70–83.
94. Goldman HH, Skodol AE, Lave TR. Revising Axis X for DSM-IV: a review of measures of social functioning. Am J Psychiatr. 1992;149:1148–56.

95. McGahuey CA, Gelemberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther. 2000;26(1):25–40.
96. Byerly M, Nakonezny P, Fisher R, Magouirk B, Rush AJ. An empirical evaluation of the Arizona sexual experience scale and a simple one item screening test for assessing antipsychotic-related sexual dysfunction in outpatients with schizophrenia and schizoaffective disorder. Schizophr Res. 2006;81(2–3):311–6.
97. Barker S, Barron N, McFarland BH, Bigelow DA. A community ability scale for chronically mentally ill consumers: Part I. Reliability and validity. Community Ment Health J. 1994;30(4):363–83.
98. Phelan M, Slade M, Thornicroft G, et al. The Camberwell assessment of need: the validity and reliability of an instrument to assess the needs of people with severe mental illness. Br J Psychiatry. 1995;167(5):589–95.
99. Slade M, Leese M, Ruggeri M, Kuipers E, Tansella M, Thornicroft G. Does meeting needs improve quality of life? Psychother Psychosom. 2004;73(3):183–9.
100. Ritsner MS, Grinshpoon A. Ten-year quality of life outcomes of patients with schizophrenia and schizoaffective disorders. Clin Schizophr Relat Psychoses. 2013;14:1–32.
101. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess. 1988;52:30–41.
102. Vaingankar JA, Abdin E, Chong SA. Exploratory and confirmatory factor analyses of the multidimensional scale of perceived social support in patients with schizophrenia. Compr Psychiatry. 2012;53(3):286–91. doi:10.1016/j.comppsych.2011.04.005.
103. Hintze JL, NCSS. Statistical system for windows. User's guide. Kaysville: Number Cruncher Statistical Systems; 2000.
104. Ritsner MS, Arbitman M, Lisker A. Anhedonia is an important factor of health-related quality-of-life deficit in schizophrenia and schizoaffective disorder. J Nerv Ment Dis. 2011;199(11):845–53. doi:10.1097/NMD.0b013e3182349ce6.
105. Douglas KA. The pleasure experience of low- and high anhedonic undergraduates. Master of Arts – MA. University of British Columbia; 1978. https://circle.ubc.ca/handle/2429/20932.
106. Leventhal AM, Chasson GS, Tapia E, Miller EK, Pettit JW. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. J Clin Psychol. 2006;62:1545–58.
107. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton pleasure scale. Br J Psychiatry. 1995;167(1):99–103.
108. Fawcett J, Clark DC, Scheftner WA, Gibbons RD. Assessing anhedonia in psychiatric patients: the pleasure scale. Arch Gen Psychiatry. 1983;40:79–84.
109. La Guardia JG, Ryan RM, Couchman CE, Deci EL. Within-person variation in security of attachment: a self-determination theory perspective on attachment, need fulfilment, and well-being. J Pers Soc Psychol. 2000;79:367–84.
110. Dichter GS. Anhedonia in unipolar major depressive disorder: a review. Open Psychiatry J. 2010;4:1–9.
111. Blanchard JJ, Collins LM, Aghevli M, Leung WW, Cohen AS. Social anhedonia and schizotypy in a community sample: the Maryland longitudinal study of schizotypy. Schizophr Bull. 2011;37:587–602.
112. Katsanis J, Iacono WG, Beiser M, Lacey L. Clinical correlates of anhedonia and perceptual aberration in first-episode patients with schizophrenia and affective disorder. J Abnorm Psychol. 1992;101:184–91.
113. Oorschot M, Lataster T, Thewissen V, et al. Emotional experience in negative symptoms of schizophrenia–no evidence for a generalized hedonic deficit. Schizophr Bull. 2013;39(1):217–25. doi:10.1093/schbul/sbr137.
114. Selten JP, Wiersma D, van den Bosch RJ. Distress attributed to negative symptoms in schizophrenia. Schizophr Bull. 2000;26:737–44.
115. Freeman D, Garety PA, Kuipers E. Persecutory delusions: developing the understanding of belief maintenance and emotional distress. Psychol Med. 2001;31:1293–306.

116. Ritsner MS, Ratner Y, Gibel A, Weizman R. Positive family history is associated with persistent elevated emotional distress in schizophrenia: evidence from a 16-month follow-up study. Psychiatry Res. 2007;153(3):217–23.
117. Fakhoury WK, Wright D, Wallace M. Prevalence and extent of distress of adverse effects of antipsychotics among callers to a United Kingdom National Mental Health Helpline. Int Clin Psychopharmacol. 2001;16:153–62.
118. Ritsner M, Kurs R. Impact of antipsychotic agents and their side effects on the quality of life in schizophrenia. Expert Rev Pharmacoecon Outcome Res. 2002;2(4):347–56. doi:10.1586/14737167.2.4.347.
119. Ritsner M, Susser E. Temperament types are associated with weak self-construct, elevated distress, and emotion-oriented coping in schizophrenia: evidence for a complex vulnerability marker? Psychiatry Res. 2004;128:219–28.
120. Bradshaw W, Brekke JS. Subjective experience in schizophrenia: factors influencing self-esteem, satisfaction with life, and subjective distress. Am J Orthopsychiatry. 1999;69:254–60.
121. Ladwig KH, Marten-Mittag B, Erazo N, Gundel H. Identifying somatization disorder in a population-based health examination survey: psychosocial burden and gender differences. Psychosomatics. 2001;42:511–8.
122. Spinhoven P, van der Does AJ. Somatization and somatosensory amplification in psychiatric outpatients: an explorative study. Compr Psychiatry. 1997;38:93–7.
123. Grillo L. Might the inability to feel pleasure (anhedonia) explain the symptoms of major depression and schizophrenia, including unmotivated anxiety, delusions and hallucinations? Med Hypotheses. 2012;78(1):98–101. doi:10.1016/j.mehy.2011.10.002.
124. Ritsner MS, Gibel A, Ponizovsky AM, Shinkarenko E, Ratner Y, Kurs R. Coping patterns as a valid presentation of the diversity of coping responses in schizophrenia patients. Psychiatry Res. 2006;144(2–3):139–52.
125. Ritsner M, Ratner Y, Gibel A, Weizman R. Familiarity in a five-factor model of schizophrenia psychopathology: findings from a 16-month follow-up study. Psychiatry Res. 2005;136(2–3):173–9.
126. Ritsner MS, Ratner Y. The long-term changes in coping strategies in schizophrenia: temporal coping types. J Nerv Ment Dis. 2006;194(4):261–7.
127. Strous RD, Ratner Y, Gibel A, Ponizovsky A, Ritsner M. Longitudinal assessment of coping abilities at exacerbation and stabilization in schizophrenia. Compr Psychiatry. 2005;46(3):167–75.
128. Bandura A. Self-efficacy: the exercise of control. New York: Freeman; 1995.
129. Bandura A, editor. Self-efficacy in changing societies. New York: Cambridge University Press; 1995.
130. Judge TA, Erez A, Joyce E, Thoresen CJ. Are measures of self-esteem, neuroticism, locus of control, and generalized self-efficacy indicators of a common core construct? J Pers Soc Psychol. 2002;83(3):693–710. doi:10.1037/0022-3514.83.3.693, doi:10.1037%2F0022-3514.83.3.693.
131. Hill K, Startup M. The relationship between internalized stigma, negative symptoms and social functioning in schizophrenia: the mediating role of self-efficacy. Psychiatry Res. 2012. pii: S0165-1781(12)00557-4. doi:10.1016/j.psychres.2012.09.056.
132. Kurtz MM, Olfson RH, Rose J. Self-efficacy and functional status in schizophrenia: relationship to insight, cognition and negative symptoms. Schizophr Res. 2013;145(1–3):69–74. doi:10.1016/j.schres.2012.12.030.
133. Bentall RP, Simpson PW, Leeb DA, et al. Motivation and avolition in schizophrenia patients: the role of self-efficacy. Psychosis. 2010;2(1):12–22.
134. Kernis MH. Measuring self-esteem in context: the importance of stability of self-esteem in psychological functioning. J Pers. 2005;73:1569–605.
135. Crocker J, Wolfe CT. Contingencies of self-worth. Psychol Rev. 2001;108:593–623.
136. Karatzias T, Gumley A, Power K, O'Grady M. Illness appraisals and self-esteem as correlates of anxiety and affective comorbid disorders in schizophrenia. Compr Psychiatry. 2007;48:371–5.

137. Silverstone PH, Salsali M. Low self-esteem and psychiatric patients: Part I – The relationship between low self-esteem and psychiatric diagnosis. Ann Gen Hosp Psychiatry. 2003;2:2.
138. Barrowclough C, Tarrier N, Humphreys L, Ward J, Gregg L, Andrews B. Self-esteem in schizophrenia: relationships between self-evaluation, family attitudes, and symptomatology. J Abnorm Psychol. 2003;112:92–9.
139. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. Psychol Med. 2001;31:189–95.
140. Lysaker PH, Davis LW, Tsai J. Suspiciousness and low self-esteem as predictors of misattributions of anger in schizophrenia spectrum disorders. Psychiatry Res. 2009;166(2–3):125–31. doi:10.1016/j.psychres.2008.03.014.
141. Thewissen V, Bentall RP, Oorschot M, et al. Emotions, self-esteem, and paranoid episodes: an experience sampling study. Br J Clin Psychol. 2011;50(2):178–95. doi:10.1348/014466510X508677.
142. Romm KL, Jan I, Rossberg JI, Hansen CF, et al. Self-esteem is associated with premorbid adjustment and positive psychotic symptoms in early psychosis. BMC Psychiatry. 2011;11:136. doi:10.1186/1471-244X-11-136.
143. Taylor DN, Pilar JD. Self-esteem, anxiety, and drug use. Psychol Rep. 1992;71:896–8.
144. Walters EE, Kendler KS. Anorexia nervosa and anorexic-like syndromes in a population-based female twin sample. Am J Psychiatry. 1995;152:64–71.
145. Erkolahti RK, Saarijarvi S, Ilonen T, Hagman H. Self-image of anorexic and bulimic female adolescents. Nord J Psychiatry. 2002;56:447–50.
146. Davis L, Kurzban S, Brekke J. Self-esteem as a mediator of the relationship between role functioning and symptoms for individuals with severe mental illness: a prospective analysis of modified labeling theory. Schizophr Res. 2012;137(1–3):185–9. doi:10.1016/j.schres.2012.02.003.
147. Xu ZY, Zu S, Xiang YT, Wang N, et al. Associations of self-esteem, dysfunctional beliefs and coping style with depression in patients with schizophrenia: a preliminary survey. Psychiatry Res. 2013;209:340–5. pii: S0165-1781(13)00084-X. doi:10.1016/j.psychres.2013.02.012.
148. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. J Am Med Assoc. 1995;273:59–65.
149. Maslow AH. Toward a psychology of being. New York: Van Nostrand; 1962.
150. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med. 1996;334(13):835–40.
151. Wolf JRLM. Client needs and quality of life. Psychiatr Rehabil J. 1997;20:16–24.
152. Ryan RM, Deci EL. On happiness and human potentials: a review of research on hedonic and eudaimonic well-being. Annu Rev Psychol. 2001;52:141–66.
153. Szoke A, Schurhoff F, Ferhadian N, et al. Temperament in schizophrenia: a study of the tridimensional personality questionnaire (TPQ). Eur Psychiatry. 2002;17:379–83.
154. Ormel J, Oldehinkel AJ, Vollebergh W. Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. Arch Gen Psychiatry. 2004;61:990–6.
155. Shayegan DK, Stahl SM. Emotion processing, the amygdala, and outcome in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29:840–5.
156. Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci. 2008;10:291–9.
157. Harvey PO, Armony J, Malla A, Lepage M. Functional neural substrates of self-reported physical anhedonia in non-clinical individuals and in patients with schizophrenia. J Psychiatr Res. 2010;44:707–16.
158. Blanchard JJ, Mueser KT, et al. Anhedonia, positive and negative affect, and social functioning in schizophrenia. Schizophr Bull. 1998;24(3):413–24.
159. Nakonezny PA, Byerly MJ, Rush AJ. The relationship between serum prolactin level and sexual functioning among male outpatients with schizophrenia or schizoaffective disorder: a randomized double-blind trial of risperidone vs. quetiapine. J Sex Marital Ther. 2007;33(3):203–16.

160. Hanssens L, L'Italien G, Loze JY, et al. The effect of antipsychotic medication on sexual function and serum prolactin levels in community-treated schizophrenic patients: results from the Schizophrenia Trial of Aripiprazole (STAR) study (NCT00237913). BMC Psychiatry. 2008;8:95. doi:10.1186/1471-244X-8-95.
161. Aubin G, Stip E, Gélinas I, Rainville C, Chapparo C. Daily activities, cognition and community functioning in persons with schizophrenia. Schizophr Res. 2009;107(2–3):313–8. doi:10.1016/j.schres.2008.08.002.
162. Ritsner MS, Lisker A, Arbitman M, Grinshpoon A. Factor structure in the Camberwell Assessment of Need-Patient Version: the correlations with dimensions of illness, personality and quality of life of schizophrenia patients. Psychiatry Clin Neurosci. 2012;66(6):499–507. doi:10.1111/j.1440-1819.2012.02383.x.
163. Cohen S, Gottlieb B, Underwood L. Social relationships and health: challenges for measurement and intervention. New York: Oxford University Press; 2000.
164. Gottlieb BH, Bergen AE. Social support concepts and measures. J Psychosom Res. 2010;69(5):511–20. doi:10.1016/j.jpsychores.2009.10.001.
165. Rabinovitch M, Cassidy C, Schmitz N, et al. The influence of perceived social support on medication adherence in first-episode psychosis. Can J Psychiatry. 2013;58(1):59–65.

Chapter 4
Anhedonia as an Indicator of Genetic Vulnerability to Schizophrenia

Anna R. Docherty and Scott R. Sponheim

Abstract The symptom of anhedonia has been central to causal theories of schizophrenia put forth by Rado and Meehl. Yet, the significance of anhedonia to the etiology of schizophrenia remains unclear. Anhedonia is regarded as a core symptom of schizophrenia and has been repeatedly observed in biological relatives of people with the disorder. This chapter summarizes findings for trait anhedonia being an indicator of genetic vulnerability for schizophrenia. Relevant studies of twins and families affected by schizophrenia, of the general population, and select animal models of the disorder, are reviewed. Evidence suggests that trait anhedonia may conform to the criteria for an endophenotype as defined by Gottesman and Gould (2003). Nonetheless, concerns about diagnostic specificity and variation in findings across self-report and experiment-based measurement warrant further investigation, to more fully understand how the symptom reflects genetic liability for schizophrenia.

Keywords Anhedonia • Gene • Schizophrenia • Relatives • Phenotype

A.R. Docherty (✉)
Virginia Institute for Psychiatric and Behavioral Genetics,
Virginia Commonwealth University, Richmond, USA
e-mail: ardocherty@vcu.edu

S.R. Sponheim, Ph.D.
Mental and Behavioral Health, Minneapolis VA Medical Center,
Departments of Psychiatry & Psychology, University of Minnesota,
Minneapolis, MN, USA
e-mail: sponh001@umn.edu

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_4,

Abbreviations

COMT	Catechol-O-methyltransferase gene
DISC1	Disrupted-in-schizophrenia 1 gene
DSM	Diagnostic and Statistical Manual of Mental Disorders
GWAS	Genome-wide association studies
MGS	Molecular Genetics of Schizophrenia
PGC	Psychiatric Genome-Wide Association Study Consortia
RDoC	Research Domain Criteria
SNP	Single nucleotide polymorphism
SPQ	Schizotypal Personality Questionnaire

4.1 Introduction

Schizophrenia is a genetically complex disorder with diverse symptoms. These symptoms have been categorized into negative, positive, and disorganized dimensions, and researchers have attempted to examine these dimensions as well as individual symptoms to better understand how they might relate to the causes of schizophrenia. Anhedonia is regarded as a negative symptom of schizophrenia that is separable from blunted affective expression noted in the disorder. Anhedonia is of particular interest in understanding schizophrenia, because high levels of the symptom have been observed in groups who carry genetic liability for the disorder (e.g., first-degree biological relatives).

Because anhedonia is an internal subjective state, it is difficult to appraise in a scientific manner. Anhedonia is often assessed by observing what are assumed to be the likely expressions of limited hedonic capacity (e.g. diminished facial expressions, lack of interest or participation in social and sexual activity, limited feelings of closeness to others, and sparse relationships with peers and friends). It is often overlooked that anhedonia and other symptoms of schizophrenia are inferred from a variety of means, including behavioral assessments with standardized procedures, behavioral observation, clinical interview, and self-report questionnaires. Each assessment method likely taps unique aspects of symptomatology, and it is largely unclear how this variance in method affects symptom descriptions. Thus, the mode of assessment likely has important implications for discerning the relationship of symptoms to etiology in schizophrenia. For instance, it is typically best to attend to trait characteristics and symptomatology in trying to capture the phenotypic expression of heritable aspects of a condition.

Although it is essentially established that schizophrenia is at least 50 % heritable, research to date suggests that specific points of variation on the genome confer only incremental risk for a clinical diagnosis of the disorder, and explain only a modest proportion of clustering of schizophrenia within families. The failure to identify specific points of genomic variation related to the disorder has been described as the "missing heritability" of schizophrenia yet to be located on the genome. It is possible that

certain trait characteristics and symptomatology that compose schizophrenia would be more tractable on the genome than an overall diagnosis.

Theorists have pointed out that specific traits, rather than a dichotomous diagnosis of a complex disease, may better account for disease etiology [1, 2]. Though the picture is incomplete, associations between anhedonia and genetic risk for schizophrenia appear to be stronger than for other symptoms of the disorder. This chapter will review several types of studies (family association, case control, psychometrically-identified schizotypy, animal, and polygenic modeling studies) that shed light on the possible relationship between anhedonia and the genetic pathogenesis of schizophrenia.

Anhedonia itself has been parsed in a number of ways in previous research (e.g. frequency and intensity of emotion [3] retrospective versus experiential reports of pleasure [4]), and in this chapter we will use *anhedonia* to denote a broad construct reflecting evidence of reduced hedonic capacity, whether it is self-reported, clinician-rated, or measured through behavioral assessment. The different means of assessing anhedonia will also be discussed. For a helpful review of assessment strategies, work by Horan and colleagues and Dworkin and colleagues is especially informative [see 5, 6].

4.1.1 Developments in the Genetic Etiology of Schizophrenia

It is widely agreed that an individual is predisposed to schizophrenia by the cumulative effects of many genetic loci (i.e., the disorder is polygenic). Thus individual points on the genome contribute incremental amounts of risk for a clinical diagnosis of the disorder. Additionally, genetic and environmental risk factors dynamically interact. Phenomena such as epistasis, methylation, and other cellular processes further complicate attempts to discern specific genetic contributions (for a review of the above concepts, see Maher [7] and Manolio [2]). Genome-wide association studies (GWAS) that scan the entire genome for risk loci have become important tools in searching for genetic mechanisms underlying the disorder. Findings from research examining the effects of single points on candidate genes have been difficult to replicate. Thus, GWAS of large samples have been used to detect alleles that, in aggregate, offer better than chance prediction of who will develop the condition.

The relatively weak predictive power of GWAS studies appears in part due to limitations of the diagnostic assessment methods used. For example, a diagnosis of schizophrenia typically requires a lengthy interview by an experienced clinician, thorough review of medical records, and when possible informant reports of the patient's history. It is difficult to obtain these kinds of assessments in large numbers to improve the accuracy of diagnoses. At times, there is little medical, historical, or informant data available. Overall, a categorical diagnosis of schizophrenia typically ends up being a best estimate based on a person's clinical presentation at the time and the report of symptoms. The difficulty of accurate and consistent categorical diagnosis is compounded by variation in assessment methods, diagnostic systems, and

training across diagnosticians. Only recently, by combining data from thousands of subjects across GWAS research consortia, have analyses become adequately powered to override probable diagnostic inconsistencies and detect promising single nucleotide polymorphisms (SNPs). Investigators have also begun to model genome-wide polygenic risk for symptom dimensions that make up the clinical presentation of the disorder [8]. GWAS efforts may eventually provide clarification about the pathogenesis of the disorder and perhaps help personalize restorative interventions, but this will likely be dependent on a more sophisticated characterization of the schizophrenia phenotype.

Throughout the evolution in genetic methodology, the study of inherited vulnerability to schizophrenia has continued to benefit from studies of unaffected biological relatives of people with the disorder. Evidence from family, twin, and adoption studies indicate that genetic factors substantially contribute to risk for schizophrenia (e.g., work by Kendler and Diehl [9]) and may manifest in family members as neurobiological and cognitive abnormalities that are similar, yet less severe, than those found in people with the disorder [10–15]. Many family studies have attempted to measure mild levels of symptoms and dimensional traits that may not reach the level of clinical concern, but nevertheless allow for the study of traits associated with a family member's magnitude of genetic vulnerability. In this way, modeling of heritable dimensional traits within biological families can assist in revealing specific risk genes and assess the utility of quantitative risk phenotypes.

An advantageous tool in dissecting genetic contributions to a complex disease is the *endophenotype*, which is an index sensitive to the pathophysiology of the disorder that reflects genetic contributions to the condition. An endophenotype is generally simpler to measure than the complex disorder itself. Quantitative indices as measures of endophenotypes, given their ratio or interval levels of measurement, can provide more statistical power for modeling genetic factors than a categorical designation such as schizophrenia or psychosis.

Overall, evidence suggests that anhedonia may be regarded as an endophenotype. Yet it is necessary to reduce the measurement error associated with the construct, so that the quantitative trait of anhedonia may more robustly explain genetic liability for the disorder. We propose that if anhedonia were more effectively and efficiently measured, it would have the potential to account for a proportion of missing heritability in schizophrenia.

4.1.2 Schizotaxia, Hypohedonia, and Endophenotypes

Historically, anhedonia has been conceptualized in several ways as an indicator of genetic liability to schizophrenia. Early on, Rado [16, 17] theorized anhedonia to be one of two inherited pathological defects, with the other being an integrative deficit. Both inherited deficits were thought to be caused by the same major gene [16–18]. Subsequently, Meehl conceptualized anhedonia as one of 13 polygenic potentiators making up the endophenotype of schizotaxia. While Meehl believed the normal-range

trait of "hypohedonia" to be strongly heritable in a way similar to general intelligence or introversion, he did not claim that the related trait of primary hypohedonia, which was proposed to reflect a deficit of the limbic system, was strongly heritable [19, page 190]. Meehl [19] left open the question of whether extreme anhedonia (i.e., primary hypohedonia) reflected one end of a broad spectrum of hedonic capacity or a latent taxon which has a binary relationship to the presence of genetic vulnerability. He also allowed for the possibility of both categorical and dimensional bases for the symptom [19]. Further, in considering secondary anhedonia, Meehl emphasized the importance of "aversive drift" reflecting the cumulative effects of schizotypy on an individual's quality of life In this review, we will examine evidence linking trait anhedonia with schizophrenia and related disorders – but we will not attempt to describe the latent structure of hedonic capacity, primary versus secondary forms of anhedonia, or schizotypal psychopathology more generally.

The genetic underpinnings of endophenotypes may explain any portion of a related complex disorder. However, error variance due to unreliable diagnosis may well be greater than the error variance attributable to methods for assessing a theoretically less complex construct like anhedonia. In the hypothetical case where trait anhedonia and schizophrenia are equally determined by genes and environment, and the anhedonia endophenotype is measured with less error, more genetic variance would be accounted for by the endophenotype than by the clinical diagnosis of the disorder. In the situation where trait anhedonia were more strongly determined by genes than the complex disorder, measures of anhedonia would garner more power for identifying genetic influence. Thus, a reliable measure of a single continuous endophenotype is expected to yield more sensitive detection of genetic effects than use of dichotomous indices dependent on a variety of traits. Nevertheless, it is important to keep in mind that anhedonia is not necessarily less genetically complex than a diagnosis of schizophrenia. For conceptual reviews of trait and endophenotype models in psychiatric disorders, work by Neale and Kendler [20, 21] is informative.

Anhedonia as it appears in schizophrenia, depressive episodes, and the daily functioning of the general population is important to consider. Differences in the phenomenology of the symptom across affected populations can help highlight aspects of the construct that are specific to genetic risk for schizophrenia – akin to the distinction between primary and normal-range hypohedonia articulated by Meehl. Ideally, this would include work that would separate environmental from genetic factors in the development of anhedonia. Researchers have initiated efforts to identify useful constructs that cut across complex diagnostic categories and improve diagnostic systems for identifying biological mechanisms of psychopathology. The United States National Institute of Mental Health has released recommendations for minimizing measurement error in the study of complex disorders like schizophrenia; for a recent review of the use of endophenotypes and efforts to refine psychopathology symptoms, see work by Miller and Rockstroh [22]. A set of Research Domain Criteria (RDoC) have been sought to refine trait measurement outside of the context of Diagnostic and Statistical Manual (DSM)-defined diagnosis. Work of this nature may provide more evidence for focusing effort on traits like anhedonia in genetic studies of psychiatric disorders [22].

4.2 Anhedonia as a Reflection of Risk for Schizophrenia

In classical Mendelian genetic models, phenotypes typically reflect genotypes, or characteristics linked to genetic risk. Polygenic phenotypes like schizophrenia with complex genetic architecture are thought to possess a looser link between phenotype and genotype. Additional variation in the phenotype, as discussed, can result from environmental influences such as family or socioeconomic factors, or from gene by environment interactions. When studying polygenic disorders, we can target genetic mechanisms by identifying endophenotypes. Endophenotypes are characteristics detectable "by some biochemical test or microscopic examination" that by meeting specific criteria indicate relationship between genes and trait. Endophenotypes, some of which may be neurophysiological, endocrinological, or cognitive, can also include self-report data [23].

Both terms, *intermediate phenotype* and *endophenotype,* have been used to describe traits influenced by genes in schizophrenia, but these terms are not necessarily interchangeable with respect to the implications of anhedonia's role in the development of schizophrenia [24]. In this chapter, Gottesman & Gould's criteria for an endophenotype will be invoked to guide the review of anhedonia as a marker of genetic liability for the disorder [23].

Figure 4.1 illustrates the endophenotype approach, where genetic influences on individual facets of the disorder lead to a continuum of liability for schizophrenia. Gottesman and Gould's five criteria for an endophenotype are: (1) it must be associated with illness in the population; (2) it must be heritable; (3) it must be primarily state-independent; (4) within families, the endophenotype and illness must co-segregate; and (5) the endophenotype must be found in family members at a higher rate than in the general population. All of these criteria are met with regard to schizotypal anhedonia, as will be reviewed, with perhaps the least compelling evidence found across studies for the fourth criterion. Others have elaborated on these criteria by indicating that endophenotypes should be associated with the causes rather than the effects of disorders, should exhibit continuous variance in the general population, and would be measured most effectively across several types of methods (e.g., questionnaire, interview, task, informant report). In addition, it is possible that some construct related to anhedonia may better meet endophenotype criteria, or several endophenotypes may reflect separable etiologies of the complex disorder, or that genetically related disorders may share the same endophenotypes [25].

4.2.1 Anhedonia in Family Members of Individuals with Schizophrenia

Research on biological relatives probably presents the strongest evidence for anhedonia's status as an endophenotype. In several studies of self-reported schizotypal

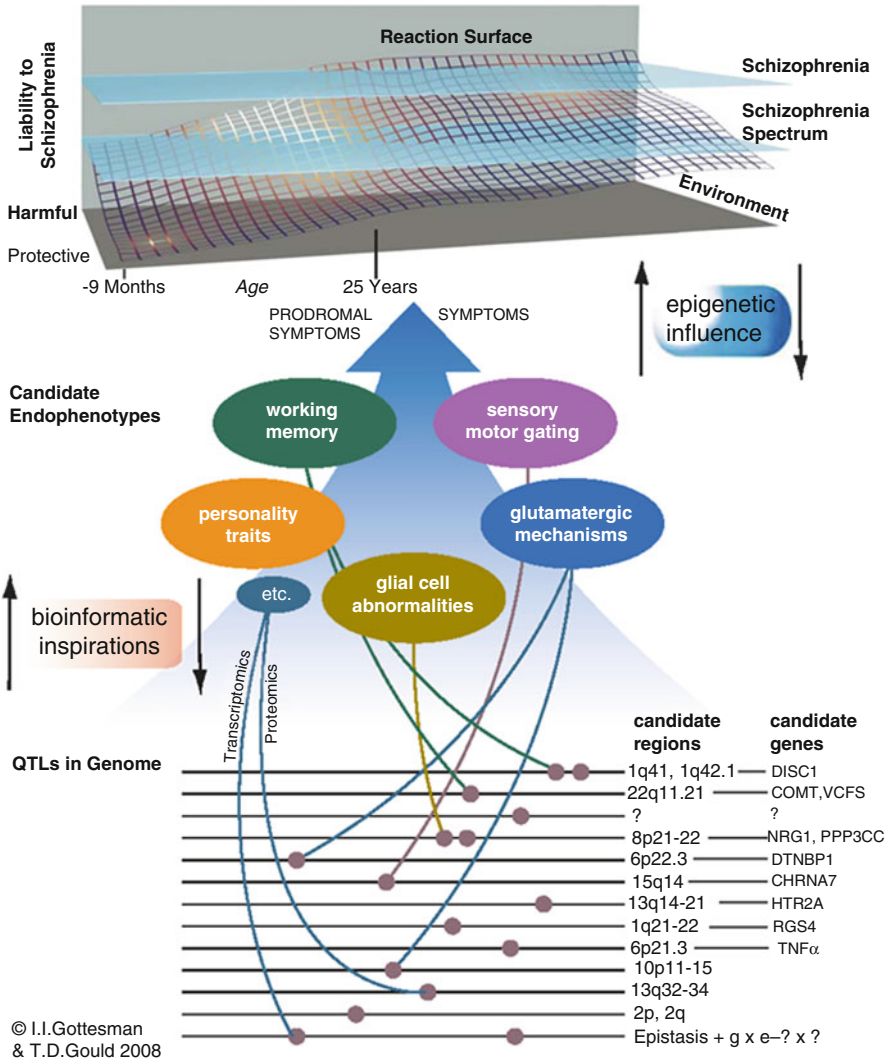

Fig. 4.1 Possible genetic basis of endophenotypes (*bottom*), associated endophenotypes, and subsequent liability for the illness (*top*) on a dimensional continuum (From Gottesman and Gould [23] with permission from the authors)

traits, anhedonia items from the Revised Social Anhedonia Scale and the Revised Physical Anhedonia Scale have consistently differentiated relatives of individuals with schizophrenia from controls. Katsanis and colleagues found elevations on the anhedonia scales, but not on positive schizotypy symptom scales, in 125 relatives of schizophrenia patients compared with 155 healthy controls [26]. Kendler and colleagues assessed twins with the Structured Interview for Schizotypy and derived

two independent dimensions of clinically rated schizotypy (positive symptom schizotypy and negative symptom schizotypy) and two independent dimensions of self-rated schizotypy (positive trait schizotypy and trait anhedonia) [27]. Correlations in monozygotic and dizygotic twins suggested that genetic factors were important in both the positive and anhedonic domains of schizotypy. In addition, higher concordance rates in monozygotic twins have been observed when probands have a greater number of negative symptoms [28].

In the County Roscommon Study, an epidemiological, case-controlled study, relatives were administered shortened and modified versions of scales for magical ideation and social anhedonia. Even in abbreviated form, scores for social anhedonia and not magical ideation successfully differentiated relatives of schizophrenia from control participants [29]. Later, MacDonald and colleagues investigated the factor structure of the schizotypy questionnaires in a young adult sample of 98 monozygotic and 59 same-sex dizygotic twin pairs. Models of genetic and environmental influence suggested that social anhedonia was influenced by either genes or shared family environment, whereas magical ideation scores appeared to be influenced by shared family environment, but not genes. Results of twin analyses were also consistent with positive schizotypy not being strongly influenced by genes [30].

Other research has documented elevations in self-reported anhedonia in people with presumed genetic liability for schizophrenia, in the absence of elevations on other self-reported schizotypal trait measures [31–33]. One study failed to replicate differences between unaffected siblings of schizophrenia probands and controls when regressing group membership onto social anhedonia scores [34]. This study used a model that controlled for variance in family membership.

When examining only perceptual aberration and physical anhedonia in relatives using self-report scales, Franke and colleagues [35] and Clementz and colleagues [36] found elevations across first-degree relatives in self-reported physical anhedonia in the absence of aberrant perceptions. Like social anhedonia, self-reported physical anhedonia may be an indicator of genetic liability for schizophrenia, but evidence is still somewhat mixed. Elevations in physical anhedonia may be less specific to diagnosis. While one study demonstrated no association of physical anhedonia with familial risk for bipolar disorder [37], other work showed an increase in scores on the Revised Physical Anhedonia Scale in relatives of people with bipolar disorder compared with nonpsychiatric controls [33]. The latter study had a modest sample size of 45, and further research is still needed with a larger cohort. In another study with still fewer participants, physical anhedonia assessed by questionnaire did not distinguish parents of patients with schizophrenia from parents of other psychiatric or nonpsychiatric control groups [38]. Glatt and colleagues have examined modest samples of adolescent and young-adult first-degree relatives (n = 35) of people with schizophrenia or schizoaffective disorder and controls (n = 55) and found that high-risk participants older than 17 generally reported more physical anhedonia, and less involvement with peers, than did controls [39]. In the New York High Risk Project, a study following youth at high risk for psychosis from childhood to adulthood, physical anhedonia negatively predicted later social outcome measures. And in contrast to people at risk for schizophrenia, people at

risk for affective disorder did not show increased levels of physical anhedonia, social dysfunction, or attention difficulties relative to control subjects [40].

Anhedonia in relatives of people with schizophrenia appears to vary with respect to the severity of the symptom in the family member with schizophrenia, and the genetic relationship of the relative to the person with schizophrenia. For instance, anhedonia scores derived from self-report questionnaires have been observed to be higher in family members of schizophrenia patients with severe anhedonic symptoms [41–44]. In Berenbaum and McGrew's analyses [41] maternal anhedonia appeared to be more relevant than paternal anhedonia to familial correlations, and maternal anhedonia accounted for the most variance in self-reported anhedonia amongst the family members. These associations conform to a larger body of evidence that neurobiological characteristics exhibited in relatives are generally positively associated with the genetic proximity to an affected relative [14, 15, 45].

Considering all possible methods for assessing anhedonia is important, and the familial correlations discussed above seem to provide support for self-report as a valid means of assessment. However, other measures of anhedonia and hedonic capacity have not consistently differentiated relatives of people with schizophrenia from controls. Discrepancies between effects found with self-report and interview measures needs to be better understood. For example, hedonic ratings of experimentally-presented olfactory stimuli have failed to differentiate groups [46]. These experimental findings are consistent with research of individuals with schizophrenia highlighting discrepancy between intact in-the-moment hedonic experience and the presence of anhedonia as indicated by elevated scores on self-report questionnaires.

4.2.2 Anhedonia in Psychometrically-Identified Schizotypy and Psychosis-Proneness

Trait anhedonia has been measured both as a clinical symptom of schizophrenia and as a subclinical characteristic of the general population akin to a mild negative symptom. In studies of general samples of college students and other populations, "negative schizotypy" has been operationalized in various ways related to trait anhedonia and social withdrawal. Often, negative schizotypy as discussed in recent literature is meant to reflect high scores on anhedonia scales relative to a same-sex control group. Studies of "psychometrically-identified" anhedonia in community and college student populations rely on score cutoffs (often 1.65–1.96 standard deviations above the same sex control mean) to identify individuals who surpass a presumed threshold for the trait. These extreme scorers are at times retested to rule out state-related anhedonia associated with transient effects of mood or other factors. Anhedonia as measured by the Wisconsin Schizotypy Scales has been shown to be independent of self-reported depressive symptoms in some of these samples [e.g., see 3].

It has been found that approximately a quarter of individuals reporting extreme levels of social and physical anhedonia have developed schizophrenia spectrum

disorders 10 years later ([47]; with replications by Kwapil [48] and Gooding and colleagues [49]). In contrast, positive schizotypy as measured by subthreshold positive and disorganized symptoms has provided less accurate prediction of later development of schizophrenia-spectrum conditions. Several studies have also compared extreme-scoring schizotypy groups when examining associations with cognitive and affective traits (anhedonic vs. disorganized schizotypy, or those evidencing positive schizotypy) [e.g., 3, 50, 51] in attempts to better understand the characteristics of schizotypal college student samples. Importantly, there is enough variance in anhedonia in college and community samples that it is possible to identify categorical groups of high scorers. However, it is still unclear how these psychometrically-identified traits overlap with traits found in genetically-vulnerable individuals, and it is unclear how traits associated with anhedonia explain and predict eventual conversion to schizophrenia-spectrum disorder. Ultimately, the field requires more longitudinal studies looking at anhedonia and additional mediators of later psychosis.

We know from family studies that anhedonia is relevant to the genetics of schizophrenia. We also know that those in the general population with elevated anhedonia exhibit some risk for the development of a schizophrenia spectrum disorder. Overall, evidence suggests that (1) anhedonia is associated with illness in the population; (2) it is heritable; (3) it is largely state-independent, though *not always*; (4) within families, anhedonia and the illness appear to co-segregate such that probands have greater anhedonia levels than their unaffected relatives; and (5) anhedonia self-report appears to be higher in relatives of probands with high levels of anhedonia.

4.3 Early Research Examining Anhedonia and Associations with Specific Genes

Research has provided evidence of some association between anhedonia and genetic risk for schizophrenia. However, there has been little examination of whether anhedonia is associated with specific locations on the genome. The most compelling evidence comes from studies of disrupted-in-schizophrenia 1 gene loci (DISC1) and catechol-O-methyltransferase (COMT) that investigated anhedonia in the general population, first-degree family members of people with schizophrenia, and laboratory animals. While other markers such as DTNBP1, TREK1, uVNTR of the MAOA gene, and DRD2 have been associated with anhedonia-like traits or negative symptoms in various samples [1, 52–54] these findings have yet to be replicated.

The DISC1 gene influences hippocampal structure and development (for a detailed analysis, see work by Hikida and colleagues [55]) and has been observed to regulate cell migration in hippocampus [56]. Research has implicated hippocampus in the experience of low positive affect [57], a construct closely tied to anhedonia. In a functional neuroimaging study of patients with schizophrenia, negative symptoms including anhedonia were associated with smaller right hippocampal volumes [58] possibly suggesting a role for DISC1 in the development of schizotypal anhedonia.

Catechol-O-methyltransferase has a critical role in the extracellular degradation of dopamine (for a review, see [59]). COMT has been found to be expressed not only within the prefrontal cortex, but also in subcortical regions of the brain involved in emotional experience such as amygdala and striatum [60]. Additionally, COMT alleles might be associated with dopamine abnormalities in schizophrenia [e.g., 61, 62]. Prior research has consistently found evidence for involvement of dopamine in the experience of incentive processing and motivation [e.g., 63]. In general, dopamine depletions result in a reduced willingness to expend effort in order to obtain rewards (for a review, see work by Salamone and colleagues [64]) which is consistent with a role for COMT in schizotypal anhedonia. A quantitative trait analysis by Li and colleagues [65] revealed that points of variation within the COMT gene (rs740603 and the rs740603-rs4818 haplotype) were associated with negative symptoms, despite no significant effect on the actual presence of schizophrenia among individuals of Han Chinese descent.

4.3.1 Animal Research

Negative symptoms, and anhedonia specifically, are difficult to measure in animals due to ambiguity in relating animal behavior to human behavior and reports of hedonic experience [66]. "Anhedonic-like" behavior in animals can include social activity and reward-seeking movements, among other observable phenomena. DISC1-altered mice have been observed to exhibit anhedonia-like deficits in addition to sensorimotor gating reductions and enlarged lateral ventricles [55]. In attempts to model neurodevelopmental aspects of schizophrenia, ventral hippocampal lesions in mice appear to reduce reward-seeking behaviors in adulthood, perhaps mimicking anhedonia observed in people with schizophrenia [67].

In another analogue study, mice that were administered tolcapone exhibited a significant level of anhedonia-like symptoms [68]. Tolcapone is an inhibitor that blocks COMT valine to methionine substitution, and thus can account for up to 60 % of the variance in prefrontal dopamine regulation. To date, studies of rodent strains have found associations of greater ventral tegmental dopamine neuron number and/or heightened dopamine transmission in the ventral tegmental-nucleus accumbens dopamine pathway, with an increased self-administration of stimulants (reward-related behavior). In humans, neuroimaging studies have found that activity in those same brain regions (i.e., the ventral striatum) is sensitive to degree of reward magnitude and probability [69, 70]. Thus, COMT's effect on dopamine may influence reward-seeking and reward-estimation in animals. This mechanism could contribute to trait-like anhedonia in schizophrenia that is associated with dopamine dysregulation.

4.3.2 General Population

Previous efforts to uncover SNPs associated with anhedonia in the general population have shown association of anhedonia with specific DISC1 SNPs across one

population cohort (n > 8,000) [71]. Tomppo and colleagues then took a subsample of this DNA and examined all DISC1 SNPs, as well as genetic mechanisms affecting DISC1 expression, finding associations of anhedonia with DISC1 and genes affecting DISC1 expression [72]. Concurrently, the same research group found that lymphoblastoid cell lines derived from schizophrenia patients mirrored an increase of CRMP1 expression, suggesting its potential role as a blood-based diagnostic marker [73]. CRMP1 directly interacts with DISC1. It will be helpful, in future research, to examine whether increased CRMP1 expression is associated with elevations in anhedonia.

Avramopoulos and colleagues [74] reported that the val allele of the COMT Val158Met polymorphism was associated with high schizotypy scores in a male normative sample. Stefanis and colleagues [75] replicated these results, and found that the val allele was specifically related to the negative and disorganization dimensions of schizotypy as measured by the Schizotypal Personality Questionnaire (SPQ [76]). These studies suggested an influence of COMT on self-reported interpersonal difficulties, which is consistent with a potential link between dopamine and schizotypal social withdrawal. However, the construct of anhedonia was not expressly measured using the SPQ.

4.3.3 First-Degree Relative and Family Research

Recent investigation of biological relatives of people with schizophrenia has directly examined anhedonia in relation to COMT by using the Revised Social Anhedonia Scale and the Revised Physical Anhedonia Scale. In 2007 Schurhoff and colleagues reported that the val allele of the COMT Val158Met polymorphism (the allele reflecting the highest level of dopamine degradation in prefrontal cortex) was associated with negative schizotypy in biological relatives of schizophrenia and bipolar patients [77]. Subsequently, a relationship of the val allele with anhedonia, and not with other schizotypal traits, was identified and then replicated in first-degree relatives of schizophrenia probands [33, 78]. Additionally, associations of the COMT polymorphism with social and physical anhedonia scales were not observed in first-degree relatives of people with bipolar disorder in the study by Docherty and Sponheim [33], providing some initial evidence of diagnostic specificity. Further, it was found that relatives of people with schizophrenia with the val allele were the only first-degree relatives in the sample with schizophrenia-spectrum diagnoses.

In samples with schizophrenia, studies of low positive emotion (theoretically related to anhedonia) as a reflection of disorder etiology are usually confounded by the effects of D1 receptor agonist medication. Impairments in social functioning, secondary to positive and disorganized symptoms like paranoid thoughts or communication disturbances, can also confound assessment of anhedonia. Thus, the study of family members is especially useful with respect to traits that may depend on dopamine [63, 79].

4.4 Symptom Dimensions and Polygenic Factor Scores

Initial efforts toward using GWAS to examine genetic contributions to clinical symptom dimensions in schizophrenia have confirmed the small effect of individual polymorphisms. Using the Lifetime Dimensions of Psychosis Scale [80] Fanous and colleagues [8] conducted analyses of positive, negative, and disorganized traits across 16 populations from the Psychiatric GWAS Consortia (PGC). Symptom factor scores (positive and negative/disorganized) were derived and tested for association with SNPs from a very large single GWAS (a European sample, Molecular Genetics of Schizophrenia or MGS). Data from the 16 PGC datasets were then used to generate polygenic scores for the MGS subjects. While no individual SNPs significantly predicted symptom factor scores, polygenic scores based on MGS GWAS results for negative/disorganized symptom scores predicted schizophrenia case status. Factor loadings of each symptom on the negative/disorganized factor included blunted affect (.67), poverty of speech (.71), formal thought disorder (.58), and bizarre behavior (.57). Depressive symptoms (conceptually related to state -anhedonia) loaded onto a separate mood symptom dimension and did not load well onto the primary polygenic risk factor (−.28). Consistent with previous evidence that positive symptoms are less relevant to genetic vulnerability for schizophrenia, positive symptoms carried high loadings on a single factor (.50–.84) but were unrelated to polygenic risk.

This overlap of negative and disorganized dimensions observed in case–control samples is consistent with some previous findings from analyses of self-report questionnaires. The SPQ [75] is a brief measure that assesses all nine criteria of DSM-III-R Schizotypal Personality Disorder and functions as a useful screen. Higher scores on the Interpersonal factor of the SPQ, which arguably includes facets of anhedonia such as a lack of close friends and constricted expression of affect, have been associated with poor sustained attention [81] and deficits in spatial working memory [82] perhaps suggesting an association with cognitive functions involving frontal cortex. Although it may be considered an aspect of the Interpersonal factor, anhedonia is not expressly measured by the SPQ. Studies of measures specifically targeting anhedonia constructs such as the Wisconsin Schizotypy Scales have provided less compelling evidence of an overlap of negative and disorganized symptom domains in people with presumed genetic vulnerability for schizophrenia. It may be that when anhedonia is directly assessed, effects of genetic risk on the phenotype are more discernible.

A recent study by Tarbox and colleagues developed schizotypy factors associated with genetic contributions to schizophrenia. Anhedonia-like characteristics were associated with the greatest level of genetic contribution relative to other schizotypal symptoms. The authors posited that relatives experience and report more negative symptoms, and relatives might also underreport and "downplay" the occurrence of positive symptoms. Factor scales were not associated with major depressive disorder or substance dependence, indicating some diagnostic specificity to schizophrenia rather than traits being shared with depression or psychopathology more generally [83].

More recently, hybrid mixture modeling techniques have been explored as a potential avenue to understanding latent dimensional and categorical structures underlying schizotypal personality in individuals with genetic vulnerability to schizophrenia. One preliminary analysis of the Magical Ideation Scale (a positive schizotypy measure) in probands, biological relatives of people with schizophrenia, and controls was able to illustrate potential item grouping strategies for the further examination of a latent structure of familial schizotypy symptoms [84]. If these strategies are applied to larger samples enriched for genetic vulnerability to schizophrenia, brief self-report measures could be used to better characterize the heritable structure of schizotypal anhedonia.

4.5 Methodological Issues and Future Considerations for Genetics Studies of Symptom Dimensions

The genetic mechanisms underlying a complex disease like schizophrenia are difficult to discern without a substantial amount of attention paid to endophenotype characterization. There are several methodological considerations for future assessment of anhedonia as an endophenotype.

First, research has yet to find satisfactory ways of parsing trait and state anhedonia to better understand how persistent schizotypal anhedonia differs from mood-related, depressive anhedonia. Some research in the area of mood disorders has characterized state anhedonia as a disruption in behavioral activation (for a review, see work by Urosevic and colleagues [85]), and others have hypothesized schizotypal anhedonia to result from dysregulation of tonic striatal dopamine levels and subsequent decreased salience of pleasurable stimuli [33, 86]. With improved assessment and understanding of anhedonia, future research may account for a greater proportion of missing heritability and also better distinguish psychoses from mood disorders. If anhedonia is largely the same phenomenon in negative symptom schizophrenia and depression this would also enhance our understanding of shared genetic vulnerability to both psychosis and mood disturbance.

Second, use of several types of studies (e.g., family association, case control, psychometrically-identified schizotypy, animal, and polygenic modeling studies) to assess traits associated with schizotypal anhedonia will better characterize the underlying heritability of schizophrenia. Each type of study has unique advantages. For example, family association studies can model effects of shared genetic material on the presence of social behaviors, animal studies can test theories relating to how the presence or absence of gene expression can affect social behaviors, and longitudinal, psychometrically-identified schizotypy studies can be used to characterize traits most related to eventual development of the disorder.

Third, anhedonia must be examined carefully across multiple methods and measurements to establish the assessments best able to differentiate probands and biological relatives from controls. Measures of schizotypal anhedonia should show

good convergent validity and should be differentiated from measures of current mood. The use of clinical symptom dimensions have been somewhat limited in GWAS because of the demand for brief, interview-rated or questionnaire-based measures in order to assess thousands of participants required for such studies. One trade-off for efficiency is a reduction in the reliability of the measure being studied, and thus unreliability and compromised validity of brief assessments may outweigh what is gained from large samples.

Fourth, analytic models of the quantitative trait need to be compatible with the presence of unequal family sizes and varying types of family structure. Models may need to account for non-normal distribution of the quantitative phenotype, as well as unequal variance across case, family, and control samples. It is more often than not that variance tends to be significantly greater in cases and family members than in control participants, yet this fact is often neglected in studies comparing these groups. When variance is unequal between groups and analyses assume the variances to be equal, statistically significant effects can be misleading and difficult to replicate.

Fifth, methodological concerns persist about self-reported symptoms, and these concerns are validated by new findings that general hedonic capacity may be self-reported in biased ways. Many of the concerns specifically derive from experimental laboratory research of people with schizophrenia: differentiating consummatory and anticipatory pleasure, positive affect intensity and frequency [3, 87], as well as beliefs about hedonic experience and actual in-the-moment experiences ([88] reviews by Strauss and Gold [89] and by Strauss, [90]), and most recently calculating risk vs. effort for reward [91–93].

Sixth, elevated anhedonia as observed in relatives is generally lower than scores for psychometrically-identified anhedonic individuals. Though relatives may carry more genetic vulnerability to schizophrenia, variance in familial anhedonia will differ from samples picked specifically on the basis of extreme scores. A larger proportion of the variation in anhedonia in psychometrically-identified individuals (not selected for familial schizophrenia) will likely be attributable to non-genetic factors.

Seventh, missing from the research to date has been efficient, cost-effective, laboratory measures of anhedonia that differentiate people with genetic vulnerability to schizophrenia from the general population. More targeted and reliable measures of anhedonia will serve to refine the phenotype. Questionnaire-based self-report measures carry value in large-scale population research, but greater understanding of how these self-reports relate to experiential assessments of anhedonia is needed. This may be particularly true as genetic testing becomes more routine and affordable: (For more extensive review of basic assessment concerns relating to schizotypy, one can refer to earlier work by Lenzenweger [94]). By focusing on first-degree relatives of individuals affected by schizophrenia, anhedonia related to schizotypal pathophysiology may also be better distinguished from anhedonia related to transient aspects of mood dysregulation.

Acknowledgements The authors wish to acknowledge Drs. Mark Lenzenweger and Irving Gottesman for their review and comment on the manuscript.

References

1. Fanous AH, van den Oord EJ, Riley BP, et al. Relationship between a high-risk haplotype in the DTNBP1 (dysbindin) gene and clinical features of schizophrenia. Am J Psychiatry. 2005;162(10):1824–32.
2. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461(7265):747–53.
3. Kerns JG, Docherty AR, Martin EA. Social and physical anhedonia and valence and arousal aspects of emotional experience. J Abnorm Psychol. 2008;117(4):735–46.
4. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32:259–73.
5. Dworkin RH, Saczynski K. Individual differences in hedonic capacity. J Pers Assess. 1984;48:620–6.
6. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia re-revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36:143–50.
7. Maher B. Personal genomes: the case of the missing heritability. Nature. 2008;456(7218):18–21.
8. Fanous AH, Zhou B, Aggen SH, et al. Genome-wide association study of clinical dimensions of schizophrenia: polygenic effect on disorganized symptoms. Am J Psychiatry. 2012;169(12):1309–17.
9. Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic epidemiological perspective. Schizophr Bull. 1993;19(2):261–85.
10. Faraone SV, Seidman LJ, Kremen WS, et al. Neuropsychological functioning among the non-psychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. J Abnorm Psychol. 1995;104(2):286–304.
11. Lawrie SM, Whalley H, Kestelman JN, et al. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. Lancet. 1999;353(9146):30–3.
12. McDonald C, Grech A, Toulopoulou T, et al. Brain volumes in familial and non-familial schizophrenic probands and their unaffected relatives. Am J Med Genet. 2002;114(6):616–25.
13. Byrne M, Clafferty BA, Cosway R, et al. Neuropsychology, genetic liability, and psychotic symptoms in those at high risk of schizophrenia. J Abnorm Psychol. 2003;112(1):38–48.
14. McIntosh AM, Harrison LK, Forrester K, et al. Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives. Br J Psychiatry. 2005;186:378–85.
15. McIntosh AM, Job DE, Moorhead TW, et al. White matter density in patients with schizophrenia, bipolar disorder and their unaffected relatives. Biol Psychiatry. 2005;58(3):254–7.
16. Rado S. Psychoanalysis of behavior: collected papers. New York: Grune & Stratton; 1956.
17. Rado S. Theory and therapy: the theory of schizotypal organization and its application to the treatment of decompensated schizotypal behavior. In: Scher SC, Davis HR, editors. The outpatient treatment of schizophrenia. New York: Grune & Stratton; 1960.
18. Rado S, Daniels G. Changing concepts of psychoanalytic medicine. New York: Grune & Stratton; 1956.
19. Meehl PE. Primary and secondary hypohedonia. J Abnorm Psychol. 2001;110(1):188–93.
20. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. Mol Psychiatry. 2010;15(8):789–97.
21. Neale MC, Kendler KS. Models of comorbidity for multifactorial disorders. Am J Human Genet. 1995;57:935–53. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. Mol Psychiatry. 2010;15(8):789–97.
22. Miller G, Rockstroh B. Endophenotypes in psychopathology research: where do we stand? Annu Rev Clin Psychol. 2013;9:15.1–15.38.
23. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636–45.
24. Lenzenweger MF. Thinking clearly about the endophenotype – intermediate phenotype – biomarker distinctions in developmental psychopathology research. Dev Psychopathol. 2013;25:1347–1357.

25. Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. Annu Rev Clin Psychol. 2006;2:267–90.
26. Katsanis J, Iacono WG, Beiser M. Anhedonia and perceptual aberration in first-episode psychotic patients and their relatives. J Abnorm Psychol. 1990;99(2):202–6.
27. Kendler KS, Ochs AL, Gorman AM, et al. The structure of schizotypy: a pilot multitrait twin study. Psychiatry Res. 1991;36(1):19–36.
28. Dworkin RH, Lenzenweger MF. Symptoms and the genetics of schizophrenia: implications for diagnosis. Am J Psychiatry. 1984;141:1541–6.
29. Kendler KS, Thacker L, Walsh D. Self-report measures of schizotypy as indices of familial vulnerability to schizophrenia. Schizophr Bull. 1996;22(3):511–20.
30. MacDonald 3rd AW, Pogue-Geile MF, Debski TT, et al. Genetic and environmental influences on schizotypy: a community-based twin study. Schizophr Bull. 2001;27(1):47–58.
31. Vollema MG, Sitskoorn MM, Appels MC, et al. Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? Schizophr Res. 2002; 54(1–2):39–45.
32. Schurhoff F, Szoke A, Meary A, et al. Familial aggregation of delusional proneness in schizophrenia and bipolar pedigrees. Am J Psychiatry. 2003;160(7):1313–9.
33. Docherty AR, Sponheim SR. Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. J Abnorm Psychol. 2008;117(4):788–98.
34. Kuha A, Suvisaari J, Perala J, et al. Associations of anhedonia and cognition in persons with schizophrenia spectrum disorders, their siblings, and controls. J Nerv Ment Dis. 2011;199(1):30–7.
35. Franke P, Maier W, Hardt J, et al. Cognitive functioning and anhedonia in subjects at risk for schizophrenia. Schizophr Res. 1993;10(1):77–84.
36. Clementz BA, Grove WM, Katsanis J, et al. Psychometric detection of schizotypy: perceptual aberration and physical anhedonia in relatives of schizophrenics. J Abnorm Psychol. 1991;100(4):607–12.
37. Etain B, Roy I, Henry C, et al. No evidence for physical anhedonia as a candidate symptom or an endophenotype in bipolar affective disorder. Bipolar Disord. 2007;9(7):706–12.
38. Catts SV, Fox AM, Ward PB, et al. Schizotypy: phenotypic marker as risk factor. Aust N Z J Psychiatry. 2000;34(Suppl):S101–7.
39. Glatt SJ, Stone WS, Faraone SV, et al. Psychopathology, personality traits and social development of young first-degree relatives of patients with schizophrenia. Br J Psychiatry. 2006;189:337–45.
40. Freedman LR, Rock D, Roberts SA, et al. The New York High-Risk Project: attention, anhedonia and social outcome. Schizophr Res. 1998;30(1):1–9.
41. Berenbaum H, McGrew J. Familial resemblance of schizotypic traits. Psychol Med. 1993;23(2):327–33.
42. Lyons MJ, Toomey R, Faraone SV, et al. Correlates of psychosis proneness in relatives of schizophrenic patients. J Abnorm Psychol. 1995;104(2):390–4.
43. Fanous A, Gardner C, Walsh D, et al. Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. Arch Gen Psychiatry. 2001;58(7):669–73.
44. Schurhoff F, Szoke A, Bellivier F, et al. Anhedonia in schizophrenia: a distinct familial subtype? Schizophr Res. 2003;61(1):59–66.
45. Seidman LJ, Kremen WS, Koren D, et al. A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. Schizophr Res. 2002;53(1–2):31–44.
46. Kamath V, Moberg PJ, Kohler CG, et al. Odor hedonic capacity and anhedonia in schizophrenia and unaffected first-degree relatives of schizophrenia patients. Schizophr Bull. 2013;39(1):59–67.
47. Chapman LJ, Chapman JP, Kwapil TR, et al. Putatively psychosis-prone subjects 10 years later. J Abnorm Psychol. 1994;103(2):171–83.
48. Kwapil TR. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. J Abnorm Psychol. 1998;107(4):558–65.

49. Gooding DC, Tallent KA, Matts CW. Clinical status of at-risk individuals 5 years later: further validation of the psychometric high-risk strategy. J Abnorm Psychol. 2005;114(1):170–5.
50. Kerns JG. Schizotypy facets, cognitive control, and emotion. J Abnorm Psychol. 2006;115(3):418–27.
51. Cicero DC, Becker TM, Martin EA, et al. The role of aberrant salience and self-concept clarity in psychotic-like experiences. Personal Disord. 2013;4(1):33–42.
52. Dillon DG, Bogdan R, Fagerness J, et al. Variation in TREK1 gene linked to depression-resistant phenotype is associated with potentiated neural responses to rewards in humans. Hum Brain Mapp. 2010;31(2):210–21.
53. Grant P, Kuepper Y, Mueller EA, et al. Dopaminergic foundations of schizotypy as measured by the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)-a suitable endophenotype of schizophrenia. Front Hum Neurosci. 2013;7:1.
54. Chien YL, Hwu HG, Fann CS, et al. DRD2 haplotype associated with negative symptoms and sustained attention deficits in Han Chinese with schizophrenia in Taiwan. J Hum Genet. 2013;58(4):229–32.
55. Hikida T, Jaaro-Peled H, Seshadri S, et al. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc Natl Acad Sci U S A. 2007;104(36):14501–6.
56. Meyer KD, Morris JA. Disc1 regulates granule cell migration in the developing hippocampus. Hum Mol Genet. 2009;18(17):3286–97.
57. Kumari V, Mitterschiffthaler MT, Teasdale JD, et al. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. Biol Psychiatry. 2003;54(8):777–91.
58. Szendi I, Kiss M, Racsmany M, et al. Correlations between clinical symptoms, working memory functions and structural brain abnormalities in men with schizophrenia. Psychiatry Res. 2006;147(1):47–55.
59. Bilder RM, Volavka J, Lachman HM, et al. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology. 2004;29(11):1943–61.
60. Hong J, Shu-Leong H, Tao X, et al. Distribution of catechol-O-methyltransferase expression in human central nervous system. Neuroreport. 1998;9(12):2861–4.
61. Tan HY, Callicott JH, Weinberger DR. Prefrontal cognitive systems in schizophrenia: towards human genetic brain mechanisms. Cogn Neuropsychiatry. 2009;14(4–5):277–98.
62. Prata DP, Mechelli A, Fu CH, et al. Epistasis between the DAT 3′ UTR VNTR and the COMT Val158Met SNP on cortical function in healthy subjects and patients with schizophrenia. Proc Natl Acad Sci U S A. 2009;106(32):13600–5.
63. Depue RA, Collins PF. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav Brain Sci. 1999;22(3):491–517.
64. Salamone JD, Correa M, Farrar A, et al. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology (Berl). 2007;191(3):461–82.
65. Li WJ, Kou CG, Yu Y, et al. Association of catechol-O-methyltransferase gene polymorphisms with schizophrenia and negative symptoms in a Chinese population. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(4):370–5.
66. O'Tuathaigh CM, Kirby BP, Moran PM, et al. Mutant mouse models: genotype-phenotype relationships to negative symptoms in schizophrenia. Schizophr Bull. 2010;36(2):271–88.
67. Le Pen G, Gaudet L, Mortas P, et al. Deficits in reward sensitivity in a neurodevelopmental rat model of schizophrenia. Psychopharmacology (Berl). 2002;161(4):434–41.
68. Moreau JL, Borgulya J, Jenck F, et al. Tolcapone: a potential new antidepressant detected in a novel animal model of depression. Behav Pharmacol. 1994;5(3):344–50.
69. Dreher JC, Kohn P, Berman KF. Neural coding of distinct statistical properties of reward information in humans. Cereb Cortex. 2006;16(4):561–73.
70. Rolls ET. The affective and cognitive processing of touch, oral texture, and temperature in the brain. Neurosci Biobehav Rev. 2010;34(2):237–45.
71. Tomppo L, Hennah W, Miettunen J, et al. Association of variants in DISC1 with psychosis-related traits in a large population cohort. Arch Gen Psychiatry. 2009;66(2):134–41.

72. Tomppo L, Ekelund J, Lichtermann D, et al. DISC1 conditioned GWAS for psychosis proneness in a large Finnish birth cohort. PLoS One. 2012;7(2):e30643.
73. Bader V, Tomppo L, Trossbach SV, et al. Proteomic, genomic and translational approaches identify CRMP1 for a role in schizophrenia and its underlying traits. Hum Mol Genet. 2012;21(20):4406–18.
74. Avramopoulos D, Stefanis NC, Hantoumi I, et al. Higher scores of self reported schizotypy in healthy young males carrying the COMT high activity allele. Mol Psychiatry. 2002;7(7):706–11.
75. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull. 1991;17(4):555–64.
76. Stefanis NC, Van Os J, Avramopoulos D, et al. Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. Biol Psychiatry. 2004;56(7):510–5.
77. Schurhoff F, Szoke A, Chevalier F, et al. Schizotypal dimensions: an intermediate phenotype associated with the COMT high activity allele. Am J Med Genet B Neuropsychiatr Genet. 2007;144B(1):64–8.
78. Ceaser A, Csernansky JG, Barch DM. COMT influences on prefrontal and striatal blood oxygenation level-dependent responses during working memory among individuals with schizophrenia, their siblings, and healthy controls. Cogn Neuropsychiatry. 2013; 18(4):257–83.
79. Ashby FG, Isen AM, Turken AU. A neuropsychological theory of positive affect and its influence on cognition. Psychol Rev. 1999;106(3):529–50.
80. Levinson DF, Mowry BJ, Escamilla MA, et al. The Lifetime Dimensions of Psychosis Scale (LDPS): description and interrater reliability. Schizophr Bull. 2002;28(4):683–95.
81. Chen WJ, Hsiao CK, Lin CC. Schizotypy in community samples: the three-factor structure and correlation with sustained attention. J Abnorm Psychol. 1997;106(4):649–54.
82. Park S, McTigue K. Working memory and the syndromes of schizotypal personality. Schizophr Res. 1997;26(2–3):213–20.
83. Tarbox SI, Almasy L, Gur RE, et al. The nature of schizotypy among multigenerational multiplex schizophrenia families. J Abnorm Psychol. 2012;121(2):396–406.
84. Eaton NR, Krueger RF, Docherty AR, et al. Toward a model-based approach to the clinical assessment of personality psychopathology. J Pers Assess. 2013;1–10.
85. Urosevic S, Abramson LY, Harmon-Jones E, et al. Dysregulation of the behavioral approach system (BAS) in bipolar spectrum disorders: review of theory and evidence. Clin Psychol Rev. 2008;28(7):1188–205.
86. Robinson MD, Clore GL. Belief and feeling: evidence for an accessibility model of emotional self-report. Psychol Bull. 2002;128(6):934–60.
87. Docherty AR. A unifying hypothesis for the pathogenesis of schizotypal anhedonia. 2010. Schizophrenia Research Forum, www.schizophreniaforum.org/images/SRFSIRSEssaytop12.pdf. Accessed 21 Aug 2013.
88. Docherty AR, Cicero DC, Becker TM, et al. Self-reported ambivalence in schizophrenia and associations with negative mood. J Nerv Ment Dis, in press.
89. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169(4):364–73.
90. Strauss GP. The emotion paradox of anhedonia in schizophrenia: or is it? Schizophr Bull. 2013;39(2):247–50.
91. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. PLoS One. 2012;7(5):e35622.
92. Gold JM, Strauss GP, Waltz JA, et al. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. Biol Psychiatry. 2013;74(2):130–6.
93. Gold JM, Waltz JA, Matveeva TM, et al. Negative symptoms and the failure to represent the expected reward value of actions: behavioral and computational modeling evidence. Arch Gen Psychiatry. 2012;69(2):129–38.
94. Lenzenweger MF. Schizotypy and Schizophrenia: the view from experimental psychopathology. New York: Guilford Press; 2010.

Chapter 5
Anhedonia in Schizophrenia: A Deficit in Translating Reward Information into Motivated Behavior

Gregory P. Strauss

Abstract Anhedonia has long been considered a core clinical feature of schizophrenia, which is thought to be an important predictor of functional outcome and disease liability. However, recent developments in the affective neuroscience of schizophrenia suggest that the traditional understanding of anhedonia as a diminished capacity for pleasure may not correctly characterize the affective abnormalities that occur in this patient population. In the current chapter, literature is reviewed to suggest that anhedonia in schizophrenia primarily reflects a deficit in initiating activities aimed at receiving rewards, rather than a reduced capacity to experience pleasure when patients are exposed to rewards. Multiple psychological and neural mechanisms appear to impair the translation of intact hedonic responses into goal directed behavior in schizophrenia. Several of these mechanisms are reviewed here, including: (1) dopamine-mediated basal ganglia systems that support reinforcement learning and the ability to predict cues that lead to rewarding outcomes; (2) orbitofrontal cortex-driven deficits in generating, updating, and maintaining value representations; (3) aberrant effort-value computations, which may be mediated by disrupted anterior cingulate cortex and midbrain dopamine functioning; (4) altered activation of the prefrontal cortex, which is important for generating exploratory behaviors in environments where reward outcomes are uncertain. Overall, findings suggest that aberrant cortical-striatal interactions are involved with the reduced frequency of pleasurable activities that characterizes schizophrenia. Suggestions are provided for the development of novel behavioral intervention strategies that make use of external cues and reinforcers designed to facilitate goal-directed behavior in light of these various reward-processing deficits. Future directions for examining anhedonia in relation to modern affective neuroscience perspectives are also discussed.

Keywords Anhedonia • Reward • Motivation • Liking/wanting

G.P. Strauss, Ph.D. (✉)
Department of Psychology, State University of New York at Binghamton,
PO Box 6000, Binghamton, NY 13902-6000, USA
e-mail: gstrauss@binghamton.edu

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_5,

Abbreviations

ACC	Anterior cingulate cortex
BG	Basal Ganglia
BNSS	Brief Negative Symptom Scale
CAINS	Clinical Assessment Interview for Negative Symptoms
CBT	Cognitive Behavioral Therapy
DA	Dopamine
DLPFC	Dorsolateral prefrontal cortex
fMRI	Functional Magnetic Resonance Imaging
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
VLPFC	Ventrolateral Prefrontal cortex
VMPFC	Ventromedial prefrontal cortex
SANS	Scale for the Assessment of Negative Symptoms

5.1 Overview

Anhedonia has long been considered a core clinical feature of schizophrenia [1–4], which has been shown to predict important clinical outcomes, such as social and vocational functioning, recovery, and disease liability [5–7]. The most common definition of anhedonia is that it reflects a diminished capacity to experience pleasure. In an early theory of anhedonia, Rado [4] proposed that individuals with schizophrenia had an "integrative pleasure deficiency". This deficiency was thought to be all-encompassing, impacting the frequency and intensity with which patients both expressed and experienced positive emotions. Although such views have guided diagnostic and treatment practices for over years now, modern research suggests that they may not be fully accurate. For example, although individuals with schizophrenia express less positive emotion in facial and vocal channels than healthy controls in response to evocative stimuli, they report experiencing levels of positive emotion that are equivalent to healthy controls [8, 9]. This disjunction between outward expression and subjective experience suggests that the common-sense notion that people who do not display emotion are not experiencing much emotion may not apply to people with schizophrenia.

Indeed, individuals with schizophrenia on average appear to report feeling as much positive emotion as healthy individuals in response to a range of pleasurable stimuli, such as film clips, complex photographs, food, drinks, social interactions, faces, and words (see [10] for a review). However, not every study has found fully normal reports of positive emotion in response to evocative stimuli (see [11–13]), particularly olfactory stimuli (e.g., [14, 15]). To gain greater clarity regarding whether individuals with schizophrenia do in fact have a diminished capacity for

pleasure, Cohen and Minor [16] conducted a meta-analysis of 26 laboratory-based studies where people with schizophrenia and healthy controls were asked to indicate their self-reported level of positive emotion to evocative stimuli. Meta-analytic results indicated that schizophrenia patients reported levels of positive emotion that were comparable to controls in response to pleasant, neutral, and unpleasant stimuli. This finding held true regardless of stimulus type and rating scale procedure (i.e., unipolar or bipolar rating scales). Cohen and Minor's [16] meta-analytic results also indicated that people with schizophrenia reported greater negative emotion than controls in response to unpleasant, neutral, and pleasant stimuli, consistent with an abnormality in state negative, rather than positive emotional experience. Although these findings on valence are informative, they provide only a partial answer to the question of whether in-the-moment positive emotional experience is intact in schizophrenia. To further explore hedonic capacity in schizophrenia, Llerena, Strauss, and Cohen [17] conducted a meta-analysis on 26 laboratory-based studies of self-reported subjective *arousal* to emotional stimuli. Arousal is the second major component of prominent models of emotional experience, which is thought to reflect the intensity of motivational activation of the positive valence system. If individuals with schizophrenia do indeed evidence reduced hedonic capacity, one might expect that their self-reports of arousal would be diminished relative to controls. However, meta-analytic results indicated that this was in fact not the case- schizophrenia patients and controls evidenced similar levels of subjective arousal to pleasant stimuli, providing additional support for intact hedonic experience in schizophrenia. These findings appear to suggest that hedonic capacity may be intact in schizophrenia, and have lead some to propose that individuals with schizophrenia should no longer be considered "anhedonic" in the strictest sense of the word [18].

Based on the self-report literature reviewed above, there are several potential problems with the conclusion that individuals with schizophrenia do not evidence a reduced capacity for pleasurable experiences. One potential problem, or caveat, could be that reductions in hedonic capacity are not characteristic of the majority of individuals with schizophrenia, but only a small subgroup. If true, this could result in a masking of hedonic deficits when data are analyzed at the group level. Suspecting that hedonic normality may be a by-product of clinical heterogeneity in schizophrenia, since only approximately 25 % of patients display clinically elevated negative symptoms [19], Strauss and Herbener [20] used a data-driven statistical approach to determine whether a subset of schizophrenia patients could be identified who displayed a diminished capacity for in-the-moment pleasure. Self-reported valence and arousal reports were obtained in response to photographs in a sample of schizophrenia patients and controls, and these scores were submitted to cluster analysis to examine whether meaningful sub-groups of patients could be identified based upon patients' in-the-moment affective self-report. Consistent with hypotheses, results supported the existence of two affective sub-groups within the patient sample: one that was affectively normal with self-reports of valence and arousal that were indistinguishable from controls, consisting of 60 % of patients, and a second sub-group that was affectively abnormal (40 %). Discriminant function analysis

confirmed that these two groups were indeed reliable and highly separable. However, contrary to expectations, the affectively abnormal sub-group did not evidence lower valence or arousal values for pleasant stimuli. Instead, they reported increased negative emotion and arousal in response to unpleasant stimuli, with reports of valence and arousal that were comparable to controls in response to pleasant stimuli. Thus, "state" affective abnormalities may indeed characterize only a minority of schizophrenia patients, and these abnormalities primarily involve negative, rather than positive emotions.

A second potential problem with the conclusion that schizophrenia patients do not display a hedonic deficit based upon the self-report literature alone is that it is possible for the neural response to pleasurable stimuli to be abnormal, even when subjective report is intact. It is possible that neural response provides a more objective estimate of hedonic capacity, which is less influenced by demand characteristics that influence self-reports. Numerous functional magnetic resonance imaging (fMRI) and Positron Emission Tomography (PET) studies have examined neural response while patients and controls reported their subjective positive emotional experience to evocative stimuli. Results of these studies have been somewhat inconsistent. Some studies have indicated that individuals with schizophrenia have diminished activation in response to pleasant affective stimuli relative to controls (e.g., [21]), whereas others have indicated that individuals with schizophrenia have levels of neural activation that are comparable to controls (e.g., [22]). Discrepancies in group-differences may in part reflect methodological differences such as stimulus type, whether activation contrasts are calculated in relation to neutral stimuli or baseline, and whether subjects are asked to rate their feelings in response to the stimulus or rate the stimulus itself [23–25]. Psychophysiological studies measuring affective modulation of startle response are also consistent with intact hedonics (see [10]). In these studies, startling noises are presented at various times while participants view emotional or neutral stimuli. Startle stimuli reliably induce a reflexive eye-blink response, and the magnitude of this response is modulated depending upon whether the startle probe is presented in the presence of pleasant, neutral, or unpleasant stimuli. Unpleasant stimuli potentiate the startle response moreso than neutral stimuli, which result in greater startle than pleasant stimuli. Studies examining affect modulated startle in schizophrenia have found that both healthy controls and people with schizophrenia evidence similar patterns of startle potentiation to pleasant, unpleasant, and neutral stimuli (i.e., unpleasant > neutral > pleasant) [10]. Thus, studies examining neural and psychophysiological response to laboratory-based stimuli are generally consistent with laboratory-based self-report studies suggesting intact hedonic responses to pleasant stimuli.

A third potential criticism of the notion that hedonic capacity is normal in schizophrenia based upon the literature described thus far is that laboratory-based studies may lack ecological validity. Is it possible that patients have intact hedonic responses in the laboratory, yet report markedly different experiences during real-world activities? Several experience-sampling studies have explored the self-report of positive and negative emotions during daily activities. Early studies concluded that patients reported less intense and less variable experiences of positive emotions

[26, 27]. However, these early studies failed to take into account that individuals with schizophrenia engage in fewer activities, and that averaging across all time points may complicate interpretations regarding capacity because patients simply have fewer opportunities for pleasurable events in their lives. In two studies where in-the-moment pleasure was examined in relation to instances when patients were engaged in activities, it was found that people with schizophrenia reported increases in positive emotion that were comparable to controls [28, 29]. Thus, contrary to the notion that schizophrenia patients are anhedonic, in-the-moment positive emotion has been found to be intact when patients report their level of positive emotion when engaged in activities during everyday life.

The aforementioned empirical studies therefore appear to support the conclusion that individuals with schizophrenia do not in fact have a diminished *capacity* for pleasure, as has long been assumed. The notion that hedonic capacity is reduced in schizophrenia primarily originated from interpretations of self-reports that patients would provide during clinical interviews. For decades, self-reports of anhedonia gathered through clinical interviews of negative symptoms have been taken as irrefutable evidence that people with schizophrenia have a diminished *capacity* for pleasure (see [30] for review of assessment strategies). Indeed, when such interviews are administered, the majority of schizophrenia patients are rated as having clinically significant anhedonia. For example, in a large sample of archival data from our research group on 385 patients who had been rated using the Scale for the Assessment of Negative Symptoms (SANS: [31]), 82 % met criteria for at least mild severity of anhedonia and 58 % for moderate or higher (i.e., the majority were rated as having clinically significant anhedonia). However, do the reports obtained from these scales reflect a diminished capacity for pleasure, or an impairment in some other aspect of affective functioning? To clarify this matter, it is helpful to carefully examine the nature of questions that are asked during a clinical interview, as well as the anchors used to make the determination that a patient is anhedonic. On clinical interviews such as the SANS [31], it is common place to ask patients to provide "retrospective" reports of how often they engaged in different pleasurable activities over the past week, past 2 weeks, or past month. Interviewers are then tasked with translating the information gleaned from their interview into a rating of anhedonia on the clinical rating scale. This involves trying to match the patient's report to several levels of anhedonia denoted by anchors on the item being rated. Examination of the individual anchors on the SANS anhedonia items provides valuable information about whether scores on these scales can actually be taken as evidence for a diminished capacity for pleasure. On the SANS, which is perhaps the most widely used clinical rating scale, anchors require the interviewer to rate the frequency with which the patient reports having recently engaged in pleasurable activities, such as social interactions, sexual activity, and recreational pursuits. They do not require an evaluation of whether the patient reports feeling maximally good when exposed to potentially pleasurable activities, which would evaluate *capacity* for pleasure. This may suggest that anhedonia in fact reflects a behavioral, rather than experiential abnormality in schizophrenia. Recognizing this possibility, newer next-generation negative symptom scales like the Brief Negative Symptom Scale (BNSS: [32]) and

Clinical Assessment Interview for Negative Symptoms (CAINS: [33]), include items examining the frequency with which patients engage in pleasurable activities. Additionally, data from real-world experience sampling studies supports the notion that a substantial proportion of schizophrenia patients engage in fewer pleasurable behaviors than controls, but do not experience reductions in pleasure when they are in fact engaged in activities [28, 29]. Thus, although self-reports obtained via clinical interview are commonly interpreted as reflecting a reduction in the *capacity* to experience pleasure, this interpretation may be incorrect; a more appropriate interpretation may be that schizophrenia patients display a behavioral deficit characterized by reductions in seeking out pleasurable activities.

In summary, there is increasing consensus that individuals with schizophrenia are not anhedonic in the traditional sense of the term. That is, they do not appear to have a diminished *capacity* for pleasure. Evidence supporting this claim comes from laboratory-based self-report studies of valence and arousal, functional neuroimaging and psychophysiology studies indicating intact neurophysiological response to pleasant stimuli, and experience-sampling studies indicating that patients report increases in positive emotion that are comparable to controls when they are engaged in activities. Instead, anhedonia appears to at least in part reflect a behavioral abnormality, whereby patients initiate fewer instances of goal-directed behavior aimed at obtaining rewards. Although this revised view of anhedonia as a behavioral, rather than experiential deficit (see also [10, 18, 25, 34] for similar suggestions), provides meaningful advances regarding the nature of anhedonia, it does not shed light onto the mechanisms that contribute to this behavioral abnormality. The remainder of this chapter is devoted to providing a mechanistic account for this behavioral component of anhedonia, capitalizing on recent advances in the field of affective neuroscience and the application of neuroscience frameworks to studying reward processing in schizophrenia.

5.2 The Behavioral Component of Anhedonia: A Deficit in Translating Reward Information into Pleasure-Seeking Behavior

The simplest understanding of why individuals with schizophrenia do not initiate pleasurable activities as often as controls would be that they do not find such activities enjoyable. However, since this explanation does not appear to be correct, an important question therefore emerges: "Why do apparently normal hedonic experiences not translate into actions aimed at obtaining rewards?"

One explanation for why normal hedonic responses do not translate into behaviors aimed at obtaining rewards is that patients have deficits in various reward-related processes that are needed to promote decision-making and action selection (see [35]). The basic neuroscience literature has identified core neural systems that are involved with processing and integrating rewards, as well as translating them into value signals that can be used to guide action selection. Several of these systems and

their corresponding reward-related processes have been studied in schizophrenia, including: (1) Reward prediction; (2) Value representation; (3) Uncertainty-driven exploration; and (4) Effort-value computations. Barch and Dowd [34] proposed that deficits in translating reward information into motivated behavior are subsumed by abnormalities in frontal-striatal circuitry. The sections that follow describe the neural mechanisms responsible for the aforementioned aspects of reward processing and review the relevant literature on how these reward components are affected in individuals with schizophrenia to evaluate the possibility that dysfunctional frontal-striatal circuitry contributes to deficits in appetitive behavior.

5.3 Reinforcement Learning and Reward Prediction

Two interactive and complementary neural systems have been shown to be involved with reinforcement learning and reward prediction [36]. The first system is mediated by the prefrontal cortex (PFC), especially the orbitofrontal cortex (OFC), and involves rapid learning. The rapid learning system updates mental representations of value for stimuli and response alternatives on a trial-by-trial basis, and guides decision-making by allowing individuals to flexibly respond to changes in reinforcement contingency. The second system is a slower learning system, which is mediated by the basal ganglia (BG). Learning achieved through this system occurs gradually across a number of trials [36]. Both of these systems have been shown to utilize prediction error signals to guide learning. Prediction errors occur in the presence of mismatches between expected and obtained outcomes, and can be either positive or negative. Positive prediction errors are signaled by phasic increases in dopamine activity when individuals receive outcomes that are better than expected. In contrast, negative prediction errors are associated with transient decreases in dopamine cell activity in response to outcomes that were worse than expected. From a functional standpoint, positive and negative prediction errors serve a critical role in informing motivated behavior by signaling which actions have resulted in outcomes that should be repeated or avoided.

Several behavioral and neuroimaging studies have investigated the integrity of the fast and slow learning systems, as well as prediction error signaling, in people with schizophrenia. There is consistent evidence that patients have deficits in rapid learning and making trial-by-trial adjustments in response to positive and negative feedback [37, 38]. Additionally, some studies suggest that higher levels of clinically rated negative symptoms, including anhedonia [37, 38], are associated with impairments in rapid learning and making adjustments to behavior in an adaptive manner. Functional neuroimaging studies indicate that deficits in rapid learning are associated with aberrant activation in the prefrontal cortex, especially the orbitofrontal cortex [39, 40].

Several studies have also investigated the integrity of the gradual, basal ganglia-driven, learning system using a variety of tasks, such as motor learning, serial reaction time, and cognitive skill-based paradigms [41, 42]. Results from these studies are

somewhat inconsistent (see [43, 44]); however, the majority of studies suggest that gradual learning may be relatively intact in schizophrenia [45]. Discrepancies among these gradual learning studies may reflect a combination of differences in task properties, as well as subject-related characteristics. In particular, antipsychotic medications may affect gradual learning, as chlorpromazine equivalent dosage has been linked to procedural learning [46] and procedural learning impairments are more mild in antipsychotic naïve patients [47]. Very high levels of D2 blockade may therefore significantly impair gradual learning. Given that the majority of studies examining the gradual learning system appear to suggest that patient performance is relatively spared, one might be tempted to infer that basal ganglia activation is relatively normal during procedural learning. However, several neuroimaging studies suggest that normal learning may in fact be accompanied by abnormal neural activation in many areas, including the basal ganglia [48, 49]. It may therefore be the case that patients achieve normal gradual learning through use of a number of cognitive processes, as well as neural substrates outside of the neostriatum.

In many reinforcement-learning paradigms, it is also possible to make a dissociation between reward-driven "Go" learning and punishment-driven "NoGo" learning. Several studies indicate that schizophrenia patients display intact NoGo learning, but impaired Go learning. Waltz et al. [50] administered the probabilistic stimulus selection task, which includes an initial learning phase for pairs of probabilistically reinforced stimuli (e.g., AB: 80/20 %; CD: 70/30 %; EF: 60/40 %) and a subsequent test phase where the stimuli presented in the initial phase are paired with each other and novel stimuli. Go learning can be assessed in test phase performance by examining the extent to which a subject selects the most highly rewarded stimulus (A) when it is paired with novel stimuli that were not paired with (A) during the acquisition phase (i.e., CDEF). NoGo learning is assessed by evaluating the number of times a subject avoids the least rewarding stimulus (B) when it is paired with novel stimuli not paired with (B) during the acquisition phase (i.e., CDEF). Consistent with spared NoGo learning, and impaired Go learning, Waltz et al. [50] found that patients had a selective deficit in choosing A at test, but no impairment in avoiding B. Importantly, these Go learning impairments were most profound in patients with a greater severity of clinically rated negative symptoms. Using different paradigms, Strauss et al. [51] and Waltz et al. [38], also found that patients had selective deficits in "Go" learning, which were associated with greater severity of negative symptoms. This pattern of performance can be considered a perfect neurobehavioral recipe for the behavioral component of anhedonia, i.e., patients can adequately learn to avoid outcomes that lead to aversive outcomes, yet have deficits in learning to select actions that had previously yielded reward.

Although these studies indicate that there is a link between negative symptoms and Go learning, they do not provide a clear indication of the cognitive and neural mechanisms that underlie this deficit. Studies using computational modeling and functional neuroimaging have offered valuable insight into these potential mechanisms. One explanation for the Go-learning deficit is that it could result from a failure to generate or learn from positive prediction errors that occur during positive outcomes. Such a deficit would likely implicate aberrant dopaminergic signaling

during prediction errors. Alternatively, orbitofrontal cortex driven deficits in value representation could keep patients from precisely representing the value of response alternatives during decision-making. To explore these two alternative explanations, Gold et al. [52] administered a probabilistic reinforcement learning task that allowed for dissociation between value representation and prediction error abnormalities. Participants were presented with four stimulus pairs: in two of the pairs, the correct choice led to a monetary reward on either 90 or 80 % of trials with incorrect choices leading to no reward; in the other two pairs, the correct choice led to the avoidance of a monetary loss on 90 or 80 % of trials. Using this design, selection of the correct response is associated with the generation of a positive prediction error (and phasic dopamine burst) in both the gain and loss avoidance pairs. Behavioral results indicated that patients with more severe avolition and anhedonia showed impaired acquisition of the gain pairs, but intact performance on the loss avoidance pairs. These findings indicate that patients are able to use prediction errors to guide learning, at least when the positive prediction error is associated with successful loss avoidance and intact learning from negative prediction errors. A second important finding was that in the transfer phase, when stimuli learned during acquisition were presented in novel pairings, only the patients with elevated avolition and anhedonia failed to prefer the stimuli associated with rewarding outcomes over those that had been associated with loss avoidance (i.e., those associated with positive prediction errors that did not have positive expected value). In essence high negative symptom patients primarily made choices based on the history of prediction errors, not by their expected value. Computational modeling confirmed this interpretation, providing separate estimates of whether prediction error signaling in the basal ganglia (actor-critic model) or prediction errors used to update value representations of actions in the OFC (Q-learning) were most representative of behavioral performance. The modeling results were very clear: performance of avolitional/anhedonic patients was well fit by a pure actor-critic model, whereas healthy controls and patients with low avolition/anhedonia were best fit by the model where the actor-critic was supplemented by the contribution of Q-learning. These modeling results provide further support for the interpretation that the deficit observed in avolitional/anhedonic patients reflects impairments in value representation, not learning from prediction errors. Thus, behavioral and modeling data indicated that prediction error signaling is largely spared in schizophrenia.

However, the functional neuroimaging literature paints a picture that is not entirely consistent with the behavioral and computational modeling data regarding prediction errors. On the one hand is imaging data indicating intact activation in the ventral striatum in relation to negative prediction errors [39, 53, 54]. These findings are consistent with the behavioral and modeling evidence. However, on the other hand, data from several imaging studies indicates that positive prediction errors are accompanied by reduced neural response in the ventral striatum, as well as other regions such as the insula, frontal cortex, amygdala, hippocampus, putamen, and cingulate [39, 53–59], although, reduced striatal response has not been universally found (see [39, 60, 61]). Discrepancies across studies may to some extent reflect characteristics of the patient samples that were studied since individual differences

in clinically rated negative symptoms predicted striatal response [39, 54, 60, 61]. Thus, the literature on the integrity of positive prediction error signaling is unclear; however, one interpretation of these imaging findings is that poor learning from positive feedback is driven by aberrant positive prediction errors and dopamine signaling in the midbrain.

Reward prediction, which refers to the ability to anticipate a reward when a predictive cue is presented, is another factor that drives pleasure-seeking behavior. Dopaminergic activity in the striatum is thought to play a key role in this process, allowing affective salience to become linked to predictive cues. The monetary incentive delay paradigm has been used to study the neural substrates of reward anticipation in several schizophrenia studies. In this task, different colored shapes predict gains, losses, and neutral outcomes and it is possible to differentiate neural response during the anticipation of rewards (ventral striatum) from neural response during the receipt of rewards (medial prefrontal cortex). Monetary incentive delay results have indicated that individuals with schizophrenia have reduced activation in the ventral striatum in response to cues predicting upcoming rewards [62–64]. These findings hold true in patients who are unmedicated or taking first generation, but not second-generation antipsychotics [63, 64]. Several studies also report that blunted striatal activation during reward anticipation is associated with greater severity of negative symptoms [39, 54, 61], and these relationships hold true in patients taking second-generation antipsychotics [39, 61]. One complication of interpreting results from the monetary incentive delay or other instrumental learning paradigms is that reward anticipation is dependent on the subject's ability to earn rewards via appropriate responding and therefore relies on several cognitive processes that are known to be impaired in schizophrenia other than prediction errors. Clarifying this matter somewhat, Pavlovian conditioning paradigms evaluate reward anticipation and prediction error signaling independent of factors like action selection and response execution. Waltz et al. [54] used a passive conditioning paradigm which presented subjects with a light cue and then a squirt of juice. To allow for an examination of neural response to positive and negative prediction errors, on 75 % of trials, juice receipt occurred exactly 6 s following light cue, whereas receipt was delayed by a further 4–7 s on 25 % of trials. Imaging results indicated reduced neural response to positive prediction errors in several brain regions, but largely intact neural response to negative prediction errors. Dowd and Barch [60] administered a Pavlovian reward conditioning paradigm with no response requirements, where subjects passively viewed cues (colored shapes) that predicted subsequent monetary reward or non-reward. Imaging results indicated that at the group level, neural response to reward receipt and anticipation were comparable between patients and controls; however, individual differences in self-reported anhedonia were associated with reduced activation in the left ventral striatum and ventromedial prefrontal cortex during reward anticipation. Thus, findings from conditioning paradigms without response demands and instrumental paradigms with significant response demands are largely consistent- patients with higher levels of anhedonia evidence reduced activation in the ventral striatum and ventromedial prefrontal cortex during reward anticipation. Thus, reward anticipation may be impaired in schizophrenia, whereas reward receipt may not.

5.4 Value Representation

Several research groups have proposed that abnormalities in "value representation" may be critically linked to anhedonia and avolition in schizophrenia [25, 34, 35]. In particular, reduced reward-seeking and goal-directed behavior is thought to be associated with impairments in generating, maintaining, and updating mental representations of value. The orbitofrontal cortex (OFC) plays a critical role in several aspects of value representation [65]. For example, the OFC is responsible for calculating the value of an outcome, evaluating how much an outcome satisfies current motivational needs, and comparing the value of an outcome with other possible outcomes [65]. Like other regions of the PFC, the OFC serves the purpose of holding information about reward value in working memory, which in turn facilitates goal-directed behavior by indicating when outcomes have changed and action plans need to be updated.

Compared to other aspects of reward processing, relatively few studies have examined the integrity of OFC function as it relates to value representation in schizophrenia. The two tasks associated with lateral and medial OFC function that have been most frequently used to study value representation in schizophrenia are Probabilistic Reversal Learning and the Iowa Gambling Task. In probabilistic reversal learning, participants are presented with pairs of stimuli that are probabilistically reinforced (e.g., selection of stimulus A reinforced 80 % of the time; Selection of stimulus B reinforced 20 % of the time) and asked to learn which is the correct stimulus. Instructions stipulate that subjects should continue selecting the stimulus they think is correct until they determine that the correct stimulus has changed. Once subjects meet some predetermined criteria for demonstrating adequate learning of the most frequently reinforced stimulus, the contingencies are reversed (e.g., Stimulus A reinforced 20 % of the time; Stimulus B reinforced 80 % of the time). In this reversal phase, the number of errors made by the subject and the number of trials needed to reach criterion have been linked to OFC function, and reflect how well and individual can integrate positive and negative feedback across trials to update value representations that are used to guide action selection. When individuals with schizophrenia have completed probabilistic reversal learning tasks, or Intra-dimensional/extra-dimensional set-shifting tasks, it has been found that they are more impaired than controls at the reversal stage of this task [37, 66–70]. Neuroimaging evidence indicates that impairments in the reversal phase are associated with reduced deactivation of the medial prefrontal cortex [71]. Additionally, elevated clinical ratings of anhedonia and avolition are associated with the magnitude of patients' deactivations in the ventromedial prefrontal cortex and ventral striatum [71]. Thus, findings confirm the role of ventrolateral prefrontal cortex and dorsomedial prefrontal cortex in updating mental representations of value, as well as a link between these regions and reduced pleasure-seeking behavior.

Individuals with schizophrenia have also demonstrated impairments on the Iowa Gambling Task ([71–78]; however see [79–81]). This task requires subjects to draw one card at a time from four decks (A-D). Each selection either results in winning or losing money, with the frequency and magnitudes of gains and losses differing

across decks. Two of the decks are disadvantageous and result in high immediate gains as well as even higher losses, such that selecting from these decks on average leads to more overall loss. The other two decks are more advantageous, with selections resulting in low immediate gains and infrequent low-value losses. Choosing these advantageous decks results in more net gains on average. Neurological patients with OFC lesions are more likely to select from the disadvantageous decks [82]. Although individuals with schizophrenia evidence volumetric reductions in the OFC, these reductions are not predictive of Iowa Gambling Test performance in patients like they are in controls [76, 83]. Thus, impaired Iowa Gambling Test performance has been noted in schizophrenia, but it is unclear whether these deficits reflect abnormalities in the OFC or other structures; it is therefore possible that aspects of cognition other than value representation may contribute to deficits observed on this task.

Another task that has been associated with OFC dysfunction is a simple preference judgment task that evaluates "relative" value assignments. In this task, participants are presented with a set of like items (e.g., pictures of cute puppies) and asked to select the stimulus that they prefer [84]. There are no correct or incorrect answers and no outcome occurs in relation to choices. All stimuli within the set are presented in conjunction with every other stimulus, making it possible to examine the hierarchy of preferred stimuli and the consistency of selections relative to preferences. For example, if a subject prefers stimulus A over B and B over C, they should also prefer A over C. Failures to maintain transitivity of preferences have been linked to the ventromedial prefrontal cortex (defined as the region encompassing both medial OFC and adjacent ventral medial PFC) in lesion studies [84]. One study administered this preference task to a sample of schizophrenia outpatients and demographically matched healthy controls [85]. Results indicated that schizophrenia patients were both less consistent in their selections (i.e., more errors in transitivity) and more likely to have larger magnitudes of discrepant responses than controls. Furthermore, whereas controls showed clear differentiation between degrees of valence in a condition that presented a set of pleasant and unpleasant stimuli selected for normative gradations in valence (i.e., highly positive > mildly positive > mildly negative > highly negative), patients showed no preference for highly positive over mildly positive items or mildly negative over highly negative items (despite preferring positive to negative stimuli). Abnormal preference judgments were also correlated with self-reported anhedonia on the Chapman scales and general working memory impairments. When viewed in relation to the broader neuroscience and lesion literature on value representation using the preference task, these behavioral results are consistent with the notion that OFC dysfunction is linked to deficits in developing or maintaining nuanced representations of value that occur in schizophrenia.

The delayed discounting paradigm has also been suggested to involve value representation. This task examines the degree to which individuals prefer smaller rewards sooner or larger rewards later. When the slope of a delayed discounting function increases, this indicates a preference for more proximal rewards. Steeper discounting rates have been linked to abnormalities in both the nucleus accumbens and ventromedial cortex, suggesting that discounting abnormalities may reflect both

dopaminergic dysfunction and deficits in value representation. Such deficits have also been found in multiple forms of psychopathology [86, 87]. In delayed discounting experiments examining individuals with schizophrenia, where participants were presented with an option for smaller immediate rewards or larger delayed rewards, it has been found that schizophrenia patients evidence steeper discounting rates than controls, i.e., they prefer smaller immediate rewards over larger delayed rewards [88, 89]. A functional neuroimaging study of delay discounting in schizophrenia patients and controls matched on behavioral performance indicated that patients had less activation in inferior frontal, dorsal anterior cingulate, and posterior parietal cortices, as well as the ventral striatum [90]. It is easy to see how deficits in representing the value of future outcomes might contribute to impairments in reward-seeking behavior in schizophrenia. Simply put, when value cannot be represented precisely, rewards that cannot be obtained immediately may not have enough pull to motivate patients to produce the actions needed to obtain them.

In addition to deficits in generating and updating value representations, there is also some evidence that schizophrenia patients have impairments in maintaining value representations. Gard et al. [91] had patients and controls perform an emotional maintenance task, where subjects were presented with two stimuli of similar valence (e.g., both pleasant) that were separated by a short delay (3 s). Participants were instructed to determine whether the first or second image was stronger in intensity, and these evaluations were compared to ratings of intensity that the subjects made later in a separate task to determine the presence of emotional maintenance errors. Results indicated that patients made more errors in maintaining intensity judgments, suggesting that they had a deficit in maintaining value representations and using them to appropriately guide decision-making. Similarly, in a psychophysiological study by Kring et al. [92], startle probes were presented during stimulus presentations of affective and neutral photographs, as well as during the delay period between stimulus presentations. Similar to prior startle studies examining startle potentiation during stimulus viewing, schizophrenia patients and controls demonstrated comparable affect modulated startle potentiation when images were on screen. However, whereas controls continued to display affect modulated startle during the delay period, schizophrenia patients did not, consistent with a deficit in maintaining value representations. A functional neuroimaging study utilized a similar paradigm, where neural activation to affective and neutral images was examined while stimuli were on screen, as well as during the delay period following stimulus offset [22]. Results indicated that schizophrenia patients had comparable neural response to controls in the presence of emotional stimuli, but reduced neural activation during the delay period in several areas, including the dorsolateral and ventromedial/orbitofrontal cortices. Furthermore, delay period activity in the dorsolateral prefrontal cortex for pleasant stimuli was correlated with individual differences in clinically rated anhedonia. Thus, schizophrenia patients may have deficits in maintaining mental representations of value and using them to guide decision-making- a problem that stems from reduced OFC activation.

Collectively, these studies provide evidence that a distributed network of regions is involved in deficits in generating, updating, and maintaining mental representations

of value. Given that some of these abnormalities occur in tasks that require simple preference judgment in the absence of learning and feedback processing, impairments in value representation do not appear to be merely byproducts of reinforcement learning abnormalities. That is not to say that value representation is not influenced by general cognitive impairments or working memory specifically. Indeed, there is strong evidence for such associations, supporting the notion that working memory deficits may underlie the ability to couple affective value and behavior [93]. The ability to seek out pleasurable activities and perform goal-directed behavior may be highly influenced by a patient's ability to generate and maintain value representations in working memory. When value representations are not sufficiently salient or not adequately sustained, it is unlikely that they will be salient enough to adequately motivate behavior. Thus, value representation impairments may be a key contributor to the behavioral component of anhedonia in schizophrenia.

5.5 Uncertainty-Driven Exploration

In everyday life, we are constantly forced to make decisions between actions that have resulted in positive outcomes in the past, versus trying out new actions that could yield even better results. For example, when at a favorite local restaurant, do you order your tried and true favorite dish? Or do you go with the special of the day which you have never tried in hopes that it is even better than your old reliable? This decision-making process, termed the exploration-exploitation dilemma, is experienced at all levels of behavior and influences decisions ranging from how to plan one's day to which job to apply for. How an individual approaches this exploration-exploitation dilemma therefore critically impacts the frequency with which they engage in behaviors aimed at obtaining rewards, as well as the variety of pleasurable activities that they are exposed to. Given that current conceptual frameworks (e.g., [18]) and newer negative symptom rating scales [32, 33] emphasize the frequency and variety of pleasurable activities as core aspects of anhedonia, it is possible that exploration and exploitation may offer hope for a mechanistic account of anhedonia in people with schizophrenia.

Sometimes it is adaptive to repeat actions that have previously lead to reward (i.e., exploit). This is particularly true when individuals encounter "stationary" environments, where reinforcement contingencies are stable. In such circumstances, individuals can make decisions based upon expected value and exploit to maximize rewards [94, 95]. In stationary environments, exploitation is heavily influenced by dopamine nuclei and target areas in the basal ganglia and prefrontal cortex [96, 97].

However, many real-life situations involve environments that are "non-stationary", where reinforcement contingencies are not stable. In such circumstances, it may be more valuable to explore the value resulting from actions with uncertain outcomes, in hopes of obtaining rewards that are greater than those previously experienced. Exploration can be achieved through several strategies. One strategy is to repeat behaviors that have best lead to reward (i.e., exploit), while also discovering over

time whether there are better options by occasionally choosing a different action at random [98]. Another strategy is more systematic and involves selecting actions based upon their level of uncertainty relative to the status quo (i.e., the exploited option). By continuously tracking both the frequency and magnitude of potential options, as well as the degree of uncertainty associated with them, individuals using this strategy maximize the amount of information learned about potentially rewarding outcomes. Uncertainty-driven exploration may therefore be a more ideal strategy for enhancing the probability of obtaining maximal rewards.

Several neurobiological processes are involved with uncertainty-driven exploration. At the neuroanatomical level, human neuroimaging evidence indicates that the rostrolateral prefrontal cortex is responsible for tracking uncertainty in an ongoing manner to promote exploratory behavior [97, 99]. Individual differences in uncertainty-driven exploration have also been linked to genes associated with prefrontal dopamine function (COMT), while individual differences in exploitation are associated with genes controlling striatal dopamine function (DARPP-32 and DRD2) [100]. Exploration may depend on one's ability to engage more dorsal and anterior regions of the prefrontal cortex that drive top-down control and limit prepotent behavioral responses in favor of selecting new actions aimed at obtaining maximal reward [94]. A second explanation is that exploratory behavior is influenced by neuromodulatory control of cortical norepinephrine [94, 101–103]. In particular, it is thought that phasic and tonic norepniephrine release serves to differentially promote exploration and exploitation as a function of ongoing utility estimates that are governed by frontal and medial regions of the prefrontal cortex. These prefrontal control regions, which are known to be impaired in schizophrenia, are critical for regulating the balance between decisions to explore or exploit under conditions of uncertainty [94, 103]. Based upon the basic and cognitive neuroscience literature, one could therefore imagine that multiple mechanisms could contribute to reduced exploration and these have been implicated in schizophrenia.

To date, few studies have examined exploration and exploitation in schizophrenia. Strauss et al. [51] administered the Temporal Utility Integration Task [104] in which participants observe a moving hand rotate throughout a clock face over a five second period. Subjects were asked to press a button to stop the clock hand at any point on the clock in order to earn a reward, with the goal of winning the most points possible throughout the task. Reward magnitude and probability was manipulated in relation to response time, such that expected value increased, decreased, or remained constant at different levels of response time. Across several conditions, denoted by blocks where clock faces appeared over different colored backgrounds, participants were required to learn the optimal strategy for maximizing rewards (e.g., responding more quickly or waiting until the hand reached the end of the clock). Via computational modeling, it was possible to examine trial-by-trial dynamics in response time adjustments to estimate a subject's degree of uncertainty-driven exploration. Modeling results indicated that patients as a whole were less likely than controls to *explore* response alternatives when the values of those alternatives were uncertain. Furthermore, reduced exploration predicted individual differences in clinically rated anhedonia on the Scale for the Assessment of Negative Symptoms (but not

other aspects of negative symptoms) in schizophrenia patients. The specificity of this association with anhedonia but not other aspects of negative symptoms may be meaningful because anhedonia on this scale reflects a behavioral abnormality characterized by reductions in the frequency of pleasurable activities. When a similar computational model was applied to behavioral data from a probability matching task administered in Kasanova et al. [105], a similar relationship between clinically rated negative symptoms and reduced exploration was found. Thus, prior schizophrenia findings provide preliminary support for a novel mechanistic understanding of anhedonia as a deficit in exploring new actions that could lead to a greater magnitude, frequency, or variety of rewarding outcomes compared to rewards gained from actions generated in the past.

Several neurobiological mechanisms may serve to link anhedonia and reduced uncertainty-driven exploration in people with schizophrenia. One possibility, as proposed by Strauss et al., is that reduced exploration results from degredations in prefrontal cortical dopamine function, an abnormality that has been implicated in the etiology of negative symptoms multiple times [106–108]. This interpretation is supported by functional neuroimaging studies indicating that the prefrontal cortex is involved in tracking uncertainty [97, 99], as well as a gene-dose effect of the val/met polymorphism of the COMT gene in healthy individuals performing the same task as Strauss et al. [51] [100]. Impaired prefrontal mechanisms may therefore reduce top-down control needed to inhibit a prepotent exploitative behavior and facilitate exploratory actions under conditions of uncertainty. Although degredation in prefrontal cortical dopamine appears to be the most likely explanation for reduced uncertainty-driven exploation, several additional mechanisms could also be involved.

Huys and Dayan [109] have suggested that major depressive disorder is associated with a deficit in processing uncertainty itself, such that depressed patients assign a negative expected value to uncertain outcomes. Since a sizeable proportion of people with schizophrenia carry a comorbid diagnosis of major depressive disorder and depression contributes to some portion of variance associated with anhedonia in schizophrenia patients, this interpretation seems plausible. However, Strauss et al. did not find an association between exploration and depression, potentially suggesting that the mechanisms underlying reduced exploration may differ between schizophrenia and depression.

Another potential explanation is that schizophrenia patients have a deficit in processing uncertainty itself, and that such deficits contribute to reductions in exploration. Yu and Dayan [101] proposed that expected and unexpected forms of uncertainty exist, and that two neuromodulatory processes may be involved with these processes: acetylcholine and norepinephrine. Decisions to explore and exploit may be critically linked to the processing of expected and unexpected uncertainty. Unexpected uncertainty, which is signaled by norepinephrine, may be particularly important for indicating the need to explore. According to Yu and Dayan's model [101], we should persist in our current behavior (i.e., exploit) when the extent that we expect an outcome to vary tracks with what we observe in the

environment. In contrast, we should select a new course of action (i.e., explore) when there are large discrepancies between our expectations and how often (or to which magnitude) an action yields the expected outcome. Perhaps individuals with schizophrenia have deficits in formulating expectations about how often outcomes should vary, and/or updating their representations of how often outcomes do vary when changes in the environment occur. Such abnormalities in tracking unexpected uncertainty could thus contribute to reductions in exploratory behavior, preventing patients from modifying their actions in non-stationary environments where reinforcement contingencies are changing.

Related to the Yu and Dayan model, [101] Aston-Jones and Cohen [103] proposed that decisions to explore or exploit are critically linked to ongoing utility estimates, which are executed by frontal structures that regulate norepinephrine release. Utility estimates are thought to be fundamental to the decision of whether to give up or persist in instances when task performance might be poor and thus not leading to adequate reward attainment. For example, in a situation where an individual has generally been performing well on a task that yields rewards, but they occasionally make errors on single trials (i.e., transient decreases in utility), it would be to their benefit to persist in the task (i.e., exploit) and try to restore their performance to a high level following errors. In contrast, when an individual is performing poorly on a task and making many errors over consecutive trials (i.e., long-term utility is low and progressively declining), the individual should be encouraged to give up and try out other actions (i.e., explore) that could result in alternative outcomes and potentially better rewards. Based on this model, one possibility is that schizophrenia patients have deficits in tracking long-term utility and using utility signals to promote exploratory behaviors aimed at obtaining rewards in contexts where they have engaged in unsuccessful behaviors that have failed to yield sufficient rewards.

Social context could be yet another important factor driving the exploration-exploitation dilemma in schizophrenia patients. In particular, healthy people may be more likely to explore potential rewards within an environment when they have access to information about the behavior of others, or when they are faced with competition from others for resources that lead to rewards [94]. It is possible that deficits in social cognition, social drive, social skills and asociality may render individuals with schizophrenia less likely to explore based upon interpersonal interactions. Studies examining exploration and exploitation in schizophrenia to date have not manipulated social context; however, this could be an important future direction.

Overall, studies examining uncertainty-driven exploration in schizophrenia have indicated an important association with anhedonia and a novel mechanistic account for reduced reward-seeking behavior. Future studies on exploration are needed to evaluate some of the alternative cognitive and neurobiological explanations posed here.

5.6 Effort-Value Computations

Another potential mechanism for why normal hedonic experiences do not translate into reward-seeking behavior is that schizophrenia patients have deficits in "effort-value computation" that prevent them from making an accurate estimation of whether the benefits associated with an action outweigh the "costs" related to obtaining them (e.g., physical effort, mental effort). Several behavioral neuroscience paradigms have been used to study the neural substrates of effort-value computation (see [110] for review). One widely used method, the progressive-ratio paradigm, requires animals to exert physical effort (e.g., pressing a lever) to obtain differing magnitudes of reward (e.g., food) [111]. In this paradigm, a reward is initially delivered after the animal has exerted a low number of physical responses, and the threshold for reward receipt is then progressively increased until the animal's "breakpoint" is determined (i.e., the number of effortful responses at which the animal will no longer work to receive a reward). Another paradigm involves offering the animal a choice between multiple rewards, where one of the rewards (which is either greater in quantity or value) requires greater expenditure of effort to obtain it (e.g., climbing a wall) [112]. This paradigm therefore forces the animal to choose between expending a high degree of effort for a large reward or less effort for a lower reward. The willingness to exert effort aimed at obtaining rewards of differing value has been critically linked to dopaminergic function. Specifically, studies have shown that willingness to work for reward has been affected by focal depletion of dopamine in the nucleus accumbens [111, 112]. Increasing dopamine levels via administration of amphetamine also enhances willingness to exert effortful behavior [113]. In humans, stimulation of dopamine release via administration of d-amphetamine has also been linked to increases in effortful behavior, and individual differences in dopamine release have been found to predict how willing an individual is to work for higher rewards [113, 114]. Striatal dopamine release and dopamine receptor availability may therefore play a critical role in whether high amounts of effort will be exerted to obtain a reward.

Although it is well-documented that schizophrenia patients have dopaminergic abnormalities, these abnormalities are not consistent with what one would expect in a disorder characterized by decreased motivation. For example, the basic neuroscience literature suggests that reduced effortful behavior is associated with *reduced* striatal dopamine receptor availability and release. However, schizophrenia patients exhibit tonic *increases* in dopamine levels and greater dopamine release in response to dopamine enhancing agents like d-amphetamine. It therefore seems likely that another mechanism must be contributing to the reductions in effortful behavior that are characteristic of schizophrenia. A recent animal model of motivational impairments in schizophrenia provides one viable explanation for this apparent inconsistency. Ward et al. [115] found that developing mice which are genetically altered to have an overexpression of postsynaptic D2 receptors are less willing to work to receive rewards, despite having normal hedonic reactions [115]. Given that schizophrenia patients do in fact display an increase in D2 receptor availability [116, 117], it seems

plausible that reductions in effortful behavior result from an overexpression of postsynaptic D2 receptors rather than reduced striatal dopamine release.

Effort computation has also been neuroanatomically linked to the anterior cingulate cortex. This association has been demonstrated both via animal lesion studies [118–120] and positron emission tomography studies of rats indicating that effortful behavior is predicted by ACC activation [121]. In humans, ACC activation also predicts decisions to expend effort [122, 123]. Consistent with a potential role of the ACC in motivational abnormalities in schizophrenia, several structural MRI studies have indicated that patients have volumetric reductions in the ACC [124, 125]. Functional neuroimaging studies also indicate that schizophrenia patients have aberrant activation in the ACC during tasks requiring conflict or error monitoring (e.g., [126]), providing indirect support for a potential role of the ACC in effort-value calculation.

There is also reason to suspect that reductions in effortful behavior may reflect a circuit-level dysfunction, rather than the ACC and nucleus accumbens making separate contributions in parallel. In a study that lesioned the connection between the ACC and nucleus accumbens, it was found that effortful behavior was reduced equivalently to when the nucleus accumbens alone was lesioned [127]. This may suggest that striatal dopamine abnormalities and the ACC function in concert to contribute to effort-based decision-making.

To date, only two published studies have examined effort-value computations in schizophrenia. In the first such study, Gold et al. [128] administered a computerized behavioral task to a sample of outpatients with schizophrenia and demographically matched healthy controls. Participants were presented with a decision-making task where they could chose between making 20 button presses to obtain $1 (low effort/low reward condition) or 100 presses to obtain rewards ranging from $3 to $7. The probability of reward receipt was also manipulated to determine whether certain (100 % probability) or uncertain (50 % probability) outcomes influenced effort-based decision-making. Results indicated that schizophrenia patients were less likely than controls to select the high effort option in the 100 % probability condition when the potential reward value that could be earned was at its highest ($5, $6, $7). Additionally, the deficit in how willing patients were to work for higher value rewards was uniquely linked to individual differences in negative symptom severity on the Brief Negative Symptom Scale [32, 129, 130]. Patients with high negative symptoms were also less willing than controls to select a high effort option in the 50 % (uncertain) condition, when they had selected a high effort option on the previous trial and been rewarded. Effort-value computation abnormalities were also accompanied by general evidence of appetitive behavioral deficits as indicated by reduced response vigor and increased time needed for task completion (despite selecting more low effort options).

The second study, conducted by Fervaha et al. [131], obtained results similar to Gold et al. [128]. Fervaha et al. [131] administered the Effort Expenditure for Reward Task (EEfRT: [132]) to a sample of schizophrenia patients and controls. This decision-making task asks participants to make either a low effort/low reward choice that requires making a set number of button presses with their dominant hand index finger within 7 s to earn $1, or a high effort/high value choice where they must

make a greater number of button presses within 21 s using their non-dominant hand pinky finger to earn higher values ranging from $1.24 to $4.30. Probability of reward receipt is also manipulated to estimate the role of certainty, with probabilities corresponding to either 12, 50, or 88 % on each trial. Importantly, Fervaha also modified the task to account for motoric abnormalities known to impact people with schizophrenia (e.g., finger tapping deficits identified on neuropsychological tests) by individually tailoring the maximum number of button presses for the easy and hard conditions based on a pre-test of the participant's finger-tapping speed. Results indicated that schizophrenia patients were less willing to expend effort to receive high value rewards, and that these deficits were correlated with clinically rated avolition.

Although few studies have directly examined effort-value computation in schizophrenia, the results of the two studies conducted to date point to an association between negative symptoms and reductions in willingness to put forth effortful responses to obtain high-value rewards. One explanation for these results is that the high negative symptom patients did not find the high-value rewards worth the effort needed to obtain them. Alternatively, deficits in value representation could undermine the decision to engage in effortful behavior, such that the cost associated with the action required to receive a reward seems prohibitively high when value is not represented precisely. Functional neuroimaging studies are needed to examine the neural factors contributing to this effort-value computation dysfunction; however, based upon the pre-clinical and human neuroimaging literature, there is reason to suspect that effort computation deficits are linked to abnormalities in the mesolimbic dopaminergic system and the ACC, and potentially the connectivity between these regions. The human schizophrenia findings are also consistent with data supporting the D2 over-expression animal model of schizophrenia, which provides evidence for intact hedonics in the context of impaired effortful behavior to obtain rewards. Further research is needed to explore the role of antipsychotic medications in unmedicated patients, as D2 antagonists have been found to reduce the extent to which rats are willing to work for rewards.

5.7 Conclusions and Future Directions

In the past decade, there have been important advances in the conceptualization of anhedonia in individuals with schizophrenia. These developments have at least in part stemmed from the application of frameworks and methods from the fields of affective science and affective neuroscience to study various aspects of reward processing and their association with clinical symptomatology. There is now compelling evidence that individuals with schizophrenia do not have a reduced capacity to experience pleasure when exposed to potentially rewarding activities. Instead, individuals with schizophrenia appear to display a behavioral deficit that manifests as a reduced frequency of engaging in pleasurable activities. The current chapter reviewed several aspects of reward processing that are disrupted in schizophrenia, and evaluated evidence suggesting that this behavioral component of

anhedonia is related to an impairment in translating reward information into motivated behavior. Aberrant cortical-striatal interactions may be associated with multiple aspects of reward processing that contribute to reductions in the frequency of pleasurable behavior in schizophrenia, including: (1) dopamine-mediated basal ganglia systems that support reinforcement learning and the ability to predict cues that lead to rewarding outcomes; (2) orbitofrontal cortex-driven deficits in generating, updating, and maintaining value representations; (3) aberrant effort-value computations, which may be mediated by disrupted anterior cingulate cortex and midbrain dopamine functioning; and (4) altered activation of the prefrontal cortex, which is important for generating exploratory behaviors in environments where reward outcomes are uncertain.

Although this mechanistic account provides clarity regarding the cognitive and neural basis of the behavioral component of anhedonia in schizophrenia, there are still several important issues left to be resolved in this area. First, there is some inconsistency among findings within the different areas of reward processing. For example, there are discrepant results among neuroimaging studies examining the integrity of positive prediction error signaling and reward anticipation. A meta-analysis would help clarify whether the neural processes underlying these functions are abnormal, and potentially identify mediators of prediction error signaling that could explain discrepancies in the literature (e.g., individual differences in anhedonia/avolition, first vs. second generation antipsychotics, D2 blockade, general cognitive impairments). There is also a need for a meta-analysis examining neuroimaging studies where subjects are exposed to pleasant stimuli in the laboratory and asked to indicate how positive they feel in response to those stimuli. Results from imaging studies to date do seem to be consistent with the self-report literature indicating intact hedonic responses, but a meta-analysis is needed to support this interpretation. Anticevic et al. [23] provided meta-analytic evidence that imaging contrast methods are a critical factor in determining whether patient neural response is intact for unpleasant stimuli, and it would be necessary to consider these variables for pleasant stimuli as well.

Several factors may contribute to inconsistent findings across neuroimaging studies examining the neural signature of prediction errors and self-reported positive emotional experiences. One factor is clearly clinical heterogeneity. Individual differences in the severity of negative symptoms have been linked to reward processing in many studies. Given that not all studies recruit samples that are enriched for negative symptoms, and only a subset of patients do in fact evidence clinically significant elevations in negative symptoms, it is possible that clinical heterogeneity hinders accurate comparisons across studies. Second, many of the tasks described in this chapter have only been explored at the behavioral level, leaving much in the way of inference to make conclusions regarding the neural circuits involved with behavioral task performance. This is particularly true of studies examining different components of value representation, effort-cost computation, and uncertainty-driven exploration. It will be critically important to conduct neuroimaging studies with some of the tasks reviewed in these sections of this book chapter to determine whether the neurobiological processes inferred to play a role in behavioral

performance are in fact correct. Third, some studies suggest differential effects of first and second generation antipsychotics on reward processing, and it may be the case that D2 antagonists explain inconsistency among findings. Few studies have systematically examined the role of antipsychotics in reinforcement learning, and there is a need to randomly assign patients to antipsychotics to disentangle the influences of patient characteristics and medication-specific effects on reward processing.

Another important point of consideration is that few studies have examined more than one aspect of reward processing in the same sample, making it difficult to gage the extent to which these processes interact to contribute to reductions in pleasure-seeking behavior. There are several reasons to think that deficits in one process may contribute to abnormalities in another. For example, prediction error signaling and value representation may be critically linked – one would not expect patients with impaired prediction error signaling to be able to represent value precisely. Similarly, aberrant value representations may contribute to a number of other reward processing deficits, such as computing whether an action is worth the effort needed to obtain it, making the decision to exploit actions that have lead to prior rewards or to explore new actions, and learning to make rapid trial-by-trial adjustments in response to probabilistic feedback. Impairments in reinforcement learning and tracking uncertainty may also interact with several other reward processes. For example, decision-making in stationary environments is highly influenced by learning rate. Schizophrenia patients have consistently been found to have deficits in rapid learning, and these deficits may influence the extent to which they can update value representations and use them to exploit actions that will consistently yield reward. In non-stationary environments, where reward contingencies are not consistent, the ability to track uncertainty may be paramount in determining whether individuals engage in reward-seeking behavior. It is possible that deficits in value and uncertainty representations may have a combined influence on decision-making and behavior in non-stationary environments, limiting the extent to which individuals learn about and explore alternative actions that lead to reward. Finally, effort-cost computations may interact with other processes, such as exploration/exploitation. In some circumstances, such as those occurring in the exploration-exploitation dilemma, there can be "costs" associated with switching from one behavior to another. If patients have difficulty in judging these costs and whether the effort needed to switch to a new action is worth it, they may be less likely to try out new actions (i.e., explore) that can yield more frequent or more maximal rewards. Thus, it is clear that individuals with schizophrenia have deficits in multiple aspects of reward processing, and these may have important interactions that influence how reward information is integrated and translated into behaviors aimed at obtaining rewards.

Although it is clear that various reward processes have important interactions, there may also be some common underlying mechanisms for these deficits. Abnormalities in cortical and subcortical dopamine may be associated with impairments in all of the aspects of reward processing described in this chapter and impede the translation of reward information into pleasure-seeking behavior. Given the role of DA in influencing different components of reward processing, and that the majority of schizophrenia patients are treated with D2 antagonists, it will be

important to systematically examine the role of antipsychotics in each of the reward processing domains reviewed in this chapter. This can be done by examining medicated and unmedicated patients, comparing first and second generation antipsychotics, and evaluating individuals at high-risk for psychosis who have not been exposed to antipsychotics. PET studies may also be very helpful in isolating the role of dopamine in different components of reward processing. Furthermore, new animal models of schizophrenia, such as the D2 post-synaptic over-expression model of negative symptoms, have significant potential to clarify the role of dopamine in different aspects of reward processing. Translating these models directly into human studies of medicated and unmedicated patients is an important next step. Additionally, the reward processes described here also place high demands on cognitive control circuits. It is possible that the reward-based deficits described here represent another means by which cognitive control impairments are manifested in the affective domain. Cognitive control circuits may also be influenced by dopaminergic function, and it will be important to explore interactions between cortical and subcortical structures using newer functional imaging connectivity methods.

It is also important to consider that the multiple reward-related processes described in the current chapter only capture some of the mechanisms that may contribute to reduced pleasure-seeking behavior. For example, Kring, Gard, and colleagues [25, 28] have proposed that while schizophrenia patients do not have deficits in experiencing pleasure in-the-moment (i.e., consumatory pleasure), they do have reductions in "anticipatory" pleasure (i.e., a between-groups difference where patients expect less pleasure in the future than healthy controls). Deficits in "affective forecasting" may underlie these impairments in anticipatory pleasure and contribute to reduced pleasure-seeking behavior. For example several cognitive and psychological mechanisms contribute to the anticipation of future pleasure, including retrieving prior pleasurable experiences from episodic memory and generating mental representations of future events that include relevant contextual details and essential features of potential situations [133]. Generating mental representations of future pleasurable events is thought to rely heavily on the ventromedial prefrontal cortex and the medial temporal lobe, as well as midbrain dopamine neurons in the ventral striatum and nucleus accumbens [133]. Abnormalities in cortical-striatal circuitry may therefore contribute to reduced anticipatory pleasure and reduced pleasure-seeking behavior. Extending this anticipatory pleasure deficit model, we recently proposed that patients not only have reductions in anticipating future pleasure, but also remembering past pleasure [18]. Specifically, we proposed that working memory and long-term memory may be critical in determining the extent to which individuals "over-estimate" future and past pleasure, respectively [18]. There is consistent evidence that healthy individuals typically expect more pleasure in the future and remember more pleasure from the past compared to what they actually experience in the moment [134]. Individuals with schizophrenia do not display this normative tendency for over-estimating past and future positive emotions [28, 135] Over-estimation of pleasure in the future and past is adaptive, as it promotes the initiation of behaviors aimed at obtaining rewards. Based upon the affective science literature, one might expect that the within-subjects comparison of

future or past relative to current positive emotion is more critical than the overall mean level of subjective future or past positive emotion alone in determining motivation. As suggested in Strauss and Gold [18], cognitive impairments may influence whether patients display the normative tendency to over-estimate future and past relative to current positive emotion. Additionally, while individuals with schizophrenia do not appear to have a reduced capacity for pleasure, there is consistent evidence that they have elevations in negative emotionality that are associated with poor functional outcome and elevated positive and negative symptoms. There has been recent interest in the link between negative emotion and anhedonia, and it has been found that increases in state and trait negative emotion are linked to difficulty down-regulating the neural response to unpleasant stimuli when patients attempt to apply various emotion regulation strategies (e.g., reappraisal) [137]. Much like the components of reward processing reviewed here, these abnormalities in regulating negative emotion appear to involve impairments in prefrontal cognitive control circuitry [136]. Abnormalities in down-regulating negative emotion may result in a chronically elevated negative emotional state, and contribute to anhedonia by limiting the extent to which individuals seek out rewarding activities [137, 138]. Finally, factor-analytic studies typically indicate that anhedonia and avolition travel together [130, 139, 140], potentially signifying overlapping neural substrates as well as cognitive and psychological processes. Reduced goal-directed and pleasure-seeking behavior may in fact go hand-in hand; however, it would be important to determine whether they do indeed have shared or separable mechanisms as these may necessitate different treatments targets.

Finally, deficits in seeking out pleasurable activities may only be one aspect of anhedonia. For example, as proposed by Strauss and Gold [18], Grant et al. [141], and Beck et al. [142], anhedonia in schizophrenia may also reflect a psychological abnormality, which can best be described as “low pleasure beliefs”. For example, many individuals with schizophrenia appear to have the belief that they generally do not experience pleasure or that specific situations are unlikely to be enjoyable. These psychological processes may be critically involved with reductions in pleasure-seeking behavior. For example, if a patient believes that certain activities are not enjoyable (social interactions), then they are unlikely to engage in them regardless of whether their capacity for pleasure is intact. These low-pleasure beliefs may be associated with impairments in reward processing. For example, a patient who is impaired at learning from and integrating positive feedback may not be able to update value representations needed to change beliefs that certain types of experiences are not enjoyable (e.g., social interactions), despite having a normal hedonic reaction when exposed to a potentially pleasurable event. Similarly, patients who have reduced uncertainty-driven exploration may not evaluate a large enough number of response alternatives to determine whether certain experiences could be pleasurable, which would limit their exposure to experiences that could provide evidence contrary to the belief that certain activities are not enjoyable. Thus, there may be several processes that contribute to reductions in pleasure-seeking behavior in schizophrenia, as well as multiple components of anhedonia in addition to the behavioral deficit that was the focus of this chapter.

5.8 Treatment Implications

Current psychosocial and pharmacological treatments for negative symptoms of schizophrenia have been minimally effective, especially in terms of improving anhedonia and avolition (see [143]). This is likely due in part to the fact that the cognitive, psychological, and neural mechanisms involved with these symptoms have not been well-delineated. The literature on reward in schizophrenia has provided important advances in this regard, lending some hints for how novel behavioral intervention strategies could be developed or adapted to enhance reward-seeking behavior in schizophrenia. For example, it is clear that patients have deficits in generating, updating, and maintaining mental representations of value. To account for these impairments, it may be necessary to incorporate external cues and reinforcers into standard behavioral therapy approaches. A new Cognitive Behavioral Therapy approach developed by Grant, Beck, [144] and colleagues at the University of Pennsylvania has incorporated some of these procedures. For example, this program has therapists adopt an engaging style (e.g., direct and crisp speaking, energetic, commanding, and confident) and aims to reduce patient lapses in engagement by having them engage in activities during the therapy session (e.g., playing cards, listening to music), as well as by using frequent and intense reinforcement of goal-directed behavior (e.g., verbal praise, tokens, stickers). Interestingly, in an extended randomized psychosocial treatment trial, Grant et al. [144] found evidence that this CBT approach significantly improved avolition more so than treatment as usual. These results are very promising, as few interventions have been found to improve negative symptoms. There was no effect on anhedonia in this trial, suggesting that additional methods may be needed to enhance pleasure-seeking behavior. Over the past decade, there have been significant advances in using mobile technology (e.g., smart phones) in the context of psychosocial treatment and these may be useful in delivering cues, reinforcers, and reminders that can enhance behavioral activation. For example, clinicians could set weekly goals with their patients for engaging in rewarding activities and have apps deliver prompts for the patient to initiate these activities and report their feelings while completing them. The "data" resulting from these reports can then be used in the therapy sessions following that week to review how successful the patient was in fulfilling their goals, as well as the diversity of pleasurable activities experienced and the strength of experiences. The mobile technology approach may therefore enable therapists to systematically shape a patient's frequency of engaging in pleasurable activities, as well as providing a means to prompt patients to think of future experiences and remember recent past pleasurable experiences. With frequent reviewing of such data, and modifying the behavioral activation program to continuously increase the frequency of pleasurable experiences, it may be possible to shift patients' beliefs that little is enjoyable and that some activities are not worth the effort.

Acknowledgments Work on this chapter was supported in part by funding from NIMH to Dr. Strauss: K23MH0925.

References

1. Kraepelin E. Dementia praecox and paraphrenia (Bradley RM, trans). Huntington, NY: Robert E Krieger Publishing Co; [1917]; 1971.
2. Bleuler E. Dementia praecox or the group of schizophrenias (Zinkin J, trans). New York: International Universities Press; 1950 [1911].
3. Rado S. Psychoanalysis of behavior: the collected papers of Sandor Rado, vol. 2. New York: Grune and Stratton; 1962.
4. Meehl PE. Schizotaxia, schizotypy, schizophrenia. Am Psychol. 1962;17:827–38.
5. Kwapil TR. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. J Abnorm Psychol. 1998;107:558–65.
6. Herbener ES, Harrow M, Hill SK. Change in the relationship between anhedonia and functional deficits over a 20-year period in individuals with schizophrenia. Schizophr Res. 2005;75:97–105.
7. Strauss GP, Harrow M, Grossman LS, et al. Periods of recovery in deficit syndrome schizophrenia: a 20-year multi-follow-up longitudinal study. Schizophr Bull. 2010;36:788–99.
8. Kring AM, Neale JM. Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? J Abnorm Psychol. 1996;105:249–57.
9. Kring AM, Kerr SL, Smith DA, Neale JM. Flat affect in schizophrenia does not reflect diminished subjective experience of emotion. J Abnorm Psychol. 1993;102:507–17.
10. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. Schizophr Bull. 2008;34:819.
11. Curtis CE, Lebow B, Lake DS, Katsanis J, Iacono WG. Acoustic startle reflex in schizophrenia patients and their first-degree relatives: evidence of normal emotional modulation. Psychophysiology. 1999;36:469–75.
12. Lee E, Kim JJ, Namkoong K, et al. Aberrantly flattened responsivity to emotional pictures in paranoid schizophrenia. Psychiatry Res. 2006;143:135–45.
13. Quirk SW, Strauss ME, Sloan DM. Emotional response as a function of symptoms in schizophrenia. Schizophr Res. 1998;32:31–9.
14. Strauss GP, Allen DN, Ross SA, Duke LA, Schwartz J. Olfactory hedonic judgment in patients with deficit syndrome schizophrenia. Schizophr Bull. 2010;36(4):860.
15. Kamath V, Moberg PJ, Kohler CG, Gur RE, Turetsky BI. Odor hedonic capacity and anhedonia in schizophrenia and unaffected first-degree relatives of schizophrenia patients. Schizophr Bull. 2011;187(1–2):30–5.
16. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36:143–50.
17. Llerena K, Strauss GP, Cohen AS. Looking at the other side of the coin: a meta-analysis of self-reported emotional arousal in people with schizophrenia. Schizophr Res. 2012;142:65–70.
18. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169:364–73.
19. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter Jr WT. A separate disease within the syndrome of schizophrenia. Arch Gen Psychiatry. 2001;58:165–71.
20. Strauss GP, Herbener ES. Patterns of emotional experience in schizophrenia: differences in emotional response to visual stimuli are associated with clinical presentation and functional outcome. Schizophr Res. 2011;128:117–23.
21. Gur RE, Loughead J, Kohler CG, Elliot MA, Lesko K, et al. Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. Arch Gen Psychiatry. 2007;64(12):1356–66.
22. Ursu S, Kring AM, Gard MG, Minzenberg MJ, Yoon JH, et al. Prefrontal cortical deficits and impaired cognition-emotion interactions in schizophrenia. Am J Psychiatry. 2011;168(3):276–85.

23. Anticevic A, van Snellenberg J, Cohen R, Repovs G, Dowd E, Barch D. Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies. Schizophr Bull. 2012;38(3):608–21.
24. Taylor SF, Kang J, Brege I, Tso I, Hosanagar A, Johnson T. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. Biol Psychiatry. 2012;71:136–45.
25. Kring AM, Elis O. Emotion deficits in people with schizophrenia. Annu Rev Clin Psychol. 2012;9:409–33.
26. Myin-Germeys I, Delespaul PAEG, de Vries MW. Schizophrenic patients are more emotionally active than is assumed based on their behavior. Schizophr Bull. 2000;268:47–85.
27. Myin-Germeys I, Nicolson NA, Delespaul PA. The context of delusional experiences in the daily life of patients with schizophrenia. Psychol Med. 2001;31:489–98.
28. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:253–60.
29. Oorschot M, Lataster T, Thewissen V, Lardinois M, Wichers M, van Os J, et al. Emotional experience in negative symptoms of schizophrenia—no evidence for a generalized hedonic deficit. Schizophr Bull. 2013;39:217–25.
30. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32(2):259–73.
31. Andreasen NC. The scale for assessment of negative symptoms (SANS). Iowa City: University Press; 1983.
32. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, et al. The Brief Negative Symptom Scale: psychometric properties. Schizophr Bull. 2011;37(2):300–5.
33. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry. 2013;170:165–72.
34. Barch DM, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr Bull. 2010;36:919–34.
35. Gold JM, Waltz JM, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull. 2008;34:835–47.
36. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997;275:1593–9.
37. Waltz JA, Gold JM. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. Schizophr Res. 2007;93:296–303.
38. Waltz JA, Frank MJ, Wiecki TV, Gold JM. Altered probabilistic learning and response biases in schizophrenia: behavioral evidence and neurocomputational modeling. Neuropsychology. 2011;25:86–97.
39. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, et al. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. Neuropsychopharmacology. 2010;35:2427–39.
40. Waltz JA, Kasanova Z, Ross TJ, Salmeron BJ, McMahon RP, et al. The roles of reward, default, and executive control networks in set-shifting impairments in schizophrenia. PLoS One. 2013;8(2):e57257. doi:10.1371/journal.pone.0057257.
41. Green MF, Kern RS, Williams O, McGurk S, Kee K. Procedural learning in schizophrenia: evidence from serial reaction time. Cognit Neuropsychiatry. 1997;2:123–34.
42. Goldberg TE, Saint-Cyr JA, Weinberger DR. Assessment of procedural learning and problem solving in schizophrenic patients by Tower of Hanoi type tasks. J Neuropsychiatry Clin Neurosci. 1990;2:165–73.
43. Foerde K, Poldrack RA, Khan BJ, et al. Selective corticostriatal dysfunction in schizophrenia: examination of motor and cognitive skill learning. Neuropsychology. 2008;22:100–9.
44. Kumari V, Gray JA, Honey GD, et al. Procedural learning in schizophrenia: a functional magnetic resonance imaging investigation. Schizophr Res. 2002;57:97–107.
45. Gold JM, Hahn B, Strauss GP, Waltz JA. Turning it upside down: areas of preserved cognitive function in schizophrenia. Neuropsychol Rev. 2009;19:294–311.

46. Keri S, Nagy O, Kelemen O, Myers CE, Gluck MA. Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia. Schizophr Res. 2005;77:321–8.
47. Scherer H, Stip E, Paquet F, Bedard MA. Mild procedural learning disturbances in neuroleptic-naive patients with schizophrenia. J Neuropsychiatry Clin Neurosci. 2003;15:58–63.
48. Reiss JP, Campbell DW, Leslie WD, Paulus MP, Ryner LN, Polimeni JO, et al. Deficit in schizophrenia to recruit the striatum in implicit learning: a functional magnetic resonance imaging investigation. Schizophr Res. 2006;87:127–37.
49. Weickert TW, Goldberg TE, Callicott JH, Chen Q, Apud JA, Das S, et al. Neural correlates of probabilistic category learning in patients with schizophrenia. J Neurosci. 2009;29:1244–54.
50. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. Biol Psychiatry. 2007;62:756–64.
51. Strauss GP, Frank MF, Waltz JA, Kasanova Z, Herbener ES, Gold JM. Deficits in positive reinforcement learning and uncertainty-driven exploration are associated with distinct aspects of negative symptoms in schizophrenia. Biol Psychiatry. 2011;69:424–31.
52. Gold JM, Waltz JA, Matveeva TM, Kasanova Z, Strauss GP, Herbener ES, Collins AGE, Frank MJ. Negative symptoms in schizophrenia result from a failure to represent the expected value of rewards: behavioral and computational modeling evidence. Arch Gen Psychiatry. 2012;69:129–38.
53. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B. Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. Psychopharmacology (Berl). 2009;206:121–32.
54. Waltz JA, Schweitzer JB, Gold JM, et al. Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. Neuropsychopharmacology. 2009;34:1567–77.
55. Schlagenhauf F, Sterzer P, Schmack K, Ballmaier M, Rapp M, et al. Reward feedback alterations in unmedicated schizophrenia patients: relevance for delusions. Biol Psychiatry. 2009;65:1032–9.
56. Murray GK, Corlett PR, Clark L, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry. 2008;13:267–76.
57. Koch K, Schachtzabel C, Wagner G, et al. Altered activation in association with reward-related trial-and-error learning in patients with schizophrenia. Neuroimage. 2009;50:223–32.
58. Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, et al. Expected value and prediction error abnormalities in depression and schizophrenia. Brain. 2011;134:1751–64.
59. Corlett PR, Murray GK, Honey GD, Aitken MRF, Shanks DR, Robbins TW, et al. Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. Brain. 2007;130:2387–400.
60. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. PLoS One. 2012;7(5):e35622.
61. Simon JJ, Biller A, Walther S, Roesch-Ely D, Stippich C, et al. Neural correlates of reward processing in schizophrenia-relationship to apathy and depression. Schizophr Res. 2009;18:154–61.
62. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage. 2006;29:409–16.
63. Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wüstenberg T, et al. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology (Berl). 2006;187:222–8.
64. Nielsen MO, Rostrup E, Wulff S, Bak N, Lublin H, Kapur S, Glenthøj B. Alterations of the brain reward system in antipsychotic naive schizophrenia patients. Biol Psychiatry. 2012;71:898–905.
65. Wallis JD. Orbitofrontal cortex and its contribution to decision-making. Annu Rev Neurosci. 2007;30:31–56.
66. Elliott R, McKenna PJ, Robbins TW, Sahakian BJ. Neuropsychological evidence for frontostriatal dysfunction in schizophrenia. Psychol Med. 1995;25:619–30. 131.

67. Tyson PJ, Laws KR, Roberts KH, Mortimer AM. Stability of set-shifting and planning abilities in patients with schizophrenia. Psychiatry Res. 2004;129:229–39.
68. Ceaser AE, Goldberg TE, Egan MF, McMahon RP, Weinberger DR, Gold JM. Set-shifting ability and schizophrenia: a marker of clinical illness or an intermediate phenotype? Biol Psychiatry. 2008;64:782–8.
69. Oades RD. Stimulus dimension shifts in patients with schizophrenia, with and without paranoid hallucinatory symptoms, or obsessive compulsive disorder: strategies, blocking and monoamine status. Behav Brain Res. 1997;88:115–31.
70. Pantelis C, Barber FZ, Barnes TR, Nelson HE, Owen AM, Robbins TW. Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage. Schizophr Res. 1999;37:251–70.
71. Shurman B, Horan WP, Nuechterlein KH. Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. Schizophr Res. 2005;72:215–24.
72. Sevy S, Burdick KE, Visweswaraiah H, et al. Iowa gambling task in schizophrenia: a review and new data in patients with schizophrenia and co-occurring cannabis use disorders. Schizophr Res. 2007;92:74–84.
73. Lee Y, Kim YT, Seo E, et al. Dissociation of emotional decision-making from cognitive decision-making in chronic schizophrenia. Psychiatry Res. 2007;152:113–20.
74. Martino DJ, Bucay D, Butman JT, Allegri RF. Neuropsychological frontal impairments and negative symptoms in schizophrenia. Psychiatry Res. 2007;152:121–8.
75. KesterHM SS, Yechiam E, Burdick KE, Cervellione KL, Kumra S. Decision-making impairments in adolescents with early-onset schizophrenia. Schizophr Res. 2006;85:113–23.
76. Premkumar P, Fannon D, Kuipers E, Simmons A, Frangou S, Kumari V. Emotional decision-making and its dissociable components in schizophrenia and schizoaffective disorder: a behavioural and MRI investigation. Neuropsychologia. 2008;46:2002–12.
77. Yip SW, Sacco KA, George TP, Potenza MN. Risk/reward decision-making in schizophrenia: a preliminary examination of the influence of tobacco smoking and relationship to Wisconsin Card Sorting Task performance. Schizophr Res. 2009;110:156–64.
78. Kim YT, Lee KU, Lee SJ. Deficit in decision-making in chronic, stable schizophrenia: from a reward and punishment perspective. Psychiatry Investig. 2009;6:26–33.
79. Evans CE, Bowman CH, Turnbull OH. Subjective awareness on the Iowa Gambling Task: the key role of emotional experience in schizophrenia. J Clin Exp Neuropsychol. 2005;27:656–64.
80. Rodriguez-Sanchez JM, Crespo-Facorro B, Perez-Iglesias R, et al. Prefrontal cognitive functions in stabilized first-episode patients with schizophrenia spectrum disorders: a dissociation between dorsolateral and orbitofrontal functioning. Schizophr Res. 2005;77:279–88.
81. Wilder KE, Weinberger DR, Goldberg TE. Operant conditioning and the orbitofrontal cortex in schizophrenic patients: unexpected evidence for intact functioning. Schizophr Res. 1998;30:169–74.
82. Li X, Lu Z, D'Argembeau A, Ng M, Bechara A. The Iowa Gambling Task in fMRI images. Hum Brain Mapp. 2009;31:410–23.
83. Nakamura M, Nestor PG, Levitt JJ, Cohen AS, Kawashima T, Shenton ME, McCarley RW. Orbitofrontal volume deficit in schizophrenia and thought disorder. Brain. 2008;131(Pt 1):180–95.
84. Fellows LK, Farah MJ. The role of ventromedial prefrontal cortex in decision making: judgment under uncertainty or judgment per se? Cereb Cortex. 2007;17:2669–74.
85. Strauss GP, Robinson BM, Waltz JA, Frank MJ, Kasanova Z, Herbener ES, et al. Patients with schizophrenia demonstrate inconsistent preference judgments for affective and nonaffective stimuli. Schizophr Bull. 2011;37:1295–304.
86. Bornovalova MA, Daughters SB, Hernandez GD, Richards JB, Lejuez CW. Differences in impulsivity and risk-taking propensity between primary users of crack cocaine and primary users of heroin in a residential substance-use program. Exp Clin Psychopharmacol. 2005;13:311–8.
87. Kirby K, Petry N. Heroin and cocaine abusers of higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction. 2004;99:461–71.

88. Heerey EA, Matveeva TM, Gold JM. Imagining the future: degraded representations of future rewards and events in schizophrenia. J Abnorm Psychol. 2011;120(2):483–9.
89. Heerey EA, Robinson BM, McMahon RP, Gold JM. Delay discounting in schizophrenia. Neuropsychiatry. 2007;12(3):213–21.
90. Avsar KB, Weller RE, Cox JE, Reid MA, White DM, Lahti AC. An fMRI investigation of delay discounting in patients with schizophrenia. Brain Behav. 2013;3:384–401.
91. Gard DE, Cooper S, Fisher M, Genevsky A, Mikels JA, Vinogradov S. Evidence for an emotion maintenance deficit in schizophrenia. Psychiatry Res. 2011;187(1–2):24–9.
92. Kring AM, Germans Gard M, Gard DE. Emotion deficits in schizophrenia: timing matters. J Abnorm Psychol. 2011;120(1):79–87.
93. Heerey EA, Gold JM. Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. J Abnorm Psychol. 2007;116:268–78.
94. Cohen JD, McClure SM, Yu AJ. Should I stay or should I go? How the human brain manages the trade-off between exploitation and exploration. Philos Trans R Soc Lond B Biol Sci. 2007;362:933–42.
95. Gittins JC, Jones DM. A dynamic allocation index for the sequential design of experiments. In: Gans J, editor. Progress in statistics. Amsterdam: North-Holland; 1974. p. 241–66.
96. Graybiel AM. Habits, rituals, and the evaluative brain. Annu Rev Neurosci. 2008;31:359–87.
97. Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ. Cortical substrates for exploratory decisions in humans. Nature. 2006;441:876–9.
98. Sutton RS, Barto AG. Reinforcement learning: an introduction. Cambridge, MA: MIT Press; 1998.
99. Badre D, Doll BB, Long NM, Frank MJ. Rostrolateral prefrontal cortex and individual differences in uncertainty-driven exploration. Neuron. 2012;73:595–607.
100. Frank MJ, Doll BB, Oas-Terpstra J, Moreno F. Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. Nat Neurosci. 2009;12:1062–8.
101. Yu A, Dayan P. Uncertainty, neuromodulation and attention. Neuron. 2005;46:681–92.
102. Usher M, Cohen JD, Rajkowski J, Aston-Jones G. The role of the locus coeruleus in the regulation of cognitive performance. Science. 1999;283:549–54.
103. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus–norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci. 2005;28:403–50.
104. Moustafa AA, Cohen MX, Sherman SJ, Frank MJ. A role for dopamine in temporal decision making and reward maximization in parkinsonism. J Neurosci. 2008;28:12294–304.
105. Kasanova Z, Waltz JA, Strauss GP, Frank MJ, Gold JM. Optimizing vs. matching: response strategy in a probabilistic learning task is associated with negative symptoms of schizophrenia. Schizophr Res. 2011;127:215–22.
106. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, et al. Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci. 2002;22:3708–19.
107. Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry. 2008;13:67–76.
108. Dolls ET, Loh M, Deco G, Winterer G. Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. Nat Rev Neurosci. 2008;9:696–709.
109. Huys QJ, Dayan P. A Bayesian formulation of behavioral control. Cognition. 2009;113:314–28.
110. Fervaha G, Foussias G, Agid O, Remington G. Neural substrates underlying effort computation in schizophrenia. Neurosci Biobehav Rev. 2013;37:2649–55.
111. Hodos W. Progressive ratio as a measure of reward strength. Science. 1961;134:943–4.
112. Salamone JD, Cousins MS, Bucher S. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. Behav Brain Res. 1994;65:221–9.
113. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. J Neurosci. 2011;31:16597–602.

114. Treadway MT, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Kessler RM, Zald DH. Dopaminergic mechanisms of individual differences in human effort-based decision-making. J Neurosci. 2012;32:6170–6.
115. Ward RD, Simpson EH, Richards VL, Deo G, Taylor K, Glendinning JI, et al. Dissociation of hedonic reaction to reward and incentive motivation in an animal model of the negative symptoms of schizophrenia. Neuropsychopharmacology. 2012;37:1699–707.
116. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part I: meta-analysis of dopamine active transporter (DAT) density. Schizophr Bull. 2013;39:22–32.
117. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F/(11)C]-DOPA PET studies. Schizophrenia Bull. 2013;39:33–42.
118. Walton ME, Bannerman DM, Rushworth MF. The role of rat medial frontal cortex in effort based decision making. J Neurosci. 2002;22:10996–1003.
119. Walton ME, et al. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J Neurosci. 2003;23:6475–9.
120. Walton ME, Groves J, Jennings KA, Croxson PL, Sharp T, Rushworth MF, Bannerman DM. Comparing the role of the anterior cingulate cortex and 6-hydroxydopamine nucleus accumbens lesions on operant effort-based decision making. Eur J Neurosci. 2009;29:1678–91.
121. Endepols H, Sommer S, Backes H, Wiedermann D, Graf R, Hauber W. Effort-based decision making in the rat: an [^{18}F]fluorodeoxyglucose micro positron emission tomography study. J Neurosci. 2010;30:9708–14.
122. Croxson PL, Walton ME, O'Reilly JX, Behrens TEJ, Rushworth MFS. Effort based cost-benefit valuation and the human brain. J Neurosci. 2009;29:4531–41.
123. Prévost C, Pessiglione M, Météreau E, Cléry-Melin ML, Dreher JC. Separate valuation subsystems for delay and effort decision costs. J Neurosci. 2010;30:14080–90.
124. Benes FM. Emerging principles of altered neural circuitry in schizophrenia. Brain Res Rev. 2000;31:251–69.
125. Barch DM, Braver TS, Sabb FW, Noll DC. The anterior cingulate cortex and response competition: evidence from an fMRI study of overt verb generation. J Cogn Neurosci. 2000;12:298–305.
126. Kerns JG, Cohen JD, MacDonald 3rd AW, et al. Decreased conflict- and error-related activity in the anterior cingulate cortex in subjects with schizophrenia. Am J Psychiatry. 2005;162:1833–9.
127. Hauber W, Sommer S. Prefrontostriatal circuitry regulates effort-related decision making. Cereb Cortex. 2009.
128. Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK, Frank MJ. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. Biol Psychiatry. 2013;74:130–6.
129. Strauss GP, Keller WR, Buchanan RW, Gold JM, Fischer BA, McMahon RP, Catalano LT, Culbreth AJ, Carpenter WT, Kirkpatrick B. Next-generation negative symptom assessment for clinical trials: validation of the Brief Negative Symptom Scale. Schizophr Res. 2012;142:88–92.
130. Strauss GP, Hong LE, Keller WR, Buchanan RW, Gold JM, Fischer BA, McMahon RP, Catalano LT, Culbreth AJ, Carpenter WT, Kirkpatrick B. Factor structure of the Brief Negative Symptom Scale. Schizophr Res. 2012;142:96–8.
131. Fervaha G, Graff-Gurrero A, Zakzanis KK, Foussias G, Agid O, Remington G. Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making. J Psychiatr Res. 2013;47:1590–6.
132. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. PLoS One. 2009;4:e6598.
133. Gilbert DT, Wilson TD. Prospection: experiencing the future. Science. 2007;317:1351–4.
134. Robinson MD, Clore GL. Belief and feeling: evidence for an accessibility model of emotional self-report. Psychol Bull. 2002;128:934–60.

135. Ben-Zeev D, McHugo G, Xie H, Dobbins K, Young M. Comparing retrospective reports to real-time/real-place mobile assessments in individuals with schizophrenia and a nonclinical comparison group. Schizophr Bull. 2012;38(3):396–404.
136. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 2002;14:1215–29.
137. Strauss GP, Kappenman ES, Culbreth AJ, Catalano LT, Lee BG, Gold JM. Emotion regulation abnormalities in schizophrenia: cognitive change strategies fail to decrease the neural response to unpleasant stimuli. Schizophr Bull. 2013;39:872–83.
138. Horan WP, Hajcak G, Wynn JK, Green MF. Impaired emotion regulation in schizophrenia: evidence from event related potentials. Psychol Med. 2013;43:2377–91.
139. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr Bull. 2006;32:238e45.
140. Horan WP, Kring AM, Gur RE, Reise SP, Blanchard JJ. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr Res. 2011;132:140–5.
141. Grant PM, Beck AT. Defeatist beliefs as a mediator of cognitive impairment, negative symptoms, and functioning in schizophrenia. Schizophr Bull. 2009;35:798–806.
142. Beck AT, Rector NA, Stolar NM, Grant PM. Schizophrenia: cognitive theory, research and therapy. New York: Guilford Press; 2009.
143. Kirkpatrick B, Fenton WS, Carpenter Jr WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006;32(2):214–9.
144. Grant PM, Huh GA, Perivoliotis D, Stolar NM, Beck AT. Randomized trial to evaluate the efficacy of cognitive therapy for low-functioning patients with schizophrenia. Arch Gen Psychiatry. 2012;69(2):121–7.

Part II
Anhedonia in Mood and Personality Disorders

Chapter 6
Neural Correlates of Anhedonia as a Trait Marker for Depression

Ciara McCabe

Abstract The classification of depression is well established in major diagnostic systems with the symptom of anhedonia defined as the loss of interest and pleasure in normally rewarding experiences. Anhedonia suggests abnormalities in neural reward mechanisms. Consistent with this, functional imaging studies of depressed patients have shown abnormalities in the neural circuitry that supports reward, which also correlates with measures on anhedonia questionnaires. Also it has been suggested that the neurobiological mechanisms underlying anhedonia could represent an endophenotype of depression which may manifest in behavioural and neural outcome changes outside acute depressive episodes. While anhedonic symptoms usually remit as depression improves it is possible that abnormalities in the neural processes underpinning reward could persist and represent vulnerability factors for future episodes of illness. It is intriguing to consider that understanding the neurobiology of reward might allow us to detect differences in reward processing in other "at risk" groups, those before the onset of a depressive episode. Taken together studies such as these might then be useful in teasing apart state from trait markers at the neural level. Early identification of risk markers for depression could then guide both early intervention and treatment strategies.

Keywords Anhedonia • Depression • Endophenotype • Trait • State • Reward • Brain • Antidepressants • Dopamine • Antipsychotics

C. McCabe (✉)
School of Psychology and Clinical Language Sciences, University of Reading, Reading RG6 6AL, UK
e-mail: C.McCabe@Reading.ac.uk; ciara.mccabe@psych.ox.ac.uk

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_6,

Abbreviations

ACC	Anterior cingulate cortex
AMPT	Amphetamine
DA	Dopamine
DSM	Diagnostic Statistical Manual
FH (+)	Family History Positive
ICD	International Statistical Classification of Diseases
MDD	Major Depressive Disorder
NAcc	Nucleus Accumbens
rACC	Rostral anterior cingulate cortex
RC	Retrosplenial cortex
rMDD	Remitted Major Depressive Disorder
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective Serotonin reuptake inhibitor
SVC	Small volume Correction
vmPFC	Ventromedial prefrontal cortex
VS	Ventral striatum
WHO	World Health Organisation

6.1 Introduction

Major depression is one of the world's most disabling mental disorders and it is predicted that by 2020 it will be the second most disabling medical condition after ischaemic heart disease [1]. Anhedonia, or loss of interest and pleasure in activities customarily enjoyed, is a key diagnostic criterion for depressive disorder in both major psychiatric diagnostic systems the Diagnostic Statistical Manual (DSM) and the International Statistical Classification of Diseases (ICD). A recent longitudinal study has shown how the symptom of anhedonia is related to increased risk for death or disability in an older population in comparison to dysphoria [2]. Importantly the authors demonstrate that clinicians should not overlook anhedonic symptomology just because dysphoria is non-existent. Unfortunately anhedonia is one of the most treatment resistant aspects of depression [3] which is undoubtedly related to our lack of understanding of the aetiology and neurobiology underpinning its symptomology. However the presence of anhedonia in depressed patients could have important implications for understanding the pathophysiology as it is suggestive of changes in the neurobiological mechanisms involved in motivation and reward [4].

The aim of this chapter is to understand what role changes in the neural circuitry of reward play in the pathophysiology of clinical depression and how we might use this information to discover neural biomarkers for depression. Thinking about biomarker discovery is of great value as it could spearhead the development of new treatments, given that the current standard pharmacological and psychological treatments are so lacking, but also and perhaps more importantly biomarker discovery might allow preventative interventions for depression.

6.2 Anhedonia in MDD

Anhedonia is usually regarded as a symptom of acute depression which resolves with clinical recovery. However, anhedonia also has some trait characteristics, and has been suggested as a potential endophenotypic marker of major depression [5]. However meeting all the criteria for an endophenotype for depression is no easy feat. The criteria are described as (1) associated with illness in the population (2) heritable (3) state-independent (manifests in an individual whether or not illness is active) (4) within families, endophenotype and illness cosegregate and finally (5) an endophenotype is identified in probands and found in unaffected relatives at a higher rate than in the general population, as described by [6].

Evidence for anhedonia as a possible endophenotype is supported by epidemiological studies showing that the presence of anhedonic features is a strong predictor of the onset of major depression over the following year [7]. Authors have long argued that anhedonia is a trait marker for psychiatric disorders as reviewed by Loas and Pierson [8] who also put forward a model of an "anhedonic constitution" which is a vulnerability to depression similar to that reported to be highly heritable in schizophrenia studies. Loas [9] suggests investigating with similar family studies, widely used in schizophrenia research, the effects of trait anhedonia on depression development. Studies since have shown that in a group of patients with chronic depression followed for a year, anhedonic symptoms remained fairly constant despite a substantial remission in severity of overall depression [10]. In addition, in the same patients, anhedonia scores correlated with the presence of depression in first degree relatives suggesting a genetic link between anhedonia and the risk of depression [10]. Moreover studies investigating anhedonia symptomology in non-clinical samples have found reduced reward processing capacity that correlated with increased scores on anhedonia measures [11, 12]. Studies examining the behavioural response to reward have also reliably shown deficits in those suffering from depression. For example when using a memory task rewarded by money Henriques et al. [13] found that compared to controls depressed individuals did not alter their pattern of responding under the reward condition but did in punishment, suggesting decreased motivation in the depressed group. Similarly McFarland and Klein [14] found that currently depressed individuals had decreased response to anticipated reward but no difference in non-reward or punishment processing. Whereas Pizaggalli et al. [15] found that MDD is characterized by an impaired tendency to modulate behavior as a function of prior reinforcements and that this correlated with anhedonia scores.

6.3 Neural Correlates of Anhedonia in MDD

Anhedonia, defined as a lack of interest and pleasure in life's usually rewarding experiences suggests deficits in the processing of rewarding information. The animal literature has well defined the neurobiology underpinning the reward system [16–18]. Furthermore, the advancements in neuroimaging and the identification of

the neural correlates of reward processing in the human brain has allowed the non-invasive scrutiny of neural signals related to reward function. For example studies examining monetary reward [19] pleasurable responses to music [20] and the viewing of pleasant pictures [21] have all been associated with increased neural activity within the ventral striatum and ventromedial prefrontal cortex (vmPFC). This is consistent with studies in animals indicating that dopaminergic activity in the ventral striatum is important in mediating positive reinforcing effects of rewards such as food and sex and may play a key role in the incentive motivation and anticipation of these appetitive stimuli [22]. By contrast, the vmPFC appears to integrate sensory experiences from different modalities and contribute to the subjective experiences of reinforcing stimuli [23, 24]. Indeed reward processing can be further divided into subtypes such as, the "appetitive/wanting" type, the "consummatory/liking" type and the "learning (pavlovian/instrumental)" type. Research to date has shown that these aspects of reward processing partly dissociate brain region, yet are multi-layered and both conscious and unconscious, they also have been shown to activate at the same time, adding to the complexity of trying to understand these subtypes [25]. As pointed out by Berridge and Kringlebach [25] future research is needed to tease apart whether activity in a particular brain region belongs most to the liking, wanting or learning sub-components of reward so that we might begin to understand the larger detailed integrated reward network in the human brain. Therefore on face validity it is likely that the symptom of anhedonia which involves a lack of interest and pleasure might be related to hypoactivity in brain regions supporting the reward system and the mesolimbic dopamine pathways [26, 27].

Studies have begun to directly assess the processing of rewarding information in the brain in relation to the symptom of anhedonia in patients. For example in a non-clinical sample Harvey et al. [28] found that trait anhedonia was inversely related to anterior caudate volume, but positively related to ventromedial prefrontal cortex activity during the processing of positive information. The authors concluded that their findings may reflect a specific kind of vulnerability for the development of psychiatric affective disorders and suggest that trait anhedonia may be linked to a volumetric reduction in the basal ganglia and to a prefrontal functional abnormality during hedonic processing. Also examining anhedonia in a non-clinical sample Wacker and colleagues [29] found that anhedonia, but not other symptoms of depression or anxiety, was correlated with reduced nucleus accumbens (NAcc) responses to rewards (gains in a monetary incentive delay task), reduced NAcc volume, and increased resting delta current density (i.e., decreased resting activity) in the rostral anterior cingulate cortex (rACC), an area previously implicated in positive subjective experience. The authors concluded that these results help elucidate the neural basis of anhedonia and strengthen the argument for anhedonia as an endophenotype for depression. Using a task involving the reward response to the sight of pleasant pictures in depressed patients it's been shown that patients with high anhedonia scores, compared to controls, have decreased activation in medial frontal cortex, and increased activation in inferior frontal cortex, anterior cingulate, thalamus, putamen and insula [30]. The authors proposed that reduced activation in medial frontal cortex may underlie abnormal positive affect processing in patients

and that increases in neural activation in putamen and thalamus, previously found in transient sadness, and anterior cingulate could point to an involvement of these structures in anhedonia. Schaefer et al. [31] also examining depressed patients response to pleasant, this time social images, found regions of prefrontal, temporal, and parietal cortices, insula, basal ganglia, and the hippocampus hypoactive in patients and interestingly the hypoactivations were normalised with SNRI treatment. Similarly reduced ventral striatal responses have been reported in depressed patients during a positively valanced words task [32] while another study found that in response to happy stimuli, anhedonia, but not depression severity per se, was positively and negatively correlated with vmPFC and amygdala/ventral striatal activity, respectively, in depressed patients [33]. Whilst examining the brains response to monetary reward Knutson and colleagues [34] found an altered pattern of responses in the anterior cingulate cortex in depressed patients and Pizzagalli et al. [35] found, also using a monetary reward task, reduced response to reward gains in the ventral striatum and caudate in major depression which was related to the consummatory phase of reward processing. They also found that in the major depression group, anhedonic symptoms and depression severity were associated with reduced caudate volume bilaterally. A similar network was identified in a study examining behavioural and neural response to feedback information during a gambling task, where depressed patients showed decreased responses in the ventral striatum and anterior cingulate to feedback information of "winning" or "losing" money and did not adjust their response times accordingly unlike the control group [36]. More recently utilising a reward learning paradigm, authors report attenuated neurophysiological response of the anteroventral striatum in depression and that this may reflect dysfunction in circuits involving afferent projections from the orbitofrontal, limbic, and/or mesostriatal dopaminergic pathways, which conceivably may, together with the ventral striatum, underlie anhedonia in depression [37]. While the reward stimuli employed have generally been indirect (happy facial expressions, positively valenced words, abstract monetary reward) a study by Kumar et al. [38] examined the response to a primary reward (water taste) and also have found abnormalities in the neural circuitry supporting reward mechanisms in patients. The authors reported that patients with MDD had reduced prediction errors in the striatum and midbrain with the extent of signal reduction in the bilateral caudate, nucleus accumbens and midbrain correlating with increased anhedonia severity. When examining schizophrenia they also found reduced prediction error signals in the caudate, thalamus, insula and amygdala-hippocampal complex, with a trend for reduced prediction errors in the midbrain, and the degree of blunting in the encoding of prediction errors in the insula, amygdala-hippocampal complex and midbrain correlating with increased severity of psychotic symptoms [39]. The authors conclude that studies such as this can differentiate across psychiatric disorders such that depression might be characterised by reduced neural signal for prediction errors whereas schizophrenia might be based on noise in the system affecting the signal [39].

Despite many studies now aiming to characterise the neural correlates of anhedonia in depression there are still some inconsistencies across reports. This might be

accounted for by the differing stimuli used in each study as a recent report shows for example that reduced reward network activation is present in MDD when anticipating rewards, but that there is relatively greater hypoactivation to pleasant images than monetary rewards [40]. Therefore it seems that perhaps one of the reasons for inconsistency across studies examining reward in depression is due to the type of reward stimuli used, for example monetary reward, one might expect to be more of a cognitive concept compared to the natural primary reward of a taste.

Taken together, it is now well established that there are differences in the functioning of the reward system in the brain of depressed patients and that this is related to the behavioural symptom of anhedonia. However, it is still unclear from these types of studies if the neural differences in response to reward are truly trait vulnerability markers or if they are in fact state markers or scars of having had the disorder. Furthermore, it is not yet known which aspects of reward processing (appetitive vs. consummatory) might fit the criteria for an endopheontype of depression. To investigate this it is necessary to examine both those during remission from depression and those who are at risk but have not yet experienced any depressive episodes.

6.4 Deficits in at Risk Populations

While it has been suggested that the neurobiological mechanisms underlying anhedonia could represent an endophenotype of depression which may manifest in behavioural and neural outcome changes outside acute depressive episodes [5] few studies have assessed this directly. Further, it is not known if the anhedonic symptoms that persist represent vulnerability factors for future episodes of illness. Furthermore, with the advances in functional neuroimaging we now have the opportunity to evaluate potential markers of disease vulnerability at the neural level. Especially given that brain-based endophenotypes might be close to delivering predictors of disease manifestation and progression as discussed by Peterson and Weissman recently [41].

One way of approaching the issue of reward dysfunction as a trait marker for depression is to examine those who are remitted from depression. However, this method in itself may not be sufficient to establish reward-processing deficit as a trait marker of depression, given that any findings might be due to scarring effects of the illness and or treatment [42–45] yet it can provide relevant information on reward dysfunction as an enduring trait, a key criteria for endophentype status. It also has the advantage of mitigating the potential confounding effects of current mood state, illness severity, non-specific effects of chronic illness and stress, and effects of psychotropic medication usage.

McCabe et al. [46] conducted the first study examining the neural reward response in a sample of recovered depressed individuals. Using a model previously shown to activate the reward system in healthy volunteers [47] involving the sight and taste of chocolate, as a direct reward and an aversive taste and picture condition,

as a control, McCabe and colleagues [46] examined whether a history of depression affected responses to all tastes and affective pictures or whether there was a specific blunting of response to positive stimuli. Areas such as the anterior cingulate, the vmPFC and the ventral striatum which had been found to activate in previous studies to unconditioned reward stimuli where hypothesised as regions of interest [19, 48–50]. The authors also hypothesised that there might be increased processing of aversion in those at risk of depression given the literature showing increased negative emotional biases across other paradigms in depression [51–53]. The authors proposed that the neural circuitry mediating disgust and aversive processing including the amygdala, caudate and anterior insula might thus be enhanced when processing aversive tastes in the recovered depressed sample [54–56]. McCabe and colleagues [46] found that participants recovered from depression showed decreased responses to chocolate in both ventral striatum and anterior cingulate cortex, suggesting that abnormalities in the neural basis of reward may indeed be a trait marker of vulnerability to depression. Interestingly they also found that there was enhanced activation to the aversive stimuli in the lateral orbitofrontal cortex and the caudate, concluding that those "at risk" of depression might also be more sensitive to unpleasant stimuli as the emotion of disgust has been shown to activate such regions [57, 58].

However, how this data relate back to the subjective experience of pleasure per se is not yet clear, as McCabe and colleagues reported no significant differences in the rates of pleasantness across the groups [46]. It is however possible that a simple visual analogue scale of pleasantness is not sensitive enough to show how the brain tracks the subjective pleasantness. One way to tease apart the sub-components of reward processing is with correlations between the brain activations and the subjective report made during the scan of the pleasant and unpleasant stimuli. This is a method that allows the parts of the brain that are tracking the change in valance of the stimuli to be identified and compared between the groups [47, 48]. Using parameter modulation analysis in SPM8, a recent analysis of the correlation between the subjective data and the brain changes in BOLD signal reveal a significant difference between the recovered depressed individuals and the healthy controls in the anterior cingulate cortex (ACC), Fig. 6.1. This new, as yet unpublished data, shows that there are indeed differences in how the brain is tracking the subjective changes in ratings of pleasantness between the recovered depressed and the healthy control individuals. Furthermore, as can be seen from Fig. 6.1 the recovered depressed individuals have a negative correlation between the blood oxygenation level dependent (BOLD) response and the subjective report whereas the healthy controls a positive correlation. This is an important addition to the previous analysis off McCabe et al. [46] which showed that the anterior cingulate was less activated in the recovered depressed compared to the controls for reward but *not* that it was more activated to aversion, which can be now seen from the recent analysis (Fig. 6.1.). This data is also important in that it shows that changes in neural signals in response to the subjective experience of pleasure can indeed be identified and that such regions as the ACC are clearly tracking both reward and aversion. This result highlights the need to examine both ends of the subjective spectrum (pleasantness) when analysing reward in relation to psychiatric disorders. Otherwise relevant information on how

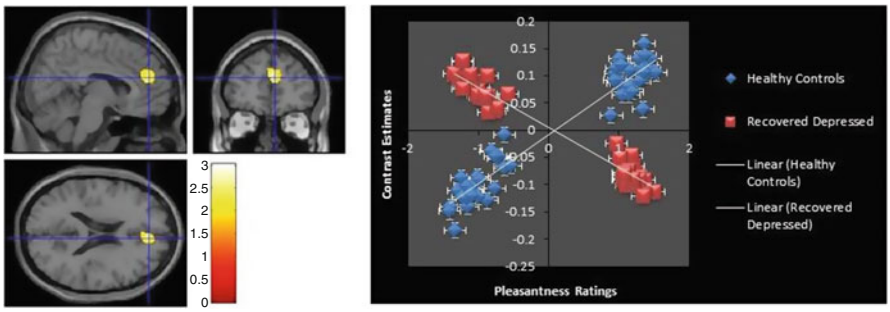

Fig. 6.1 Figure 6.1 shows where significantly stronger positive correlations with the pleasantness ratings in the Healthy Controls vs. the Rec Dep in the ACC ([4 46 24] Z = 2.8 svc p = 0.04)

the same brain areas might be dealing with both negative and positive experiences will be missed. Furthermore, this data is consistent with the literature suggesting that negative stimuli are more salient compared to positive rewarding stimuli in depression. Taken together it seems that understanding how the neural systems are tracking both subjective reward and aversion responses might be beneficial in investigating the symptom of anhedonia as a trait marker. It is possible that variations in the interactions between positive and negative stimuli in brain regions, such as that reported here, might account for the various subtypes of depressive characteristics reported.

Subsequent papers have also begun to examine reward function in those recovered from depression with reports of those recovered from depression requiring significantly greater emotional intensity in faces to correctly identify happy expressions [59]. This is consistent with the notion of a problem with the ability to recognise the positive, rewarding stimuli even in recovery. Furthermore Hasler and colleagues [60] reported that during catecholamine depletion (AMPT) recovered depressed individuals were robustly differentiated from control subjects by their development of performance deficits on a reward processing task. The authors report how the performance deficits correlated directly with the return of depressive symptoms after AMPT administration. They concluded that sensitivity of central reward processing systems to reductions in brain catecholamine levels might then represent a trait-like marker for depression. Interestingly a recent study examining 23 euthymic patients with Bipolar Disorder type 1, 19 remitted patients with MDD, and 19 healthy persons undergoing a task which discriminates whether persons learn better from negative or positive feedback found that Bipolar Disorder type 1 patients who last experienced a manic episode learned well from positive but not negative feedback, whereas those who last experienced a depressive episode showed the opposite pattern [61]. The authors concluded that their data identify differences in response to positive and negative consequences that carry over into the euthymic state that are qualitatively related to the polarity of the preceding episode, whereas

other disease-related variables had no significant influence. This data highlights the importance of understanding in remitted patients how individual differences in depression history might be used to guide treatment course. A study by Hankin et al. [62] also examined the response to positive and negative feedback this time in a novel reward striving task designed to activate the appetitive/approach motivation system whereby objective facial expressions of emotion were videotaped and coded throughout both failure (i.e., nonreward) and control (success and reward) conditions. Three groups of youths (N = 98, ages 9–15; remitted depressed, n = 34; externalizing disordered without depression, n = 30; and healthy controls, n = 34) participated. Observational coding of facial expressions as well as youths' subjective emotion reports showed that the remitted depressed youth specifically exhibited more negative emotional reactivity to failure in the reward striving task, but not the control condition. The authors suggest that depression among youth is related to dysregulated appetitive motivation and associated negative emotional reactivity after failing to achieve an important, self-relevant goal and not attaining reward. The authors also compared this to externalizing disordered youth and found that the deficits in reward processing appear to be specific to depression [62]. This provides further evidence for dysfunction in the processing of reward, even in young people remitted from depression. Others have also recently reported residual reward dysfunction in remitted depressed patients as measured by anhedonia questionnaires which also suggest the symptom of anhedonia as a trait marker, as it persists into recovery [63].

Since the McCabe et al. [46] study there has only been one more study by Dichter and colleagues [64] reporting on the neural response to reward in remitted depressed patients (rMDD). The authors studied the chronometry of neural responses to rewards in euthymic individuals with a history of MDD. However unlike McCabe et al. [46] who used both primary taste and secondary sight rewards, they used a monetary incentive delay task, during fMRI scanning, to measure the neural responses in frontostriatal reward regions during reward anticipation and outcomes. They report that their data suggests a double dissociation between reward network reactivity and the temporal phase of the reward response in rMDD, such that rMDD is generally characterized by reward network hyperactivation during reward anticipation and reward network hypoactivation during reward outcomes. More broadly, they suggest that aberrant frontostriatal response to rewards may potentially represent a trait marker for MDD. The same group also publish another paper on the results of the monetary loss conditions in their task with recovered depressed patients, they find reduced activity to loss in the prefrontal cortex during loss anticipation and outcomes, and they report that the degree of superior frontal gyrus hypoactivation was also associated with rumination [65]. The authors concluded that abnormal prefrontal cortex responses to loss may reflect a trait-like vulnerability to depression, although as theirs was a small sample size, larger numbers would be needed to truly evaluate the utility of this functional neural endophenotype as a prospective risk marker.

Taken together the recent literature has begun to consistently report reward dysfunction in those remitted from depression, mostly showing hypofunctioning of

reward function behaviourally and at the neural level supporting the idea of the symptom of anhedonia as a trait marker, detectable in those at risk of depression. It is also possible, however, that changes in the behavioural and neural response to reward could simply be a consequence of recurrent depression itself or the particular treatments involved [44]. One way to resolve this question is to study reward in people at increased risk of depression before the onset of illness. Numerous risk factors for depression have been described but one of the most reliable is family inheritance. For example, it has been estimated that by young adulthood up to 40 % of children of parents with a clinical mood disorder will have suffered a personal episode of depression [66].

In a follow up to their previous paper in recovered depressed patients McCabe et al. [67] recently examined the neural response to sight and taste of rewarding and aversive stimuli in young people with a depressed parent but no personal history of depression (FH+) compared to matched controls. Using the same methodology as before, they examined the neural response to pleasant sights and tastes of chocolate and sights and tastes of unpleasant strawberry. They found that relative to the controls, young at-risk individuals show abnormalities in the neural representation of reward and punishment, notably in the cortical areas relevant to this processing, particularly anterior cingulate (both dorsal and rostral) but also orbitofrontal cortex and insula. However, they found no differences in ventral striatal responses to reward between the control and at-risk groups, which appears to distinguish the latter from recovered depressed patients [46]. Relatively few studies report on rewarding and aversive processing in high-risk individuals prior to the onset of depression. Gotlib and colleagues [68] examined how girls aged 10–14 years, whose mothers suffered from recurrent depression, responded in a monetary incentive task. They found that compared to controls the high risk group showed lower activation in ventral striatum to the anticipation and receipt of reward. Activity in the left insula to reward anticipation was also lowered while that in right insula was increased, consistent with a role for the latter structure in prediction error [68, 69]. Also by studying children and adolescents at increased risk of depression (mean age 14 years), Monk and colleagues [70] found increased amygdala response to fearful facial expressions while accumbal responses to happy faces was blunted. More recently, a study by Macoveanu et al. [71] has shown that in a sample of individuals who have a first degree relative with depression there are deficits in the processing of rewarding and punishing stimuli using a monetary reward task. The authors report that those with a family history have increased processing of aversive and reduced processing of reward in areas similar to that reported by McCabe et al. [67] namely the increased orbitofrontal cortex activation to aversion/loss. Thus far, the few studies examining at risk individuals have some inconsistencies in their results which may be because of the nature of the population studied or the tasks employed, however they do support the suggestion that abnormalities in the neural representation of reward may be present in at-risk individuals prior to the onset of depressive disorder. McCabe et al. [67] suggest that the differences in anterior cingulate, orbitofrontal and insula activity might indicate impairments that increase the risk of affected individuals experiencing adverse life events which are in turn key triggers

for early episodes of depression [72]; interestingly there is evidence that people at increased genetic risk of depression may inadvertently "select" environments in which adversity is more likely [73]. It is therefore possible that impairments in reward and punishment-based learning could contribute to difficulties in social decision-making. However, it will be important in future studies to assess whether in young people at increased familial risk of depression, impaired neural processing of reward is indeed associated with deficits in behavioural tasks designed to tap both social and reward-based learning [74]. It is also possible that the abnormalities described might lead to impaired neural and behavioural responses to independently occurring adverse life events, making adaptive coping more difficult. To test these hypotheses it will be necessary to follow-up high-risk individuals to ascertain whether any of the neural abnormalities identified might predict the occurrence of increased negative life events as well as the psychological responses to them, including clinical depression.

6.5 Effects of Drug Treatment on the Reward Response

Despite the advancements made in the pharmacological treatments available for disorders like depression not all the symptoms of depression seem to be treated effectively such as the loss of pleasure, loss of interest, fatigue and loss of energy. These symptoms are consistent with the description of anhedonia as one of the main symptoms of depression and indicate that perhaps for some patients at least with predominant baseline symptoms of decreased pleasure, interest and energy new pharmacological treatment approaches are surely needed [3, 75]. Early investigations into the effects of current pharmacological treatments on the neural response to differing emotional tasks found that antidepressants [76–78] mostly attenuate the neural response to fearful or aversive stimuli which is thought to underpin the increased processing of negative information. However it wasn't until Kumar and colleagues [38] that the effects on the brains reward system was directly assessed under antidepressant treatment. Kumar et al. [38] found that depressed patients had blunted learning signals in relation to reward but that acute antidepressant administration did not increase this. They also found that the SSRI antidepressant citalopram blunted learning signals in the control subjects, concluding that it's possible that antidepressants fail to normalize reward-learning function in antidepressant-unresponsive MDD. Subsequently in 2010, McCabe and colleagues [44] reported on a study of 45 healthy participants who were randomly allocated to receive citalopram, the noradrenaline re-uptake inhibitor, reboxetine, or placebo for 7 days in a double-blind, parallel group design. They used functional magnetic resonance imaging to measure the neural response to rewarding (sight and/or flavour of chocolate) and aversive stimuli (sight of mouldy strawberries and/or an unpleasant strawberry taste) on the final day of drug treatment. They found that citalopram reduced activation to the chocolate stimuli, in the ventral striatum and the ventral medial/orbitofrontal cortex. In contrast, reboxetine did not suppress ventral striatal activity and in

fact increased neural responses within medial orbitofrontal cortex to reward. Citalopram also decreased neural responses to the aversive stimuli conditions in key 'punishment' areas such as the lateral orbitofrontal cortex. Reboxetine produced a similar, though weaker effect. They concluded that they were the first to show that treatment with SSRIs can diminish the neural processing of both rewarding and aversive stimuli. They suggested that the ability of SSRIs to decrease neural responses to reward might underlie the questioned efficacy of SSRIs in depressive conditions characterised by decreased motivation and anhedonia and could also account for the experience of emotional blunting described by some patients during SSRI treatment. Further to this a recent study also showed that the single acute administration of serotonin antidepressant paroxetine could diminish brain activity induced by motivation in healthy subjects [79]. Muratani et al. [79] concluded that this may partially explain the increased lack of motivation seen in patients with relatively mild symptoms after taking a dose of paroxetine for the first time. However a recent study by Ossewaarde and colleagues [80] when also examining the reward response to money, this time in healthy volunteers, found the opposite result i.e. that short-term antidepressants (duloxetine (60 mg once a day) or placebo for 14 days) enhanced ventral striatal responses compared with placebo. The authors conclude that antidepressants augment neural activity in mesolimbic DA incentive processing circuits likely caused by the increase in monoamine neurotransmission in the ventral striatum and that antidepressants may alleviate anhedonia by stimulating incentive processing. The resulting discrepancies between directions of effects across studies could of course be accounted for by a number of factors; firstly, some studies report primary reward processing whilst others abstract secondary rewards (money). Secondly there are differences in recruitment, some patients some healthy controls. Thirdly, different types of antidepressants are examined and finally different treatment periods, all of which contribute to the differences in results reported. Therefore future research would benefit from a combined strategy across research groups so that replication might be better achieved and protocols can be validated, only then can these methodologies be translational and the results truly meaningful.

6.6 Conclusions and Future Directions

Taken together is seems that reward dysfunction at the neural level is related to the symptoms of depression, specifically anhedonia. It is also becoming clearer that the deficits in the processing of rewarding information might also be a trait marker for depression as they are apparent in both those recovered from depression but also in young people at risk of future episodes of depression. There are relatively few studies examining reward at the neural level in those at risk of depression and the data are not entirely consistent. One obvious reason might be the differences across samples selected. For example although Gotlib and colleagues [68] found reduced ventral striatal activity in young females at risk, McCabe et al. [67] did not, this might simply be due to the age range recruited. Gotlib recruited girls aged 10–14 years whilst

McCabe 16–21 years, therefore McCabe et al. [67] may in fact have been recruiting those at risk but who have not had depression by the age of 21 and therefore a highly resilient sample instead [67, 68]. Furthermore different groups have used differing paradigms which again could be tapping various different aspects of the reward system i.e. appetitive vs. consummatory aspects, not all of which might be true trait markers.

Yet despite these issues the bulk of the evidence points to some neural deficits in the processing of reward in those at risk of depression. As a next step future studies would greatly benefit from the implementation of longitudinal studies that can examine at risk individuals at baseline (approx. age 12–14 years) and again (approx. 20–22 years) so the difference in those who are at risk but who do not develop depression compared to those who do can be examined this approach would be important in allowing us to understand which brain areas/networks are involved in risk and resilience so that targeted intervention strategies could be developed.

References

1. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and Projected to 2020, Global burden of disease and injury series. Cambridge: Harvard University Press; 1996.
2. Covinsky KE, et al. Dysphoria and anhedonia as risk factors for disability or death in older persons: implications for the assessment of geriatric depression. Am J Geriatr Psychiatry. 2013 Apr 18. pii: S1064–7481(12)00097-8. doi: 10.1016/j.jagp.2012.12.001. [Epub ahead of print]
3. Nutt D, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. J Psychopharmacol. 2007;21(5):461–71.
4. Nestler EJ, Carlezon Jr WA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006;59(12):1151–9.
5. Hasler G, et al. Discovering endophenotypes for major depression. Neuropsychopharmacology. 2004;29(10):1765–81.
6. Lemoult J, Joormann J. Attention and memory biases in social anxiety disorder: the role of comorbid depression. Cogn Ther Res. 2012;36(1):47–57.
7. Dryman A, Eaton WW. Affective symptoms associated with the onset of major depression in the community: findings from the US National Institute of Mental Health Epidemiologic Catchment Area Program. Acta Psychiatr Scand. 1991;84(1):1–5.
8. Loas G, Pierson A. Anhedonia in psychiatry: a review. Ann Med Psychol. 1989;147(7):705–17.
9. Loas G. Vulnerability to depression: a model centered on anhedonia. J Affect Disord. 1996;41(1):39–53.
10. Schrader GD. Does anhedonia correlate with depression severity in chronic depression? Compr Psychiatry. 1997;38(5):260–3.
11. Liu WH, et al. Deficits in sustaining reward responses in subsyndromal and syndromal major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(4):1045–52.
12. Treadway MT, et al. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. PLoS One. 2009;4(8):e6598.
13. Henriques JB, Glowacki JM, Davidson RJ. Reward fails to alter response bias in depression. J Abnorm Psychol. 1994;103(3):460–6.
14. McFarland BR, Klein DN. Emotional reactivity in depression: diminished responsiveness to anticipated reward but not to anticipated punishment or to nonreward or avoidance. Depress Anxiety. 2009;26(2):117–22.

15. Pizzagalli DA, et al. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. J Psychiatr Res. 2008;43(1):76–87.
16. Hoebel BG, Avena NM, Rada P. Accumbens dopamine-acetylcholine balance in approach and avoidance. Curr Opin Pharmacol. 2007;7(6):617–27.
17. Ikemoto S, Panksepp J. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res Brain Res Rev. 1999;31(1):6–41.
18. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning. Curr Opin Pharmacol. 2009;9(1):65–73.
19. O'Doherty J, et al. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci. 2001;4(1):95–102.
20. Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc Natl Acad Sci U S A. 2001;98(20):11818–23.
21. Lane RD, et al. Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia. 1997;35(11):1437–44.
22. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998;28(3):309–69.
23. Robbins TW, Everitt BJ. Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol. 1996;6(2):228–36.
24. Cardinal RN, et al. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev. 2002;26(3):321–52.
25. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008;199(3):457–80.
26. Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology. 2010;35(1):192–216.
27. Russo SJ, Nestler EJ. The brain reward circuitry in mood disorders. Nat Rev Neurosci. 2013;14(9):609–25.
28. Harvey PO, et al. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry. 2007;12(8):703, 767–775.
29. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage. 2009;46(1):327–37.
30. Mitterschiffthaler MT, et al. Neural response to pleasant stimuli in anhedonia: an fMRI study. Neuroreport. 2003;14(2):177–82.
31. Schaefer HS, et al. Event-related functional magnetic resonance imaging measures of neural activity to positive social stimuli in pre- and post-treatment depression. Biol Psychiatry. 2006;60(9):974–86.
32. Epstein J, et al. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. Am J Psychiatry. 2006;163(10):1784–90.
33. Keedwell PA, et al. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005;58(11):843–53.
34. Knutson B, et al. Neural responses to monetary incentives in major depression. Biol Psychiatry. 2008;63(7):686–92.
35. Pizzagalli DA, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166(6):702–10.
36. Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. Brain. 2007;130(Pt 9):2367–74.
37. Robinson OJ, et al. Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. Am J Psychiatry. 2012;169(2):152–9.
38. Kumar P, et al. Abnormal temporal difference reward-learning signals in major depression. Brain. 2008;131(Pt 8):2084–93.
39. Gradin VB, et al. Expected value and prediction error abnormalities in depression and schizophrenia. Brain. 2011;134(Pt 6):1751–64.

40. Smoski MJ, Rittenberg A, Dichter GS. Major depressive disorder is characterized by greater reward network activation to monetary than pleasant image rewards. Psychiatry Res. 2011;194(3):263–70.
41. Peterson BS, Weissman MM. A brain-based endophenotype for major depressive disorder. Annu Rev Med. 2011;62:461–74.
42. Kerestes R, et al. Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. Psychol Med. 2012;42(1):29–40.
43. McCabe C, Mishor Z. Antidepressant medications reduce subcortical-cortical resting-state functional connectivity in healthy volunteers. Neuroimage. 2011;57(4):1317–23.
44. McCabe C, et al. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. Biol Psychiatry. 2010;67(5):439–45.
45. McCabe C, et al. SSRI administration reduces resting state functional connectivity in dorso-medial prefrontal cortex. Mol Psychiatry. 2011;16(6):592–4.
46. McCabe C, Cowen PJ, Harmer CJ. Neural representation of reward in recovered depressed patients. Psychopharmacology (Berl). 2009;205(4):667–77.
47. Rolls ET, McCabe C. Enhanced affective brain representations of chocolate in cravers vs. non-cravers. Eur J Neurosci. 2007;26(4):1067–76.
48. McCabe C, Rolls ET. Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. Eur J Neurosci. 2007;25(6):1855–64.
49. O'Doherty J, et al. Representation of pleasant and aversive taste in the human brain. J Neurophysiol. 2001;85(3):1315–21.
50. Rolls ET, Kringelbach ML, de Araujo IE. Different representations of pleasant and unpleasant odours in the human brain. Eur J Neurosci. 2003;18(3):695–703.
51. Bradley BP, Mogg K, Lee SC. Attentional biases for negative information in induced and naturally occurring dysphoria. Behav Res Ther. 1997;35(10):911–27.
52. Murphy FC, et al. Emotional bias and inhibitory control processes in mania and depression. Psychol Med. 1999;29(6):1307–21.
53. Surguladze SA, et al. Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. Neuropsychology. 2004;18(2):212–8.
54. Fitzgerald DA, et al. Neural correlates of internally-generated disgust via autobiographical recall: a functional magnetic resonance imaging investigation. Neurosci Lett. 2004; 370(2–3):91–6.
55. Zald DH, Hagen MC, Pardo JV. Neural correlates of tasting concentrated quinine and sugar solutions. J Neurophysiol. 2002;87(2):1068–75.
56. Zald DH, Pardo JV. The neural correlates of aversive auditory stimulation. Neuroimage. 2002;16(3 Pt 1):746–53.
57. Shapira NA, et al. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. Biol Psychiatry. 2003;54(7):751–6.
58. Phillips ML, et al. Neural responses to facial and vocal expressions of fear and disgust. Proc Biol Sci. 1998;265(1408):1809–17.
59. Lemoult J, Yoon KL, Joormann J. Affective priming in major depressive disorder. Front Integr Neurosci. 2012;6:76.
60. Hasler G, et al. Neural response to catecholamine depletion in unmedicated subjects with major depressive disorder in remission and healthy subjects. Arch Gen Psychiatry. 2008;65(5):521–31.
61. Linke J, Sonnekes C, Wessa M. Sensitivity to positive and negative feedback in euthymic patients with bipolar I disorder: the last episode makes the difference. Bipolar Disord. 2011;13(7–8):638–50.
62. Hankin BL. Future directions in vulnerability to depression among youth: integrating risk factors and processes across multiple levels of analysis. J Clin Child Adolesc Psychol. 2012;41(5):695–718.
63. Di Nicola M, et al. Reduced hedonic capacity in euthymic bipolar subjects: a trait-like feature? J Affect Disord. 2013;147(1–3):446–50.

64. Dichter GS, et al. Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. J Affect Disord. 2012;136(3):1126–34.
65. Schiller CE, et al. Remitted major depression is characterized by reduced prefrontal cortex reactivity to reward loss. J Affect Disord. 2013;151(2):756–62.
66. Beardslee WR, Versage EM, Gladstone TR. Children of affectively ill parents: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 1998;37(11):1134–41.
67. McCabe C, et al. Neural processing of reward and punishment in young people at increased familial risk of depression. Biol Psychiatry. 2012;72(7):588–94.
68. Gotlib IH, et al. Neural processing of reward and loss in girls at risk for major depression. Arch Gen Psychiatry. 2011;67(4):380–7.
69. Preuschoff K, Quartz SR, Bossaerts P. Human insula activation reflects risk prediction errors as well as risk. J Neurosci. 2008;28(11):2745–52.
70. Monk CS, et al. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. Am J Psychiatry. 2008;165(1):90–8.
71. Macoveanu J, et al. Altered reward processing in the orbitofrontal cortex and hippocampus in healthy first-degree relatives of patients with depression. Psychol Med. 2013;1–13. doi: http://dx.doi.org/10.1017/S0033291713001815.
72. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. Am J Psychiatry. 2000;157(8):1243–51.
73. Kendler KS, Karkowski-Shuman L. Stressful life events and genetic liability to major depression: genetic control of exposure to the environment? Psychol Med. 1997;27(3):539–47.
74. Behrens TE, et al. Associative learning of social value. Nature. 2008;456(7219):245–9.
75. Argyropoulos SV, Nutt DJ. Anhedonia revisited: is there a role for dopamine-targeting drugs for depression? J Psychopharmacol. 2013;27(10):869–77.
76. Del-Ben CM, et al. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an FMRI study. Neuropsychopharmacology. 2005;30(9):1724–34.
77. Vollm B, et al. Serotonergic modulation of neuronal responses to behavioural inhibition and reinforcing stimuli: an fMRI study in healthy volunteers. Eur J Neurosci. 2006;23(2):552–60.
78. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br J Psychiatry. 2009;195(2):102–8.
79. Marutani T, et al. Functional magnetic resonance imaging study on the effects of acute single administration of paroxetine on motivation-related brain activity. Psychiatry Clin Neurosci. 2011;65(2):191–8.
80. Ossewaarde L, et al. Two-week administration of the combined serotonin-noradrenaline reuptake inhibitor duloxetine augments functioning of mesolimbic incentive processing circuits. Biol Psychiatry. 2011;70(6):568–74.

Chapter 7
Anhedonia in Trauma Related Disorders: The Good, the Bad, and the Shut-Down

Jonathan M. DePierro, Wendy D'Andrea, and Paul Frewen

Abstract The present chapter reviews the evidence for anhedonia in trauma-related disorders. Clinical observations and empirical evidence are presented as arguments for distinguishing between two clinical presentations of anhedonia in trauma-related disorders: (1) Hedonic Deficit, defined as an inability to experience positive affect, and (2) Negative Affective Interference, defined as the experience of negative emotions in situations that normally would be considered positive. We situate these two forms of anhedonia within existing models of affective experience, suggest ways in which this formulation may be tested empirically, and argue for the clinical relevance of increasing understanding of positive affect intolerance in trauma-related disorders.

Keywords Anhedonia • Negative affective interference • Trauma • Posttraumatic stress disorder • Borderline personality disorder • Emotional numbing

Abbreviations

BPD	Borderline Personality Disorder
ERP-R	Emotion Regulation Profile-Revised
FCPCS	Fawcet Clark Pleasure Capacity Scale
HD	Hedonic Deficit
HDIS	Hedonic Deficit and Interference Scale

J.M. DePierro • W. D'Andrea
Psychology (Clinical), The New School for Social Research,
80 Fifth Ave (7th Floor), 10011, NY, New York

P. Frewen, Ph.D., C.Psych. (✉)
Department of Psychiatry, The University of Western Ontario,
University Hospital (Rm A10-222), London, ON, Canada

Department of Psychology, The University of Western Ontario, London, ON, Canada
e-mail: pfrewen@uwo.ca

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_7,

NAI	Negative Affective Interference
PE	Positive Emotionality
PTSD	Posttraumatic Stress Disorder
SHAPS	Snaith-Hamilton Pleasure Scale

This chapter reviews research on the associations between anhedonia and Posttraumatic Stress Disorder (PTSD). We present evidence for a particular form of anhedonia that Frewen, Dean, and Lanius [1] titled "negative affective interference" (NAI). NAI is expressed as negative affective responses to positive events, a clinical phenomenon that appears to be prevalent in complexly traumatized persons. Throughout this chapter we argue that parsing NAI from anhedonia as it is traditionally defined, as involving an inability to experience positive affect in situations that would normally provoke it, can advance research into the nature of emotional processing in trauma-related disorders, and add to clinical case conceptualization and treatment planning for affected individuals. We begin by reviewing what is known concerning anhedonia as expressed as an inability to experience positive affect in PTSD, which we term Hedonic Deficit (HD); thereafter, we discuss evidence for NAI in PTSD.

7.1 Hedonic Deficit

Although investigations of emotional processing in trauma-related disorders have largely focused on hyperarousal responses to threatening-aversive stimuli, traumatized persons have also been shown to exhibit deficiencies or alterations in their affective response to pleasant stimuli including pictures of nature, others' joyful expressions, and infants. One way to characterize these deficits is as an expression of anhedonia, the inability to experience positive affect in the context of stimuli and events that should normally provoke it.

Anhedonia expressed as a hedonic deficit appears closely related to a prototypic symptom of PTSD, *emotional numbing*, which is characterized by decreased interest or participation in activities, feelings of detachment or estrangement, and an inability to experience positive emotions [2]. Kashdan, Elhai, and Frueh [3] argue that anhedonia and emotional numbing are conceptually similar in that both experiences are characterized by decreased appetitive behavior and positive emotion, particularly in an interpersonal context. Kashdan et al. [3] further provided evidence that anhedonia and numbing are distinct from the negative emotionality often found in individuals with PTSD (e.g. re-experiencing and hyperarousal symptoms). In a combat Veteran sample, only the frequency and intensity of emotional numbing uniquely predicted levels of anhedonia (assessed by items extracted from a depression inventory) after controlling for the shared variance among the PTSD symptom clusters. Moreover, greater emotional numbing was associated with an increased likelihood of being diagnosed with comorbid major depression in this Veteran sample. A follow-up study also indicated that the association between anhedonia and emotional numbing

was strongest in individuals who were characterized as potentially over-reporting their level of symptoms; at the same time, the authors raised the possibility that the symptom over-reporting index (the MMPI F_p scales) may instead be capturing a truly heightened degree of impairment [4]. Taken together with literature suggesting that emotional numbing is a significant prospective predictor of PTSD [e.g., 5], these initial studies support the clinical significance of hedonic deficits and emotional numbing in understanding PTSD.

That said, compared to work in other disorders, such as schizophrenia [6, 7] and depression [8, 9], laboratory studies of anhedonia in PTSD are considerably smaller in number. Spahic-Mihajlovic, Crayton, and Neafsey [10] found that pleasant pictures were rated as less arousing and salient by Bosnian refugees suffering from PTSD. In men with combat-related PTSD, images of attractive women provoked less interest as measured by viewing time [11]. Further, expectancy and satisfaction with winning in a "wheel-of-fortune" game was reduced relative to controls [12]; a neuroimaging study with the same task further found that healthy individuals activated reward circuitry (right nucleus accumbens, caudate, and putamen) during anticipated and actual winning while playing the game whereas such effects were absent in combat veterans with PTSD [13]. Finally, in response to viewing amusing cartoons, healthy men showed increased response within the bilateral temporal poles, response within which has been implicated in social cognitive processing (e.g., mentalizing, theory of mind), whereas men with PTSD showed increased response within right middle frontal cortex, potentially indicative of response inhibition of associated negative affect [14].

7.2 Negative Affective Interference

Generally speaking, when pleasant events happen in everyday life (e.g. a new job or life opportunity, a warm bath, or a vacation), any number of common responses, including laughter, boost in mood, collective celebration, and a sense of calm or relaxation are expected. However, clinical observations suggest that for certain individuals, especially those who have had early and sustained exposure to trauma, the same events are often met instead with negative affect and distress, for example fear, anxiety, anger, guilt, and shame. Importantly, this conceptualization of anhedonia does not veer far from both other early and contemporary writings on the topic. For example, Meehl [15] hypothesized that individuals who were unable to feel pleasure may feel "secondary" guilt and shame when comparing themselves to others who can experience pleasure; that is, people may feel ashamed of their inability to experience joy. This secondary emotional response may yield an experience of further exaggerated negative affect because one lacks the cache of positive affects to buffer against negative experiences. More recently, Nelis, Quodbach, Hansenne, and Mikolajczak [16] designed the *Emotion Regulation Profile-Revised* (ERP-R) in order to distinguish between emotion regulation strategies that "savor" versus tend to "dampen" positive affect in the context of what would be nominally considered

positive events. The positive emotion regulation strategies they identified as adaptive were: (1) behavioural displays (i.e., making one's positive affect known to others through vocal or non-verbal behaviours, e.g., smiling, laughing out loud), (2) "mindfully savouring the moment" (i.e., intentionally paying attention to pleasant experiences), (3) "capitalisation" (i.e., communicating and socially celebrating positive events such as birthdays and achievements), and (4) "positive mental time travel" (i.e., intentionally recalling positive memories and imagining positive future events). In comparison, the four maladaptive ("dampening") positive emotion regulation strategies they identified were: (1) inhibition of emotion expression, (2) "fault finding" (e.g., focussing on less than ideal aspects of otherwise generally positive occurrences), (3) inattention (focusing on activities or thoughts ostensibly unrelated to the positive event, or engaging in worry), and (4) "external attribution/nostalgia" or "negative time travel" (involving attributing non-personal cause for positive events and anticipating negative future outcomes as likely following positive occurrences). Nelis, Quoidbach, and colleagues [16, 17] found that emotion regulation strategies that were dampening of positive affect were strongly negatively associated with a number of indicators of mental health and well-being.

Research with individuals with PTSD demonstrates that affected individuals interpret both negative and positive stimuli as negative at the level of subjective ratings and neural responses [18–20]. Orsillo et al. [18] found that women with PTSD related to being victims of interpersonal violence (IPV) endorsed negative affect not only in response to aversive films but also to films intended to serve as positive stimuli as well; at the same time, there were no differences in facial EMG during viewing between those individuals with vs. without PTSD. Frewen et al. [19] found that, compared with healthy women, women with PTSD rated more negative than positive trait adjectives as self-descriptive, and endorsed greater negative and less positive affect during a task in which they viewed pictures of themselves and listened to positive and negative trait adjectives. Evidence has also suggested that heightened arousal may be associated with alterations in stimulus ratings. Armony et al. [20], in a neuroimaging paradigm, asked individuals with PTSD and healthy controls to view masked and unmasked fearful and positive faces. Their findings indicated that within the PTSD group, PTSD symptom severity was positively correlated with amygdala response to unmasked happy relative to fearful faces, potentially signifying a pronounced fear-based or salience response more so to normally positive stimuli (happy faces) than to intrinsically negative stimuli (fearful faces).

7.3 The Hedonic Deficit and Interference Scale (HDIS)

Frewen and colleagues [1, 21] recently developed a self-report measure to assess altered emotional processing in PTSD, in part to quantify the degree to which response to positive situations was fraught with negative affect. The *Hedonic Deficit and Interference Scale* (HDIS) evaluates a range of experiences associated with the

construct of anhedonia by means of: (1) a 5-item subscale capturing the extent to which the individual experiences a range of positive emotions over the past month (Positive Emotionality; PE), (2) a 5-item subscale capturing the extent to which the individual feels they cannot experience given positive feelings in general (Hedonic Deficit; HD), and (3) and an 11-item subscale capturing the extent to which individuals feel that specific negative feelings interfere with positive events in their lives (Negative Affect Interference; NAI). Items were developed through consultation with clinicians treating individuals with PTSD and affected individuals themselves, and by review of other mood and symptom rating scales.

In the initial validation study [1] with a convenience sample of 90 undergraduates, the HDIS was validated against the *Fawcett-Clark Pleasure Capacity Scale* (FCPCS; [22]), which was modified to assess the extent to which participants not only experienced pleasure in response to pleasant events, but also to ask about the extent to which participants felt that they would experience negative feelings in response to the positive situations listed in the FCPCS. Significant positive correlations were observed between NAI and all FCPCS negative emotions (emotional numbing, anger, anxiety, sadness, shame, and disgust), and a negative correlation was observed between NAI and FCPCS joy. Further, the NAI subscale correlated negatively with PE and positively with HD, indicating that individuals with elevated NAI endorsed a greater inability to experience pleasure and decreased positive affective responses to pleasant situations. Providing concurrent predictive validity, the authors report that childhood emotional and sexual abuse were both associated with lower PE, and higher HD and NAI.

In a follow-up study [21], women with current chronic PTSD and healthy controls completed a number of interview and self-report procedures, and engaged in a script-driven imagery task that required them to imagine audiotaped positive social and non-social vignettes. HDIS-NAI scores positively correlated with negative mood ratings and negatively correlated with positive mood ratings following the task. Blood oxygen-level dependent (BOLD) fMRI imaging data acquired during the task was also analyzed (see Fig. 7.1; adapted with permission from [21]). BOLD data indicated that within the PTSD group, high NAI was related to decreased activity in the right temporal-parietal junction, bilateral cerebellum, and right middle temporal gyrus during socially-oriented script-driven imagery. These brain regions have been implicated in a range of activities, including imaging and anticipating future events, emotion processing, executive control, and theory of mind [e.g., 23–25]. NAI scores positively predicted activation in areas including the left amygdala, in line with previously mentioned findings of Armony et al. [20]. The neuroimaging study thus appears to elucidate several relative activation-deactivation patterns specifically predicted by NAI while imagining socioemotional events, possibly indicative of increases in negative emotional arousal in the relative absence of higher-order self-reflective processing and/or mentalizing during imagery of socioemotional events.

Concurrent self-report data helped to establish the nomological network for the HDIS. Frewen et al. [21] found mean HDIS-HD scores greater than 1.0 had 90 % sensitivity and 94 % specificity in differentiating groups (PTSD vs controls), and

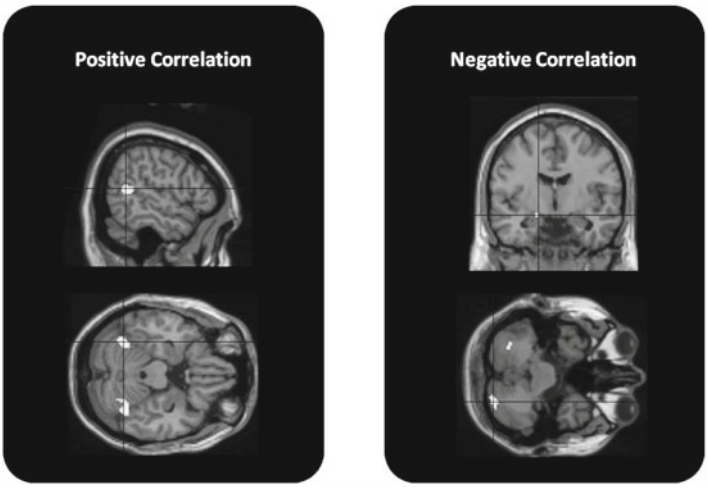

Fig. 7.1 fMRI study of negative affective interference as a predictor of functional neural response to positive emotional imagery in 14 women with PTSD (Neuroimaging effects of hedonic negative affective interference during positive imagery in traumatized women with PTSD (n = 14; data from Frewen et al. [21]))

mean NAI scores greater than 1.0 had 91 % sensitivity and specificity (all HDIS items, including those on the NAI subscale are 0–10 ratings). HD and NAI were positively and PE was negatively correlated with the FCPCS [22], and PE correlated negatively and HD correlated positively with the *Snaith-Hamilton Pleasure Scale* (SHAPS) [26]. Further, NAI and HD correlated with PTSD symptom severity as assessed by structured clinical interview, whereas SHAPS and FCPCS scores did not, providing incremental validity for the HDIS. PE and HD were more closely related to concurrent depressive than anxiety self-report ratings; however, NAI was as strongly related to depression as anxiety, suggesting that NAI may be associated with a wider range of negative affect types.

To expand upon these data, the first and second authors conducted an internet-based study with a community sample of adults in the United States. Results are preliminary, but pilot findings suggest that both NAI and HD were both strongly positively correlated with self-reported PTSD symptoms, borderline personality features, depression, dissociation, and broad psychiatric distress. These results argue for the relevance of these two purported forms of anhedonia to understanding trauma-related disorders. To investigate alterations in emotional processing further, the first and second authors also asked participants to complete simultaneous valence (positive to negative) and arousal (low to high) ratings of a total of 40 positive, negative, and neutral images. They found that NAI (but not HD) was consistently positively correlated with arousal ratings, but *not* valence ratings, across all three image categories, suggesting NAI may be associated with heightened emotional response to a range of stimuli rather than only to inherently positive stimuli alone.

We are following up upon this investigation of self-reported symptoms and affect with physiological and behavioral paradigms that will examine the unique contribution of NAI to symptoms and physiological reactivity.

7.4 Two Kinds of Anhedonia

In summary, two purportedly distinctive responses to generally positive stimuli have been observed in people with trauma-related disorders. In the first case, individuals may report feeling affectively blunted, detached, or numb, failing to experience joy or pleasure at times that most of us would be expected to (e.g., after being complimented, or receiving gift, or at the warm embrace of a loved one). We refer to such responses as "*hedonic deficits*" (HD), emphasizing that participants are unable to experience positive affect in such circumstances. Traumatized persons may also report experiencing *negative* emotional responses to positive events, such as feelings of fear, anxiety, anger, guilt, shame, and unworthiness when being complimented, receiving the gift, or at signs of another's affection as being directed towards oneself. We refer to these responses as "*negative affective interference*" (NAI), thereby emphasizing that intrusive, distressing feelings such as anxiety and shame are preventing an individual from experiencing positive affect. Both HD and NAI responses can be measured by self-report utilizing the *Hedonic Deficit and Interference Scales* (HDIS; [1, 21], reproduced with permission from [1] in the Appendix). The critical, clinically-significant point from a psychological assessment perspective is that ***most other anhedonia scales fail to measure NAI; one's scores as derived from such measures indicate only the lack of experienced positive affect toward positive events, failing to take account of the presence*** **versus** ***absence of accompanying negative emotions such as fear, anxiety, anger, guilt, and shame***.

As a further theoretical means of understanding these dual expressions of anhedonia in traumatized persons, Frewen and Lanius [27] hypothesized that HD and NAI may structure differentially within affective circumplex models of emotion (e.g., [28, 29]; see Fig. 7.2, reproduced with permission from [27]). Specifically, Frewen and Lanius [27] suggest that HD can be characterized between 210° and 240° on an affective circumplex, akin to experiences of "deactivated displeasure" and "unpleasant deactivation" [28, 29]. In comparison, NAI was hypothesized to structure between 120° and 150°, associated with experiences of "activated displeasure" and "unpleasant activation" [28, 29]; such hypotheses require empirical evaluation.

What is also required to give justice to this topic is the understanding that emotional responses are not static entities; although the newly-released DSM-5 diagnostic criteria for PTSD [2] parse negative affective responses and numbing, these symptoms likely interact dynamically over the course of minutes, hours, days, and weeks within traumatized persons. An example of this interaction is that emotional numbing symptoms are generally understood to follow chronic hyperarousal [30]. Within the context of the HDIS, it is highly likely that HD and NAI phenomena

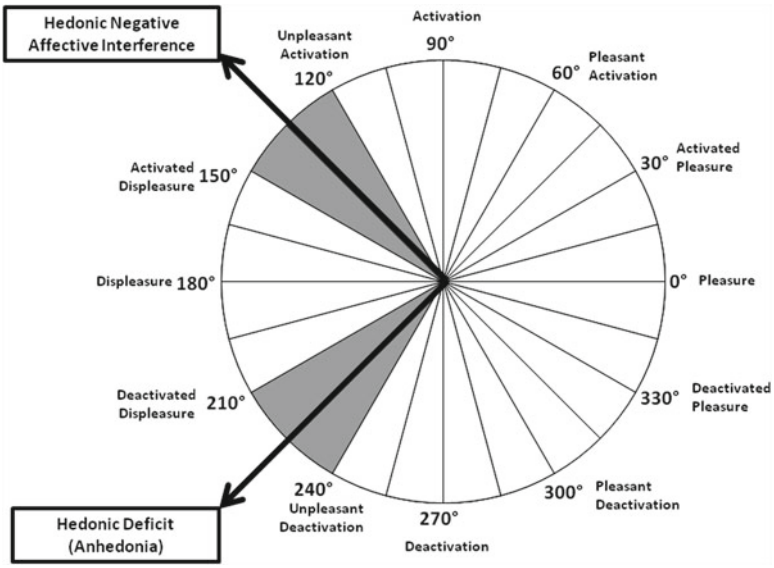

Fig. 7.2 Affective circumplex indicating hypothesized location of hedonic deficit (Anhedonia) vs. hedonic negative affective interference

co-occur, indeed as evidenced by a positive correlation between these two measures as administered to both predominantly healthy and PTSD samples. Further research should track the time course of anhedonia responses in trauma-exposed individuals to investigate how NAI and HD interact.

7.5 Contributions of Early Trauma to Negative Affect Interference

As described above, Frewen et al. [1, 21] found evidence for NAI and low positive affect by self-report in individuals from clinical and non-clinical samples with histories of childhood abuse and neglect, and advanced patterns of neural response that may underpin these alterations in subjective emotional experience. Why should being the victim of early maltreatment frequently culminate in the development of anhedonia and NAI?

We hypothesize that individuals who are traumatized early in life develop altered patterns of emotional processing particularly in reference to interpersonal material. From an attachment perspective, such an outcome may be supported by caregivers who associate pleasurable events with physical and emotional pain, for example, associating physical touch and affection (naturally positive) with sexual abuse, or

rewarding experiences (e.g., scholastically or in sports) with emotional abuse (e.g., informing the child that he/she is stupid, worthless and insignificant nonetheless). In these situations, the child, instead of relinquishing necessary attachment ties, may turn the blame on themselves [e.g., 31]. These experiences should then shape how individuals process affective information later in life; that is, for individuals for whom early close relational bonds were traumatic, stimuli evocative of these memories, which for others are normally pleasant and calming, should induce a fearful, shaming, or otherwise aversive response. As a clinical example, one of our clients described poignantly how any source of affect became a trigger for the chronic incest she had experienced:

> He abused me in every room of the house…in the kitchen, in the shed, in the yard, in the car. He abused me every season of the year, when it was warm, when it was spring, when it was fall, when it was chilly. On every holiday. So now, instead of enjoying life, I am triggered by holidays, by seasons, by random environmental events. When I feel good, I feel disgusted of how I sometimes felt good with [the perpetrator]. Everything is contaminated.

Clearly, chronic relational abuse such as this has the capacity to be tremendously destructive. One of the most unfair aspects of trauma may be how it interferes with everyday pleasures, particularly those involving the warmth and human connection of satisfying intimate relationships. In addition, such problems may interfere with a person's ability to delight in the caregiving of the young. For example, Frewen and Lanius [27] describe several clinical examples of traumatized persons who were unable to experience joy in the context of their children; such persons, whilst *"knowing"* they loved their children were nevertheless unable to *"feel"* or express such love without re-experiencing the memories of their own maltreatment, often provoking numbing responses, anger, fear, and/or shame.

Current research integrating cognitive-behavioral and psychodynamic theories suggests that individuals with histories of early abuse are likely to have internalized malevolent representations of themselves and others that are highly resistant to change, and act from the position of these representations outside full awareness [32]. In their clinical writing on borderline personality disorder, for example, Young and colleagues [32, 33] suggest that affected individuals typically alternate among mostly-maladaptive modes or ways of relating. One of these modes is the "*punative parent mode*", which is an internalization of a rejecting or punative parent that generates views of the self as devalued or unworthy. This "mode" and others conflict with an often less-dominant "*healthy adult mode*" which seeks to meet basic emotional needs. From this perspective it follows that an affected individual may be caught between some degree of wanting a pleasurable experience and having dysfunctional thoughts about themselves in relation to it (e.g. "I don't deserve it"), which would be supported by lived phenomenological experiences of internal conflict. A more interpersonally-focused manifestation can be found in Sullivan's [34] writing on what he terms the "*malevolent transformation*"; for Sullivan, this occurred when the child, having learned that his need for close relationships represents a source of pain and vulnerability, begins to mistrust others' ability to meet his needs and minimizes others' opinions.

7.6 Response to Treatment

As far as we are aware, no studies of trauma-related disorders have specifically examined anhedonia as a treatment outcome, much less distinguished between hedonic deficits (HD) and negative affective interference (NAI). Accordingly, this represents a significant future research agenda. From a psychotherapeutic standpoint, Frewen, Lanius, and their colleagues [1, 21, 27] have suggested that persons with HD in the absence of NAI may respond adequately to behavioural activation and motivation enhancement strategies that encourage greater engagement and absorptive experience in pleasurable stimuli and events. However, the latter are considered potentially harmful to persons with NAI, exacerbating their tendency toward intrusive re-experiencing of traumatic events and negative social emotions such as shame in the pursuit of positive experiences. In comparison, with individuals exhibiting prominent NAI we recommend therapists encourage greater positive affect tolerance and self-compassion. For example "metta"/"lovingkindness" meditations that gently encourage practitioners to relate to themselves with compassion and good will have been frequently of good use in our own clinical experience (see also [35]). At the PTSD treatment clinic with which Frewen and Lanius [27] are affiliated, which incorporates practices of mindfulness and metta meditations as part of standard practice, preliminary results with the HDIS administered over the course of treatment and follow-up have also shown increases in positive affect and strong decreases in both HD and NAI. Such results have been accompanied by reduced PTSD symptom severity as assessed by self-report and clinician interviews as well as other positive clinical outcomes.

7.7 Future Directions: Anhedonia and Trauma-Related Disorders

Future studies should seek to expand upon the results outlined in the present chapter in investigating the clinical and theoretical significance of differentiating between hedonic deficits (HD) in the company versus absence of negative affective interference (NAI) in trauma-related disorders. At the present time it is clear that most research has examined anhedonia in individuals with PTSD. The new DSM-5 criteria [2] parse negative affective responses to trauma (e.g. anger, guilt, and shame) from emotional numbing into separate symptom clusters. In this chapter, we suggested that the construct of NAI may represent a clinically useful way to understand the dynamic interaction between these two symptom clusters. *Perceived Causal Relations*, a psychological assessment methodology developed by our group [36, 37], may also be one means of investigating such dynamic interactions from the patient's own experiential point of view. Furthermore, a dissociative subtype of PTSD has

recently been established [2, 38, 39], increasing the theoretical relevance of investigations into blunted emotional reactivity (i.e., hedonic deficits) commonly associated with dissociative states of depersonalization and derealization.

Beyond the study of PTSD, it will be important to investigate whether NAI plays a role in other trauma-related disorders where anhedonia is a prominent clinical feature, including schizophrenia, depression, substance abuse, and borderline personality disorder (BPD). In fact pilot data from our research group suggests that HD and NAI may be useful transdiagnostic constructs, and much more research regarding clinical presentations in trauma-related disorders other than PTSD is needed. Referring to BPD as another paradigmatic trauma-related disorder, Marissen, Arnold, and Franken [40] investigated relationships among anhedonia, impulsivity and trait BPD symptoms in individuals with BPD and healthy controls. They found that individuals with BPD reported high levels of anhedonia, and that these symptoms were related to dysfunctional impulsivity in this clinical group; conversely, in healthy controls, anhedonia was related to withdrawal behaviors. Anhedonia was positively correlated with dimensional ratings of BPD, and anhedonia, impulsivity, and positive and negative affect ratings together predicted 72 % of the variance in BPD symptoms. These data even suggest that individuals with BPD may engage in potentially harmful behaviors to escape anhedonia. One possible research direction will be to examine associations between HD and NAI and self-harm, which is often understood as an attempted escape from negative affect and/or an emotionally numb or "shut-down" affective state [e.g., 41, 42]. An analysis of NAI may help to elucidate situational factors associated with both of these common precipitants to self-harm.

Another avenue for further investigation, which has been taken up in part by our research group, involves examining startle reactivity. Exaggerated eyeblink startle response and decreased conductance habituation to startle sounds have been identified in PTSD samples (for a review, see [43]) although there is comparably less work that examines positive and negative images in startle paradigms in trauma-exposed samples (for exception, with male veterans with PTSD, see [44]). Viewing of positively valenced slides (e.g. erotic images, family scenes, or food) in particular is generally found to decrease startle reactivity [45]. However, if they are instead processed as aversive, particularly for survivors of childhood sexual abuse, startle response may be enhanced rather than downregulated. Relevant to the present discussion are Nock and Mendes' [42] findings that adolescents who engage in self-harm show enhanced physiological arousal during a stressful lab task; these data complement our own pilot results suggesting that NAI is related to enhanced arousal ratings in response to emotional images. In addition, Limberg, Barnow, Freyberger, and Hamm [46] found that individuals with BPD rated pleasant scripts presented during an affect modulated startle paradigm as more unpleasant than controls. Moreover, these researchers' analyses of event-related physiological responses excluded erotic scripts from their analyses due to their reportedly finding that such stimuli were rated highly unpleasant by individuals with BPD in comparison with controls, consistent with the concept of NAI.

7.8 Summary and Conclusion

In this chapter we reviewed research investigating anhedonia in trauma-related disorders, most notably Posttraumatic Stress Disorder (PTSD). We argued for the clinical significance of distinguishing a particular form of anhedonia labelled "negative affective interference" (NAI) from anhedonia as traditionally defined, referring to the inability to experience positive affect in the context of stimuli and situations that should normally provoke it (hedonic deficit [HD]). NAI in particular is expressed as negative affective responses to positive events, a clinical phenomenon we have found to be prevalent in complexly traumatized people, likely with an etiology particularly associated with early childhood trauma exposure. Preliminary results suggest that NAI may be differentiable from HD in terms of functional neural expression, psychophysiology, and treatment response as reviewed herein, although much more research remains to be done.

Appendix: Hedonic Deficit & Interference Scale (HDIS)

Please answer each question in terms of **how true** or **frequent** it has been of your experience **over the past month**. When answering each question, please give a number **from 0 (zero) to 10 (ten)**, where **"0"** indicates the statement has been **"Not At All or Never True"**, **"5"** indicates the statement has been **"Moderately True or Moderately Frequent"**, and **"10"** indicates the statement has been **"Completely True or *Very* Frequent" (Always or Almost Always the Case) of your experience over the past month**. There are no right or wrong answers.

The first set of questions ask about how often you have experienced different positive emotions and positive feelings over the past month. *Over the past month,* would you say that you have experienced…

1. … feelings of true happiness, cheerfulness, and joy? _____
2. … feelings of physical or sensory enjoyment, like pleasure, euphoria, and 'bliss'? _____
3. … feelings of interest, enthusiasm, and excitement? _____
4. … pleasant and serene feelings like relaxation and peacefulness? _____
5. … feelings of inner contentment, self-esteem, and pride? _____

The next set of questions ask to what extent you think you CAN'T, that is, you are NOT able to experience positive feelings in general.

Would you say that you *can't* (you are *not able to*) experience… *even when you try, and even when good things in your life happen?* (Remember: 0 indicates this is NOT TRUE, that you CAN experience positive feelings, and 10 indicates this IS TRUE, you CAN'T experience positive feelings)

6. feelings of true happiness, cheerfulness, and joy, …*?* _____
7. feelings of physical or sensory enjoyment, like pleasure, euphoria, and 'bliss', …*?* _____

8. feelings of interest, enthusiasm, and excitement, …*?* _____
9. pleasant and serene feelings like relaxation and peacefulness, …*?* _____
10. feelings of inner contentment, self-esteem and pride, …*?* _____

For some people, negative feelings tend to get in the way of their experiencing positive feelings. For these people, when something positive happens in their life, they tend to experience negative feelings. The next set of questions ask about the extent to which you experience various negative feelings when positive events happen in your life. When positive events happen in your life: (examples of positive events include social praise, getting a reward or gift, or physical/sensory pleasures like taking a bath, walking on the beach)…

11. do you feel 'numb', like you *can't feel* emotions and feelings? _____
12. do you feel *'out-of-touch'* with your emotional response, as if you are detached, separated, or disconnected from your feelings? _____
13. do you experience anxiety (nervousness, agitation)? _____
14. do you experience fear or panic? _____
15. do you experience guilt (for example, *wondering if* you are worthy or deserving of)? _____
16. do you experience self-criticalness? (for example, *clearly feeling* unworthy, undeserving of)? _____
17. do you experience shame and humiliation? _____
18. do you experience disgust (strong aversion, 'grossness', like feeling 'sick to your stomach')? _____
19. do you feel emotional emptiness, or feel empty inside? _____
20. do you feel lifeless inside, as if there's nothing positive there *to feel*? _____
21. do you purposely attempt to suppress positive emotions and feelings? (trying to 'stop', 'push away', 'turn off', 'not feel', 'distance yourself from' positive feelings, e.g., by distracting yourself, denying what is happening, or controlling your feelings)? _____

References

1. Frewen PA, Dean JA, Lanius RA. Assessment of anhedonia in psychological trauma: development of the Hedonic Deficit and Interference Scale. Eur J Psychotraumatol. 2012;3:8585.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: Authors; 2013.
3. Kashdan TB, Elhai JD, Frueh BC. Anhedonia and emotional numbing in combat veterans with PTSD. Behav Res Ther. 2006;44:457–67.
4. Kashdan TB, Elhai JD, Frueh BC. Anhedonia, emotional numbing, and symptom overreporting in male veterans with PTSD. Pers Individ Differ. 2007;43:725–35.
5. Feeny NC, Zoellner LA, Fitzgibbons LA, Foa EB. Exploring the roles of emotional numbing, depression, and dissociation in PTSD. J Trauma Stress. 2000;13:489–98.
6. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry. 2010;67:902–11.
7. Buck B, Lysaker PH. Anhedonia in schizophrenia: a brief history and overview of the construct. In: Ritsner MS, editor. Anhedonia: a comprehensive handbook, vol 2. Neuropsychiatric and physical disorders. Dordrecht: Springer; 2013.

8. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55.
9. McCabe C. Neural correlates of anhedonia as a trait marker for depression. In: Ritsner MS, editor. Anhedonia: a comprehensive handbook, vol 2. Neuropsychiatric and physical disorders. Dordrecht: Springer; 2013.
10. Spahic-Mihajlovic A, Crayton JW, Neafsey EJ. Selective numbing and hyperarousal in male and female Bosnian refugees with PTSD. J Anxiety Disord. 2005;19:383–402.
11. Elman I, Ariely D, Mazar N, et al. Probing reward function in post-traumatic stress disorder with beautiful facial images. Psychiatry Res. 2005;135:179–83.
12. Hopper JW, Pitman RK, Su Z, et al. Probing reward function in posttraumatic stress disorder: expectancy and satisfaction with monetary gains and losses. J Psychiatr Res. 2008;42:802–7.
13. Elman I, Lowen S, Frederick BB, et al. Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. Biol Psychiatry. 2009;66:1083–90.
14. Jatzko A, Schmitt A, Demirakca T, et al. Disturbance in the neural circuitry underlying positive emotional processing in post–traumatic stress disorder (PTSD). Eur Arch Psychiatry Clin Neurosci. 2006;256:112–4.
15. Meehl PE. Hedonic capacity: some conjectures. Bull Menninger Clin. 1975;39:295–307.
16. Nelis D, Quoidbach J, Hansenne M. Measuring individual differences in emotion regulation: the emotion regulation profile-revised (ERP-R). Psychol Belg. 2011;51:49–91.
17. Quoidbach J, Berry EV, Hansenne M, Mikolajczak M. Positive emotion regulation and well-being: comparing the impact of eight savoring and dampening strategies. Pers Individ Differ. 2010;49:368–73.
18. Orsillo SM, Batten SV, Plumb JC, et al. An experimental study of emotional responding in women with posttraumatic stress disorder related to interpersonal violence. J Trauma Stress. 2004;17:241–8.
19. Frewen PA, Dozois DJA, Neufeld RWJ, et al. Social emotions and emotional valence during imagery in women with PTSD: affective and neural correlates. Psychol Trauma Theory Res Pract Policy. 2010;2:145–57.
20. Armony JL, Corbo V, Clément M-H, Brunet A. Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. Am J Psychiatry. 2005;162:1961–3.
21. Frewen PA, Dozois DJA, Lanius RA. Assessment of anhedonia in psychological trauma: psychometric and neuroimaging perspectives. Eur J Psychotraumatol. 2012;3:8587.
22. Fawcett J, Clark DC, Scheftner WA, Gibbons RD. Assessing anhedonia in psychiatric patients: the pleasure scale. Arch Gen Psychiatry. 1983;40:79–84.
23. Schacter DL, Addis DR. On the nature of medial temporal lobe contributions to the constructive simulation of future events. Philos Trans R Soc B Biol Sci. 2009;364:1245–53.
24. Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. Annu Rev Neurosci. 2009;32:413–34.
25. Scholz J, Triantafyllou C, Whitfield-Gabrieli S, et al. Distinct regions of right temporo-parietal junction are selective for theory of mind and exogenous attention. PLoS One. 2009;4:e4869.
26. Snaith RP, Hamilton M, Morley S, et al. A scale for the assessment of hedonic tone: the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995;167:99–103.
27. Frewen PA, Lanius RA. Healing the traumatized self: consciousness, neuroscience, treatment. New York: Norton Publishing Company; 2013.
28. Russell JA. A circumplex model of affect. J Pers Soc Psychol. 1980;39:1161–78.
29. Yik M, Russell JA, Steiger JH. A 12-point circumplex structure of core affect. Emotion. 2011;11:705–31.
30. Weems CF, Saltzman KM, Reiss AL, Carrlon VG. A prospective test of the association between hyperarousal and emotional numbing in youth with a history of traumatic stress. J Clin Child Adolesc Psychol. 2003;32:166–71.
31. van der Kolk BA. The compulsion to repeat the trauma: re-enactment, revictimization, and masochism. Psychiatr Clin N Am. 1989;12:389–411.

32. Young JE, Klosko JS, Weishaar ME. Schema therapy: a practitioner's guide. New York: Guilford Press; 2003.
33. Kellogg SH, Young JE. Schema therapy for borderline personality disorder. J Clin Psychol. 2006;62:445–58.
34. Cooper AB, Guynn RW. Transcription of fragments of lectures in 1948 by Harry Stack Sullivan. Psychiatry Interpers Biol Process. 2006;69:101–6.
35. Hoffmann SG, Grossman P, Hinton DE. Loving-kindness and compassion meditation: potential for psychological interventions. Clin Psychol Rev. 2011;31:1126–32.
36. Frewen PA, Allen SA, Lanius RA, Neufeld RWJ. Measuring perceived symptom causal relations: examination with posttraumatic stress, depression, and anxiety symptomatology. Assessment. 2012;19:480–93.
37. Frewen PA, Schmittman VD, Bringann LF, Borsboom D. Perceived causal relations between anxiety, posttraumatic stress and depression: extension to moderation, mediation, and network analysis. Eur J Psychotraumatol. 2013;4:20656.
38. Lanius RA, Vermetten E, Loewenstein RJ, Brand B, Schmahl C, Bremner JD, Spiegel D. Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. Am J Psychiatry. 2010;167:640–7.
39. Lanius RA, Brand B, Vermetten E, Frewen PA, Spiegel D. The dissociative subtype of post-traumatic stress disorder: rationale, clinical and neurobiological evidence, and implications. Depress Anxiety. 2012;29:701–8.
40. Marissen MA, Arnold N, Franken IH. Anhedonia in borderline personality disorder and its relation to symptoms of impulsivity. Psychopathology. 2012;45:179–84.
41. Nock M, Prinstein MJ. Contextual features and behavioral functions of self-mutilation among adolescents. J Abnorm Psychol. 2005;114:140–6.
42. Nock M, Mendes WB. Physiological arousal, distress tolerance, and social problem solving deficits among adolescent self-injurers. J Consult Clin Psychol. 2008;76:28–38.
43. Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. Psychol Bull. 2007;133:725–46.
44. Miller MW, Litz BT. Emotional-processing in posttraumatic stress disorder II: startle reflex modulation during picture processing. J Abnorm Psychol. 2004;113:451–63.
45. Bradley MM, Codispoti M, Cuthbert BN, Lang PJ. Emotion and motivation I: defensive and appetitive reactions in picture processing. Emotion. 2001;3:276–98.
46. Limberg A, Barnow S, Freyberger HJ, Hamm AO. Emotional vulnerability in borderline personality disorder is cue specific and modulated by traumatization. Biol Psychiatry. 2011;69:574–82.

Chapter 8
Anhedonia and Anorexia Nervosa: A Neurocognitive Perspective

Charlotte Keating and Susan L. Rossell

Abstract Individuals with a diagnosis of anorexia nervosa (AN) persistently engage in behaviors aimed to reduce their weight, which leads to severe underweight status, and death in up to 20 % of cases. Theoretical models applied in seminal investigations of the etiology of the disorder have focused on various constructs, including anhedonia – the reduced capacity to experience pleasure or reward. Anhedonia has been utilized as a model for multiple symptoms in AN including; food, i.e., the reduced capacity to experience reward associated with palatable foods, social impairments, i.e., reduced capacity to experience pleasure or reward from social interactions and exercise reward, i.e., excessive exercise, aimed to compensate for an anhedonic and dysphoric mood state. These symptom domains have been researched via various modalities including; behavioral and neuroimaging investigations. While there is an established literature on taste reward processing in AN, body image and particularly exercise and social reward have received comparatively less attention. Up to 80 % of individuals with AN reportedly excessively exercise, and social impairments are considered both causal and maintaining in the illness. Despite the relevance of reward and reinforcement in maintaining the illness, a unified model for reward processing in AN is yet to be agreed upon. The purpose of this chapter is to discuss the relevance of anhedonia as an explanatory framework for symptoms of AN.

Keywords Anorexia nervosa • Anhedonia • Reward • Motivation • Social cognition • Food • Exercise • Neuroimaging • Orbitofrontal cortex • Anterior cingulate cortex • Striatum • Insula

C. Keating (✉) • S.L. Rossell
Brain and Psychological Sciences Research Centre (BPsyC), Swinburne University of Technology, Melbourne, Australia

Monash Alfred Psychiatry Research Centre, Melbourne, Australia
e-mail: ckeating@swin.edu.au; charlottekeating1@gmail.com; srossell@srossell.com

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_8,

Abbreviations

ACC	Anterior cingulate cortex
AN	Anorexia nervosa
BOLD	Blood oxygen level dependent
DLPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
HC	Healthy control(s)
OFC	Orbitofrontal cortex
REC AN	Recovered anorexia nervosa

8.1 Introduction

Anorexia nervosa (AN) is characterised by a fear of weight gain, food restriction and a disturbance in the way in which one's body weight and shape are experienced. Individuals with AN often resist or refuse treatment [1] and have the highest mortality rate of any psychiatric illness. Up to 10 % of individuals with AN will die as a direct result of the disorder [2]. Although Family-Based Treatment (FBT) has some evidence for those patients who are young (<19 years) and have relatively short duration of illness (<3 years) [3], it is generally agreed upon, that there are few treatments which have a convincing evidence base for AN [4].

Associated features of AN include: social withdrawal, depressive symptoms and diminished interest in sex [5]. Collectively, these features imply involvement of the reward system [5]. Indeed, characteristic reinforcements, even those necessary for survival (e.g., food) have impaired salience for individuals with AN [4]. Notwithstanding the multi-factorial nature of AN [6], research over several decades has revealed impairments in the reward system in individuals in the acute (AN) and recovered phases (REC AN) of the illness when compared to healthy controls (HCs) [4, 7–10]. This suggests that the reward/motivation system may be a biomarker for the illness [4]. Despite convincing evidence for alterations in the reward system in AN, including in response to e.g., food and body image processing tasks [4, 6, 7, 9, 11] the relevance of these alterations to treatment have been challenging to translate in AN [6]. We, and others, have suggested that the lack of clinical translation may be partly due to models of reward in AN, which overlook the true complexity of patients' experiences of conventionally rewarding stimuli [6]. This paper presents a theoretically driven discussion of the relevance of anhedonia to AN. In this regard, we have presented a synthesis of literature which illustrates the relationship between anhedonia and specific symptoms in AN.

8.2 Anhedonia: A Model of Taste Hedonics in Anorexia Nervosa

Anhedonia is the reduced capacity to experience pleasure or reward [5] and is the most common explanation for altered experiences of rewarding stimuli for individuals with AN [6]. Anhedonia implies that patients with AN have reduced motivation for seeking out particular stimuli (e.g., food) as they are not greatly pleasurable or reinforcing. Anhedonia operationalizes rewarding or pleasurable experiences from the healthy control's point of view [6]. That is, food is a pleasurable stimulus. We, and others, have proposed that this conventional definition of reward is in opposition to what is rewarding or motivating in AN [6, 12].

Typically, for a HC, eating a meal is a pleasurable experience. For an individual with AN, however, rather than a pleasant experience, having to eat a meal is considered anxiety provoking, aversive [6, 13], and even punishing [14]. In spite of this, research over the past decade has employed taste hedonics to investigate mechanisms underpinning food restriction in AN [6]. Typically, these studies involve viewing or tasting food related stimuli of different calorie contents and categories (i.e., savory, sweet or diary), where individuals rate both intensity and pleasantness of the stimuli. Results of such studies tend to show that individuals in the acute stage of the illness (and REC AN) report reduced preferences for glucose and diary solutions [15, 16], when compared with HCs. These outcomes have originally been interpreted to reflect that individuals with AN (and REC AN) have a reduced capacity to experience pleasure or reward compared with healthy controls (HCs).

In contrast, Eiber et al. [15], demonstrated that individuals with eating disorders (AN subtypes and Bulimia Nervosa) were able to rate the intensity of a sucrose solution (correctly identify its hedonic nature); however, they preferred the stimuli less when they were required to ingest the sucrose (condition 1) compared to greater pleasantness ratings when they were required to taste and then discard/spit out the sucrose (condition 2). It was concluded that, because preference ratings dropped when individuals were required to ingest the calorie-containing solution (condition 2), that this reflected a fear of weight gain associated with calories in the sucrose solution [15]. That is, rather than the inability to experience pleasure, individuals may experience fear in relation to ingesting the stimuli which biased their pleasantness ratings. These results therefore question whether anhedonia can explain complex, cognitive aspects of experiences (including fear) related to food [6, 14, 15].

One of the earliest neuroimaging investigations in AN also supports that fear or anxiety related to food may bias pleasantness ratings of traditionally rewarding stimuli. For example, individuals with AN and healthy controls (HCs) were required to view stimuli (chocolate milkshake and water) for 5 min via videotape, during functional magnetic resonance imaging (fMRI). Results of the study demonstrated elevated activation of the anterior cingulate cortex (ACC), insula and striatum in response to chocolate (versus water contrasts) for individuals with AN compared

with HCs. Furthermore, when asked to imagine that they were drinking the chocolate milkshake, individuals with AN reported significantly greater anxiety (via visual analog scale) when compared with the HCs. Although there were no clinically significant correlations between subjective anxiety ratings and areas of BOLD activation in response to food stimuli, it was concluded that these outcomes reflect calorie related fear for individuals with AN [17]. Taken together, behavior (e.g., [15]) and neuroimaging studies [17] suggest that, rather than a reduced capacity to experience reward associated with food stimuli (anhedonia), individuals with an eating disorder including AN (or REC AN) experience calorie related fear, which may bias (and reduce) their pleasantness ratings attributed to typically palatable stimuli.

Results from multiple taste hedonic studies also consistently show that individuals with AN (and REC AN) tend to report reduced preferences toward higher calorie (palatable stimuli) versus lower calorie stimuli, when compared with HCs, again, suggesting that a fear of weight gain related to the calories contained in the stimuli influences preferences toward food stimuli [14].

In sum, a relatively consistent finding across the taste hedonic literature is that individuals with AN (or REC AN) accurately identify and rate the intensity of taste-stimuli, nevertheless, they do not find it pleasurable, or like it [6]. This literature suggests that reduced preferences toward hedonic stimuli are unlikely to better accounted for by perception based abnormalities [6]. These findings demonstrate a clear role for 'calorie fear' influencing pleasantness ratings of otherwise palatable food. Anhedonia thus, has limited utility in explaining the experience of food in AN.

8.3 'Liking' and 'Wanting,' Palatable Stimuli: Dissociable Components of Reward

More recently, there has been a shift in the reward processing literature, generally, to the investigation of more complex aspects related to the construct of reward. Specifically, Berridge, Robinson and others [18], have developed a model of reward in animals. The model is called, Incentive Salience Attribution. At its core: Incentive Salience Attribution highlights the importance of the motivational value of a stimuli, as distinct from its likability. The model has two components, 'liking' and 'wanting.' Liking reflects the capacity to identify and rate the hedonic nature of stimuli, wanting on the other hand, represents the motivational value of the stimuli (incentive salience). Wanting has both explicit and implicit components. According to this model, both liking and wanting are necessary for the full experience of reward [18]. When applied to AN, it has been suggested that although individuals are able to identify the hedonic nature of stimuli ('like' it) they do not 'want' or feel motivated for typical or traditional rewards, when compared with HCs [6].

Recently, Incentive Salience Attribution has been empirically tested with respect to individuals with current AN (AN-C) AN weight restored (AN-W), REC AN and

HC [19]. Participants were required to rate how much they 'liked' and 'wanted' stimuli that depicted 16 pictures food of different categories (savory and sweet) and calories (low and high). Overall, results revealed that mean ratings of explicit liking were significantly greater for the sweet food category than for the savory food category, for all participants. Individuals with AN-C, demonstrated lower preferences (reduced 'liking') for high relative to low calorie stimuli, compared with HCs. The same pattern was observed for ratings of 'wanting': ratings of explicit wanting were significantly greater for the low-calorie-food category than for the high-calorie-food category, for all participants. Post hoc analyses revealed that AN-C and the AN-W groups explicitly wanted high-calorie foods less than did the HCs [19]. These outcomes are broadly consistent with previous research on taste hedonics in AN, such that 'liking' and motivation toward food in eating disorders (current or past diagnosis) are influenced by the calories perceived (in this case) to be contained in the food stimuli.

Implicit 'wanting' was measured via response time to questions asking individuals to select as quickly as they could between two pairs of stimuli that were presented from different categories (sweet or savory) [19]. Individuals with AN-C and AN-W showed reduced response time toward lower calorie compared with higher calorie stimuli pairs, when compared with HCs. For implicit "wanting," results revealed that AN-C and AN-W implicitly "wanted" high-calorie foods significantly less than did the HCs [19]. The AN-C group also implicitly "wanted" the high-calorie foods significantly less than did the AN-R participants [19]. For low-calorie foods, results revealed significantly greater implicit "wanting" in the AN-C and AN-W groups than in the HC group. A significant difference between the AN-C and AN-R groups was also found, with the AN-C group demonstrating significantly greater "wanting" for low-calorie foods than the AN-R group [19].

Outcomes from this study supports the hypothesis that 'liking' and 'wanting' for traditionally rewarding stimuli (food) are two separate psychological processes that likely contribute to aberrant eating behaviors in individuals with AN [19]. Consistent with the application [6] of Incentive Salience Attribution Theory, the results suggest that individuals experiencing the psychopathological symptoms of AN (whether current or weight restored) may not have difficulties experiencing the hedonic (liking) properties of rewarding food, but rather show a reduced motivation ('wanting') to consume energy-dense foods, and instead exhibit a greater motivational drive (implicit "wanting") to consume low-calorie foods [19]. These findings also support that individuals with AN (current, weight restored or recovered) possess an intact ability to perceive the likeable (hedonic) component of the stimuli. Consistent with these findings, it would seem that the utility of anhedonia is limited in accounting for differential drives toward low versus high calorie stimuli.

Several neuroimaging investigations have explored food related reward in AN. For example, in a recent study in REC AN and HCs, BOLD response to a rewarding i.e., sight and taste of chocolate, and aversive stimuli, i.e., sight and taste of mouldy strawberries were measured during fMRI [4]. There were no group differences in

ratings of pleasantness (liking), wanting, or intensity, of the stimuli presented, which is inconsistent with other reports (e.g., [19]). The difference in pleasantness outcomes between the studies, may reflect individuals' responding as they think they 'should/ought to' rather than how they actually feel. Greater BOLD response in the ventral striatum, cingulate cortex, occipital cortex was revealed in response to the sight and taste of chocolate in individuals with REC AN compared with HCs [4]. In the aversive condition (mouldy strawberries), greater BOLD response was revealed in the caudate, ACC, insula and occipital cortex in REC AN compared with HCs. There were no correlations between BOLD responses and subjective ratings for either group. It was concluded that greater BOLD response to rewarding and aversive food stimuli in REC AN suggests hyperactivity or greater salience attribution for food stimuli in REC AN [4].

The absence of a significant correlation between subjective (self-reported pleasantness) and objective (BOLD response) measures in response to the food related stimuli, is relatively common of neuroimaging literature in AN. The lack of such a relationship makes it difficult to discern the clinical significance of hyperactive neurocircuits to food stimuli in REC AN. One hypothesis is that individuals with REC AN (and AN) engage cognitive strategies to override their desire for otherwise palatable foods [19]. This explanation is consistent with areas of activation demonstrated in response to both conditions of the task e.g., cingulate cortex during the reward condition, and the dorsolateral prefrontal cortex and ACC in the aversive condition [4]. This interpretation by Cowdrey et al. [19] is also indirectly supported by a recent study which found greater BOLD response in regions involved in rumination and cognitive and emotional regulation in restricting-type AN participants, than in binge-eating/purge-type AN participants [20]. Inconsistencies between the two studies likely owed to different food-presentation paradigms involved, and differences in illness versus recovered states of the study participants. Given the consistency with which calorie content influences preference ratings of individuals with AN toward palatable stimuli, future studies investigating reward (and aversion) will need to control for organoleptic level differences between stimuli conditions [21].

Individuals with AN tend to report that, although individuals can identify the 'likeable' nature of palatable stimuli, they do not 'want' it in the same way that HCs do. Behavioral evidence in particular [19], adds to support to the hypothesis that individuals with AN (and REC AN) experience impaired motivation (wanting) toward typically palatable stimuli [6]. Furthermore, hyperactive BOLD responses of various regions of the brain to food stimuli, regardless of its valence (e.g., rewarding or aversive), suggests impaired neural processing of food stimuli [4]. In the absence of a relationship between neural and subjective responses to stimuli, however, it remains to be determined as to whether this owes to a cognitive response style (reflecting how individuals think they should/ought respond) or other illness related processes.

8.4 Body Image Reward in Anorexia Nervosa

The reward system has also been investigated in terms of its involvement in body image processing. In a recent neuroimaging investigation, individuals with AN and HCs were required to view canonical female bodies of different weights (overweight, underweight and normal weight) as if they were of their own self, and then provide a preference rating for their experience of the images. Typically, from a HC point of view, it would be expected that viewing the normal weight body image as if it was of their own self, would be rated as the preferred body image. Indeed, for HCs viewing the normal weight image as if it was of their own self, produced a BOLD response in the ventral striatum which correlated with pleasantness ratings [7]. Conversely, for individuals with AN, viewing the underweight body image as if it was of their own self, produced activation in the same ventral striatal region, which similarly correlated with pleasantness ratings [7]. The fact that individuals with AN demonstrated preference for, and activation in response to a stimuli that is otherwise aversive or punishing to a HC [6], provides clear evidence that individuals with AN do experience reward, as opposed to anhedonia, in relation to a key symptom, body image.

There are numerous neuroimaging investigations of body image in AN. This body of research has provided evidence of neurocircuitry involved in processing body image in AN, however, these studies did not specifically intend on, or measure whether the processing of body images (as if they were of the self, or passive viewing of the images) was a pleasurable (or aversive) experience for participants. Thus, while providing key evidence regarding neurocircuitry that is involved in processing of body image, the relevance of reward to this experience was not assessed, and as such, commenting on the utility of a reward processing model such as anhedonia, in relation to these studies, would be speculative.

8.5 Does Exercise Alleviate an Anhedonic and Dysphoric Mood State?

Up to 80 % of individuals with AN are reported to engage in excessive exercise, despite starvation [22], which has been hypothesised to assist individuals in alleviating an anhedonic and dysphoric mood state [22]. Results from early behavioural studies show that individuals with AN experience greater physical anhedonia than those with other eating disorders [22], which has been interpreted as consistent with an explanation of anhedonia, that is, reduced reward from physical sensations.

Nevertheless, the physiological sequalae of exercise (and self-starvation) involves stimulation and secretion of dopamine (DA) [23]. In this context, it has been suggested that individuals who engage in self-starvation and excessive

exercise become conditioned to the initial experience of reward associated with these behaviors. Individuals with AN demonstrate levels of corticotropin releasing factor (CRF) in the order of 170 % of normal [23]. In animal models, it has been revealed that CRF administration can lead to a reduction in feeding [24]. The physiological consequence of upregulated CRF (or corticotropin releasing hormone, CRH) levels is the downstream stimulation and secretion of cortisol from the adrenal glands. This leads to a state of hypercortisolism which is also known to cause a loss of body weight [23]. Chronic self-starvation leads to increased HPA activity and high blood levels of cortisol. Glucocorticoids have been proposed to cause euphoria and dependence in humans [25] because adrenocortical hormones lead to the stimulation and secretion of mesolimbic DA neurons in the brain, thus enhancing the reward value of relevant experiences by increasing the release of DA in the terminals of these neurons [23].

Bergh and Sodersten [23] suggest that in the initial phase of the illness, individuals experience high levels of stress (which manifest as elevated cortisol concentrations) which stimulate DA release, leaving the individual with AN, in this state, particularly prone to conditioning [23]. In this state, an initially neutral stimulus is likely to get coupled to the primary reinforcer (the mesolimbic DA neurons). Hence, self-starvation is initially rewarding and subsequently controlled by conditioning to previously neutral stimuli [23]. There are no 'real time' investigations of the role of the reward system in excessive exercise in AN, per se. Nevertheless, it can be deduced that the physiological sequalae of excessive exercise (and self-starvation) is upregulation of the HPA axis, and stimulation and secretion of DA. While this would seem to support that such behaviours are indeed rewarding and reinforcing for individuals with AN, it does not discount the possibility that the drive or motivation for these behaviors is initially underpinned by a desire to alleviate an anhedonic and dysphoric mood state. Further research is required to disentangle the relationship between anhedonia and the apparent pathological drive for behaviors (e.g., excessive exercise) which are, by virtue of their physiological consequences, highly rewarding and reinforcing in AN [14].

8.6 Social Anhedonia in Anorexia Nervosa

An associated feature of AN is social withdrawal. Social impairments are considered causal and maintaining in AN [26] and manifest as pervasive interpersonal difficulties in the sharing of friendships, relationships and family interactions [26–28]. Social maladjustment persists even after behavioral symptoms of the disorder have resolved [29] suggesting they may also be a trait marker of the illness [5]. Anhedonia is also proposed as one etiological theory for social withdrawal. Social anhedonia describes that individuals with AN, have a reduced capacity to experience social pleasure or reward [5, 13], implying involvement of the brain reward system, and that social interactions are neither greatly pleasurable nor reinforcing for patients with AN [5]. Social reward, indeed social impairments generally

have received less investigation relative to other symptoms of AN. In support of social anhedonia, previous research shows that individuals with AN demonstrate higher self-report levels of social anhedonia (revised social anhedonia scale) compared with HCs [5]. Experimental studies also show that individuals with AN demonstrate reduced markers of positive affect in response to pleasant; pictures of faces [30] or film clips depicting social scenarios [31]. Despite this, other studies have not shown any difference (BOLD activation) in the way that REC AN process pictures of emotional faces (fear versus happy), when compared with HCs [32].

The relationship between social reward and attention has also been investigated [33]. The reward value (implicit and explicit) of social stimuli for females with and without a diagnosis of AN was investigated via an econometric choice task and eye gaze patterns [33]. Results of the study revealed that, for explicit ratings of attractiveness, the reward value of viewing bodies varied inversely with observed body weight for women with AN, however not for control women [33]. Furthermore, women with AN, did not find female faces rewarding and avoided looking at both the face and eyes, unlike HC women. While it could be considered that avoidance of face and eyes was driven by selective attention for body weight, it was noted that avoidance of face and eyes by individuals with AN was independent of observed body weight [33]. Hence it was interpreted that body weight was not a factor that biased whether women focused on facial features. It is also possible, however, that a general preoccupation with the weight (irrespective of low or high weight) could have driven attention away from the face and eyes for individuals with a diagnosis of AN.

The limited number of investigations of social processing in AN, and the use of the use of primarily behavioural (including self-report) paradigms limits the capacity to draw inferences about more complex cognitions that may underlie the experience of social stimuli. Despite the impact of social impairments on causation and illness maintenance in AN [26], little is known about how individuals experience social interactions [5, 26] and there are few etiological models to guide the development of interventions targeting this domain [26]. Similar to other symptoms of AN, anhedonia may not account for patients' more complex cognitions related to social experiences. Nevertheless, social impairments in AN represent an under-represented area of investigation.

8.7 Conclusions and Future Directions

AN is currently characterized as an illness reflecting a fear of weight gain, refusal to maintain minimally normal body weight, and concern with weight and shape. Nevertheless, emerging psychological and biological evidence supports the relevance of reward to each of these symptoms of the illness. Until recently, anhedonia has traditionally been the accepted model for reward related to various symptoms of AN. Despite this, anhedonia appears to be too simplistic to explain more complex experiences related to the illness.

One direction for research in reward processing in AN, will be to consider definitions for reward which are consistent with what is considered rewarding to individuals with the illness. More specifically, experiences which are egosyntonic to the illness. While reward processing investigations to date have tended to focus on stimuli which are rewarding in a traditional sense (from the HC point of view), in future, greater consideration of what is rewarding from the AN point of view, may assist in the development of reward based models that better account for the complex, often paradoxical nature of what is rewarding and reinforcing in AN.

In addition to the development of models of reward which are in keeping with features of AN, characterizing the relationship between systems that have conventionally been conceptualized as relevant for processing rewarding (e.g., dopamine) or aversive (e.g., serotonin) experiences, may also be investigated in terms of their role in reward, punishment and reinforcement specific to AN. Better understanding the relationship between reinforcement based experiences and neural mechanisms underpinning these may provide scope for the development of novel neural stimulation approaches, or pharmacological treatments, for severe cases, as adjuncts to psychotherapy.

Acknowledgements CK is Research Fellow at Swinburne University of Technology. SLR is a Professorial Research Fellow at Swinburne University of Technology and Monash University.

References

1. Kaye WH, et al. Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. Trends Neurosci. 2013;36(2):110–20.
2. Pratt BM, Woolfenden SR. Interventions for preventing eating disorders in children and adolescents. Cochrane Database Syst Rev. 2002(2):CD002891.
3. Fisher CA, Hetrick SE, Rushford N. Family therapy for anorexia nervosa. Cochrane Database Syst Rev. 2010(4):CD004780.
4. Cowdrey FA, et al. Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa. Biol Psychiatry. 2011;70(8):736–43.
5. Tchanturia K, Davies H, Harrison A, Fox JR, Treasure J, Schmidt U. Altered social hedonic processing in eating disorders. Int J Eat Disord. 2012 Dec;45(8):962–9. doi: 10.1002/eat.22032.
6. Keating C, et al. Reward processing in anorexia nervosa. Neuropsychologia. 2012;50(5):567–75.
7. Fladung AK, et al. A neural signature of anorexia nervosa in the ventral striatal reward system. Am J Psychiatry. 2010;167(2):206–12.
8. Wagner A, et al. Altered reward processing in women recovered from anorexia nervosa. Am J Psychiatry. 2007;164(12):1842–9.
9. Frank GK, et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [11c]raclopride. Biol Psychiatry. 2005;58(11):908–12.
10. Frank GK, et al. Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology. 2012;37(9):2031–46.
11. Barbato G, et al. Increased dopaminergic activity in restricting-type anorexia nervosa. Psychiatry Res. 2006;142(2–3):253–5.

12. Zink CF, Weinberger DR. Cracking the moody brain: the rewards of self starvation. Nat Med. 2010;16(12):1382–3.
13. Kaye WH, Fudge JL, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. Nat Rev Neurosci. 2009;10(8):573–84.
14. Keating C. Theoretical perspective on anorexia nervosa: the conflict of reward. Neurosci Biobehav Rev. 2010;34(1):73–9.
15. Eiber R, et al. Hedonic response to sucrose solutions and the fear of weight gain in patients with eating disorders. Psychiatry Res. 2002;113(1–2):173–80.
16. Sunday SR, Halmi KA. Taste perceptions and hedonics in eating disorders. Physiol Behav. 1990;48(5):587–94.
17. Ellison Z, et al. Functional anatomy of calorie fear in anorexia nervosa. Lancet. 1998;352(9135):1192.
18. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning. Curr Opin Pharmacol. 2009;9(1):65–73.
19. Cowdrey FA, Finlayson G, Park RJ. Liking compared with wanting for high- and low-calorie foods in anorexia nervosa: aberrant food reward even after weight restoration. Am J Clin Nutr. 2013;97(3):463–70.
20. Brooks S, et al. A systematic review and meta-analysis of cognitive bias to food stimuli in people with disordered eating behaviour. Clin Psychol Rev. 2011;31(1):37–51.
21. Vicario CM, Crescentini C. Punishing food: what brain activity can tell us about the representation of food in recovered anorexia nervosa. Biol Psychiatry. 2012;71(8):e31–2; author reply e33.
22. Davis C, Woodside DB. Sensitivity to the rewarding effects of food and exercise in the eating disorders. Compr Psychiatry. 2002;43(3):189–94.
23. Bergh C, Sodersten P. Anorexia nervosa, self-starvation and the reward of stress. Nat Med. 1996;2(1):21–2.
24. Dunn AJ, Berridge CW. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? Brain Res Brain Res Rev. 1990;15(2):71–100.
25. Piazza PV, et al. Corticosterone in the range of stress-induced levels possesses reinforcing properties: implications for sensation-seeking behaviors. Proc Natl Acad Sci U S A. 1993;90(24):11738–42.
26. Treasure J, Corfield F, Cardi V.A three-phase model of the social emotional functioning in eating disorders. Eur Eat Disord Rev. 2012 Nov;20(6):431–8. doi: 10.1002/erv.2181.
27. Tiller JM, et al. Social support in patients with anorexia nervosa and bulimia nervosa. Int J Eat Disord. 1997;21(1):31–8.
28. Schmidt U, Treasure J. Anorexia nervosa: valued and visible. A cognitive-interpersonal maintenance model and its implications for research and practice. Br J Clin Psychol. 2006;45(Pt 3):343–66.
29. Yager J, Landsverk J, Edelstein CK. A 20-month follow-up study of 628 women with eating disorders, I: course and severity. Am J Psychiatry. 1987;144(9):1172–7.
30. Soussignan R, et al. Hedonic reactivity to visual and olfactory cues: rapid facial electromyographic reactions are altered in anorexia nervosa. Biol Psychol. 2011;86(3):265–72.
31. Davies H, et al. Evoked facial emotional expression and emotional experience in people with anorexia nervosa. Int J Eat Disord. 2011;44(6):531–9.
32. Cowdrey FA, et al. Neural responses to emotional faces in women recovered from anorexia nervosa. Psychiatry Res. 2012;201(3):190–5.
33. Watson KK, et al. Altered social reward and attention in anorexia nervosa. Front Psychol. 2010;1:36.

Chapter 9
Anhedonia and Negative Symptom Schizotypy

Thomas R. Kwapil, Georgina M. Gross, Charlotte A. Chun, Paul J. Silvia, and Neus Barrantes-Vidal

Abstract Current conceptualizations of schizophrenia indicate that the underlying vulnerability for the disorder is expressed across a broad continuum of impairment referred to as schizotypy. Trait-like anhedonia has long been recognized as a central component of schizophrenia and schizotypy. Our understanding of the etiology, experience, and expression of anhedonia, however, has evolved in large part due to advances in social and emotion psychology regarding the nature of pleasure, advances in the neurosciences regarding the brain mechanisms underlying hedonic capacity and experience, and the integration of measures from clinical, social, and biological psychology. Current studies have differentiated deficits in anticipatory pleasure from deficits in consummatory pleasure. The study of anhedonia has also been enhanced by the use of experience sampling research methods that expand investigations from the laboratory and the clinic to real world environments. Anhedonia appears to be a core component of the negative or deficit symptom dimension of schizotypy and schizophrenia, whereas the positive or psychotic-like dimension appears to be characterized by affective dysregulation. Furthermore, schizotypic anhedonia is differentiated from conditions such as depression, which involve episodic anhedonia combined with elevated negative affect. The present chapter presents an overview of theoretical conceptualizations of anhedonia in schizotypy, reviews cross-sectional, longitudinal, and daily life research findings, and considers issues and directions for future study of the construct.

T.R. Kwapil (✉) • G.M. Gross • C.A. Chun • P.J. Silvia
University of North Carolina at Greensboro, Greensboro, NC, USA
e-mail: t_kwapil@uncg.edu; p_silvia@uncg.edu

N. Barrantes-Vidal
University of North Carolina at Greensboro, Greensboro, NC, USA

Universitat Autònoma de Barcelona, Barcelona, Spain

Sant Pere Claver – Fundació Sanitària, Barcelona, Spain

Instituto de Salud Carlos III, CIBERSAM, Madrid, Spain

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_9,

Keywords Anhedonia • Schizotypy • Social anhedonia • Physical anhedonia • Schizophrenia • Personality disorders

Abbreviations

ESM	Experience sampling methodology
NEO-PI-R	NEO Personality Inventory-Revised
TEPS	Temporal Experience of Pleasure Scale
COMT	Catechol-O-methyltransferase
VAL	Valine
BOLD	Blood Oxygenation Level Dependent
fMRI	functional magnetic resonance imaging

9.1 Introduction and Overview

Trait-like anhedonia or deficits in the anticipation and experience of pleasure have long been recognized as central aspects of the schizophrenia spectrum. These deficits not only represent symptomatic outcomes of these disorders, but also appear to play an important role in the etiology and development of these conditions and seem to be part of the broader phenotype of schizotypy. However, our understanding of the etiology, experience, and expression of anhedonia, has developed dramatically given recent advances in social and emotion psychology regarding the nature of pleasure, advances in the neurosciences regarding the brain mechanisms underlying hedonic capacity and experience, and the integration of measures from clinical, social, and biological psychology. The present chapter provides an overview of theoretical conceptualizations of anhedonia in schizotypy, reviews cross-sectional, longitudinal, and daily life research findings, and considers issues and directions for future study of the construct. Furthermore, the chapter argues that schizotypy and schizophrenia must be conceptualized as multi-dimensional constructs and that anhedonia is a central component of the negative symptom dimension of schizotypy and schizophrenia.

9.2 Schizotypy, Schizophrenia, and Anhedonia

Despite well over 100 years of study, the exact causes of schizophrenia continue to evade researchers. However current etiological models assume that genetic and environmental factors beginning in utero initiate a pattern of neurodevelopmental risk that interacts with biopsychosocial stressors across development to leave the individual at heightened risk for the onset of schizophrenia-spectrum symptoms

and disorders [1, 2] The manifestations of this vulnerability are referred to as schizotypy, and are expressed over a dynamic continuum of severity ranging from relatively healthy or minimally impaired functioning, to abnormal but subclinical deviance, to clinically significant personality disorders, to full-blown psychosis (e.g., [3–6]). As such, schizotypic individuals are at heightened risk for developing schizophrenia-spectrum psychopathology; however, this risk does not make future disorders inevitable. In fact, only a minority of schizotypes will actually go on to develop schizophrenia; however, many others will exhibit mild schizophrenic-like deficits, symptoms, or impairment [7]. Expanding the definition of schizophrenia to a broader continuum of clinical and subclinical manifestations that captures the breadth of these symptoms provides a promising framework for understanding the etiology, expression, and treatment of schizophrenia and related disorders.

Schizotypy, and by extension schizophrenia, is a heterogenous construct in terms of etiology, expression, and trajectory. This heterogeneity appears to be captured in a multidimensional structure, with two or more underlying factors. Consistent with multidimensional models of schizophrenia, positive and negative schizotypy factors are the most reliably replicated, and cognitive disorganization, paranoia, nonconformity and other factors have been implicated as well [7, 8]. A universally agreed upon latent structure of schizotypy has not been established, however these proposed factors are consistent with the positive, negative, and disorganization symptom dimensions hypothesized to underlie schizophrenia [9–11]. Positive schizotypy is comprised of magical, suspicious, and referential thinking, and perceptual abnormalities, which are expressed as delusions and hallucinations in schizophrenia [7, 12, 13]. Negative schizotypy, on the other hand, includes flat or blunted affect, avolition (lack of motivation), alogia (poverty of thought and speech), social disinterest, and anhedonia that are expressed at increasing levels as one approaches full-blown schizophrenia spectrum disorders [7, 14]. Barrantes-Vidal et al. [15] argued that the "conceptualization and measurement of schizotypy and schizophrenia as multidimensional are essential for advancing our understanding of these constructs. Studies that treat them as homogenous often produce mixed, equivocal, or non-replicable results because these dimensions are associated with distinct etiologies, presentations, and treatment responses." (p. 50).

9.3 Schizotypic Anhedonia

Anhedonia is defined as markedly diminished interests and deficits in the experience of pleasure that have consistently been identified as a core component of negative schizotypy and schizophrenia [16, 17] Schizotypic anhedonia may be manifested in various forms, including deficits in sensory and aesthetic pleasure associated with eating, touching, feeling, sex, temperature, movement, sight, and sound (often referred to as physical anhedonia), and a lack of motivation to engage in social interactions (asociality), lack of pleasure when in social situations, and indifference towards others (known as social anhedonia). There appears to be a cognitive component of

anhedonia that includes both beliefs about diminished expectations of pleasure that impact reporting of noncurrent feelings, as well as impairment in memory processes such as encoding and retrieval that serves to maintain these impaired beliefs and expectation despite the actual experience of positive emotional states [18]. These features of schizotypic anhedonia are present in an exacerbated form among patients with schizophrenia, such that there can be markedly diminished enjoyment associated with all activities, and very low, if any, interest in or pleasure from social contact.

Ample evidence suggests that anhedonia is elevated among people with schizophrenia [19–21] nonclinical schizotypes [7, 22], and first-degree relatives of schizophrenic probands [23]. Longitudinal research has demonstrated that schizotypic anhedonia is a long-term, stable characteristic related to personality factors, as opposed to the more state-dependent anhedonia associated with clinical symptoms in other disorders such as depression [14, 24, 25]. There is mixed evidence regarding the relationship among anhedonia and the other symptoms of schizotypy and schizophrenia, likely due in part to limitations in definition and measurement [14]. However there is ample evidence to suggest that anhedonia is associated with other negative symptoms and is distinguishable from symptoms within other (non-negative) dimensions in both schizotypy and schizophrenia research (e.g., [7, 26–28]). Further, anhedonia represents diminished hedonic functioning, which is consistent with the classification of negative symptoms as deficiencies in normal functioning. Overall, there is sufficient evidence to suggest that anhedonia is a core component of the negative symptom dimension.

9.4 Social Anhedonia

Social psychologists conceptualize humans as social animals, with a basic drive for belongingness and close interpersonal relationships [29, 30]. As identified above, social anhedonia, or asociality and indifference towards others, is a form of anhedonia that is commonly distinguished from physical anhedonia in the literature. Diminished motivation to engage in social contact, and decreased pleasure experienced from doing so, are particularly striking in light of the basic human need to form strong and enduring social attachments, and to engage in frequent interpersonal interactions [31, 32]. People high in social anhedonia experience a reduced or absent drive for social contact and relationships, resulting from diminished positive affect experienced during social situations (as compared to people without social anhedonia; [33]). Social anhedonia is distinguished from social anxiety, in which avoidance is driven by social discomfort/anxiety, and from paranoia, in which avoidance is driven by a belief that others are dangerous. In both social anxiety and paranoia, reduced social interactions are driven by elevated negative affect, not by reduced positive affect or approach motivation [33, 34]. It should also be noted that social anhedonia does not refer to normative behavior such as the enjoyment of solitary activities, or personality traits such as

introversion [35]; instead, it is defined as a stable, trait-like disinterest in social contact and diminished pleasure in social settings [32].

Like anhedonia in general, social anhedonia is associated with several psychiatric disorders (e.g., schizoid personality disorder), and is conceptualized as a core component of negative schizotypy, and by extension, the negative-symptom dimension of schizophrenia [32]. Studies have consistently reported a relationship between social anhedonia and negative schizotypy (e.g., [7, 36]) and schizophrenia (e.g., [21]) and longitudinal research indicates that social anhedonia predicts the development of schizophrenia-spectrum symptoms and disorders [22, 37, 38]. Further, social anhedonia is related to poorer overall functioning [38] and may further increase risk for schizophrenia by removing the benefits of social support [22].

9.5 Contrasting Schizotypic Anhedonia with Depressive Anhedonia and Normal Personality

A natural question concerns how the anhedonia that characterizes negative schizotypy differs from other expressions of anhedonia. The most salient contrast is with depressive anhedonia, which is also characterized by heightened physical anhedonia (e.g., diminished pleasure from previously enjoyable activities) and social anhedonia (e.g., heightened solitude, social withdrawal, and social disinterest).

We argue that two major points of difference distinguish depressive anhedonia and the anhedonia characteristic of negative schizotypy. First, the anhedonia seen in depression is episodic: people show heightened anhedonia during episodes of normal dysphoria or clinical depression and then return to their prior levels of physical and social interest and enjoyment. A study by Blanchard, Horan, and Brown [24], for example, examined the time course of social anhedonia in a sample of adults with either schizophrenia, clinical depression, or no disorder. At the start, both the depression and schizophrenia groups had significantly higher levels of social anhedonia. After 1 year, however, social anhedonia had declined in the depression group but remained elevated in the schizophrenia group, a finding consistent with the view of anhedonia as a transient feature of a depressive episode. Second, depressive anhedonia is typically accompanied by the heightened negative affect typical of depression, but negative schizotypy is not. Many cross-sectional and experience-sampling studies, for example, have shown that only positive, not negative, schizotypy routinely predicts heightened negative affect (e.g., [7, 15, 38]). Instead, negative schizotypy, as one would expect, more commonly reflects diminished affect for a range of positive and negative states.

Another worthwhile contrast is between negative schizotypy and normal dimensions of personality. As one would expect, self-report measures of negative schizotypy correlate moderately with self-report measures of individual differences in normal personality traits. In a large-sample study reported by Kwapil et al. [7], 780 young adults completed the NEO-PI-R, a broad measure of the five major factors of personality, along with questionnaire measures of schizotypy which were

then formed into positive and negative factor scores. Negative schizotypy, largely characterized by anhedonia, had significant negative associations with extraversion (positive affectivity), openness to experience, and agreeableness. Note that negative schizotypy was not significantly associated with neuroticism (negative affectivity). The pattern of findings is consistent with our characterization of negative schizotypy. In contrast, positive schizotypy, which is characterized by negative affect and affective dysregulation, was positively associated with neuroticism, but unassociated with extraversion—nicely demonstrating the differentiation of positive and negative schizotypy in terms of affectively laden personality dimensions. Specifically, negative schizotypy is characterized by diminished social engagement and positive affect typical of extraversion; diminished curiosity, rich inner experience, and subtle emotional experience typical of openness; and diminished social engagement typical of agreeableness.

We should note that these findings speak against a simple interpretation of negative schizotypy as merely "high introversion," in which people display both the low positive affect and low gregariousness. Negative schizotypy has a more rounded profile of relationships with other individual differences, such as openness and agreeableness, as we have seen. Moreover, people low in normal extraversion typically show features that speak against social anhedonia. Normal introversion is linked to shyness and normal social fears, which indicate normal social interest: people who are shy and socially anxious seek social belongingness like nearly everyone else but have dysfunctional beliefs that make forming those connections stressful. In negative schizotypy, however, the high social anhedonia reflects social disinterest, in which people are unconcerned with forming normal relationships.

9.6 Historical Roots of Anhedonia in Schizotypy and Schizophrenia

The concept of anhedonia is represented in the landmark writings of Kraepelin [39] and Bleuler [40] who both identified reduced pleasure capacity as an important feature of "dementia praecox" or schizophrenia. Rado's [41] model of the development of schizophrenia included an "integrative pleasure deficiency" that was pervasive across all areas of life and included a reduced capacity for sympathy, affection, and ability to function in family or other groups. Building upon Rado's [17, 41] formulations of anhedonia (and schizotypy in general) as a genetically transmitted trait, Meehl [6, 16] developed his landmark theory of schizotypy, which included a pervasive pleasure deficit as central to schizotypy and schizophrenia. Taking issue with the severity of Rado's terminology (anhedonia literally means a complete lack of pleasure), Meehl [42] later coined the term hypohedonia, defined as an impaired disposition to experience pleasure, and a diminished effect of positive reinforcement in future learning. Despite this, the majority of the subsequent literature on the topic has maintained the use of the term anhedonia to refer to this fundamental

hedonic deficit. Meehl's later writings (e.g., [6]) diminished the role of anhedonia in his theory, despite his initial formulations identifying anhedonia as a central component of schizotypy. Specifically, he suggested that anhedonia, especially in the social domain, may be a result of secondary, polygenic factors of a continuous nature, as opposed to a core, etiological characteristic of the schizotypy taxon.

In contrast to Meehl's later revisions, subsequent research has suggested that social anhedonia is taxonic in nature [43] and is a powerful predictor of the future development of schizophrenia and related disorders [22, 38]. Overall, anhedonia, including physical, social, and other deficits in the motivation to seek out or experience pleasure, is a core component of negative schizotypy and schizophrenia, and understanding its etiology, development, and treatment is essential for elucidating the multidimensional nature of schizophrenia. Approaching the study of anhedonia using a schizotypic model captures the breadth of its manifestations, ranging from mild loss of interest and pleasure to marked and pervasive anhedonia in schizophrenia, and provides a promising framework for understanding this construct.

9.7 Current Conceptualizations and Assessment of Schizotypic Anhedonia

As noted above, historical views of schizophrenia assumed that patients broadly experienced diminished pleasure. However, beginning in the 1980s and 1990s, a number of studies began to challenge some of the basic assumptions regarding anhedonia in schizophrenia. For example, as reviewed by Horan et al. [27], patients with schizophrenia often report diminished pleasure on self-report questionnaires and interviews, but do not necessarily exhibit diminished pleasure during laboratory and physiological tasks. Gard et al. [44] differentiated between anticipatory and consummatory pleasure, and reported that patients exhibit a deficit in the former, but not the latter. Furthermore, they linked deficits in anticipatory pleasure to motivational processes that are associated with reductions in goal-directed behavior, characteristic of negative symptom schizophrenia. However, as noted below, considerable controversy remains about these distinctions.

Although anhedonia has long been considered a core negative symptom of schizophrenia (e.g. [45]), its expression is captured differently across methods of assessment. A wealth of data shows elevated levels of self-reported social and physical anhedonia in patients with schizophrenia compared to healthy controls (e.g. [20]) and to patients with bipolar disorder (e.g. [21]). Likewise, diminished experience of pleasure in negative symptom schizophrenia is found using interview assessments (e.g. [46, 47]). However, some laboratory studies fail to find elevated levels of anhedonia in patients with schizophrenia as compared to controls (e.g. [48]). A meta-analysis of 26 laboratory studies showed that patients with schizophrenia experience levels of pleasure comparable to controls in response to pleasurable stimuli during emotion induction tasks (Hedges D = −.16; [49]). Thus it appears that

the construct of anhedonia may reflect a cognitive-perceptual bias, as well as a true experiential deficit (see [18] for a review of emotional self-report of anhedonia in schizophrenia).

Research has shown anhedonia to have a number of adverse correlates: social anhedonia in schizophrenia is associated with stress and low well-being [21], and physical anhedonia is associated with obsessiveness, low self-efficacy, and low self-esteem [14]. Within schizophrenia, both types of anhedonia are positively associated with poor premorbid functioning [50–52], low self-reported social functioning [21, 48], and emotional distress, and negatively associated with coping and perceived social support [14]. In sum, anhedonia in schizophrenia, which is primarily associated with negative symptoms, appears to be at least in part cognitive-interpretational and behavioral in nature and is linked with poor global and social functioning.

Schizophrenia represents the most severe manifestation of the schizotypic continuum. However, the diminished ability to experience pleasure manifests across the entire schizotypy spectrum; in addition to schizophrenia, anhedonia has been identified in schizophrenia-spectrum personality disorders, at-risk or prodromal patients, and non-clinical schizotypy. Advancement in the study of schizotypic anhedonia has benefitted from converging evidence across different domains of research, including—but not limited to—clinical, biological, neurological, social and personality psychology, and from a variety of assessment methods, including psychometric, interview, laboratory, psychophysiological, cross-sectional, longitudinal, and ecological assessments.

9.7.1 Assessment of Schizotypic Anhedonia

Although a variety of measures of schizotypic anhedonia have been developed, the majority of this chapter will focus on self-report, psychometric screening inventories, which have proven to be a useful method for assessing the construct. Although this method lacks the precision and specificity of other forms of assessment, such as structured interviews, it has several advantages: namely, it is relatively quick and inexpensive to administer, it is non-intrusive, and can easily be used to test large groups. Although there are a number of self-report measures that assess schizotypic anhedonia, our discussion will primarily focus on the Physical Anhedonia Scale [50] and the Revised Social Anhedonia Scale [53]. These scales were designed to measure symptoms and traits characteristic of the preschizophrenic condition, in line with descriptions from Meehl's operationalization of schizotypy [16, 54]. The Physical Anhedonia Scale assesses deficits in sensory and aesthetic pleasure, whereas the Revised Social Anhedonia Scale measures schizoid asociality and indifference to others.

Interview assessments provide an in-depth and standardized method to define and rate anhedonia. Typically, a trained clinician rates the presence and severity of various symptoms after making behavioral observations and gathering information

from the participant and other informed individuals. For example, the Scale for the Assessment of Negative Symptoms [45, 55] Anhedonia-Asociality subscale includes a severity rating from 0 to 5 for four relevant items, a subjective awareness item, and a global rating. There are a variety of interview assessments designed to measure anhedonia; the majority focus on the frequency of participation in social and recreational activities.

The benefit of using interview assessments is that they provide a level of detail that is not obtained with self-report questionnaires, although they require greater time and expense than psychometric screening measures. The main disadvantage for the study of schizotypy is that many of the interview measures were created for patients with schizophrenia and are not sensitive enough to detect variation at the level of subclinical schizotypy. However, more recent interviews of negative symptoms of schizotypy and schizophrenia include assessments of anhedonia across a broad range of the construct. These include the Structured Interview for Prodromal Symptoms [56], the Comprehensive Assessment of At-Risk Mental States [57], the Negative Symptom Manual [58], and the Clinical Assessment Interview for Negative Symptoms [59].

Even for use with patients with schizophrenia, there are a number of shortcomings of the current interview assessment systems for anhedonia and other negative symptoms (e.g. [26, 27, 60]). Problems include the use of outdated items and items that do not cohere with other negative symptoms in factor analyses. Skewed informant ratings and patient characteristics, such as cognitive deficits, retrospective bias (e.g., [18]), and blunted facial (e.g. [19, 61]) and vocal (e.g., [62]) expressivity can also lower the accuracy of data collected. Threats to validity include using observations of external behavior to infer internal states, as well as tautological reasoning in which 'functional' negative symptom criteria are used to predict functional outcomes. Other common weaknesses are measurement of the consequences of anhedonia instead of the construct itself and measurement of concepts with similar manifestations yet different underlying processes; for example, many measures cannot properly distinguish avolition from anhedonia and thus primarily tap motivational deficits. Barrantes-Vidal et al. [15] also commented that some measures of schizotypic anhedonia (and negative symptoms in general) are highly correlated with depression, in contrast to formulations of negative schizotypy. Additionally, some measures focus on frequency of engagement without capturing true in-the-moment enjoyment. This shortcoming is similar to the failure to discriminate between anticipatory and consummatory pleasure, which recent research has shown to be a key distinction.

Consummatory pleasure is experienced while directly engaging in an experience, whereas anticipatory pleasure is related to future experiences [63] and is composed of both prediction of eventual reward and momentary pleasure of the anticipation. This leads to a cyclical conceptual representation of an experience as pleasant or unpleasant as memory, anticipation, and experience interact across time [64]. Research using a scale that distinguishes anticipatory and consummatory pleasure, the Temporal Experience of Pleasure Scale (TEPS; [63]) has yielded promising, although in some cases inconsistent, results. The original findings from Gard et al. [44] indicated that patients with schizophrenia exhibited deficits in anticipatory,

but not consummatory pleasure. However, other studies have suggest that patients exhibit deficits in consummatory, but not anticipatory pleasure [65], or deficits in both forms of pleasure [66]. Furthermore, Buck and Lysaker [67] indicated that anticipatory pleasure is more stable over time than consummatory pleasure; however, this is contrasted by findings from Strauss et al. [65]. In schizophrenia, anticipatory pleasure is positively correlated with social and familial functioning [44, 67], and negatively correlated with social and physical anhedonia [44], positive symptoms [65, 67], and emotional discomfort [67]. Consummatory pleasure is negatively associated with physical—but not social anhedonia [44] and with positive symptoms [67]. A 6-month follow-up showed that low anticipatory pleasure is associated with emotional discomfort over time but that consummatory pleasure is unassociated with symptoms or quality of life at follow-up. It is therefore possible that anticipatory pleasure reflects difficulty with emotion regulation and anxiety about future social and recreational activities [67].

Although the TEPS was designed using a college sample, relationships between anticipatory and consummatory pleasure with subclinical schizotypy have remained under-researched. Initial validity studies showed both types of pleasure to be negatively associated with social and physical anhedonia and positively associated with reward responsiveness, though responsiveness to reward was more strongly linked with anticipatory pleasure [63]. These results were corroborated in Chinese [66] and American [68] samples with psychometrically identified schizotypy. Both anticipatory and consummatory pleasure were negatively associated with social and physical anhedonia in the Chinese sample, though the relationships with physical anhedonia were stronger. Interestingly, both types of pleasure were positively associated with cognitive perceptual (positive) schizotypic symptoms and negatively associated with interpersonal (negative) schizotypic symptoms [69]. In the American sample, a high social anhedonia group had lower anticipatory and consummatory pleasure than a control group [68]. Likewise, Gooding and Pflum [70] reported that social anhedonia was associated with both anticipatory and consummatory deficits on the TEPS. This suggests that the differential associations of temporal pleasure and the link between anticipatory deficits and emotion dysregulation found in schizophrenia may not be present in subclinical groups. Nonetheless, subclinical anhedonia does appear to be related to experiential deficits in pleasure across time.

The widespread use of psychometric screening measures has broadened our knowledge of associations between anhedonia and other factors. The next section provides an overview of the association of psychometrically assessed schizotypic anhedonia with cross-sectional clinical and laboratory studies, longitudinal high-risk assessments, and daily life assessments using experience sampling methodology (ESM). Associations of anhedonia have been examined in clinical and non-clinical samples. Bailey et al. [71] examined correlates of social and physical anhedonia in an adult inpatient psychiatric sample. Anhedonia measures were found to correlate positively with Axis II schizoid, schizotypal, and avoidant personality disorders (r-values = .40–.59). Likewise, within a college sample, a high social anhedonia-low magical ideation group had significantly higher schizotypal, schizoid, and paranoid clinical scores than a low social anhedonia group, while still not meeting full

diagnostic criteria for any of the three personality disorders [72]. These studies indicate that anhedonia is associated with clinically relevant symptoms, even in individuals without full-blown psychopathology.

The use of family studies and genetic techniques provides insight into the biological basis of schizophrenia. Interview assessments in siblings of patients diagnosed with schizophrenia [73], as well as interpersonal behavioral ratings—but not clinical symptom ratings—in parents of putative schizotypes [74] provide evidence for elevated levels of social anhedonia in first-degree relatives compared to the general population. Furthermore, a group of relatives of patients with schizophrenia with a homozygous VAL allele of the COMT polymorphism scored higher on physical anhedonia than non-homozygous relatives and controls [75]. Similarly, Kaczorowski et al. [76] found that a negative symptom index largely based upon physical and social anhedonia was associated with the number of COMT VAL alleles in a healthy college student sample. The association of VAL allele frequency and anhedonia/negative symptoms makes sense given that VAL allele frequency is associated with diminished dopamine availability in the prefrontal cortex—a putative mechanism for negative symptoms. Finally, research with ultra high-risk groups has shown higher levels of social anhedonia in those who eventually transition to psychosis, compared to those who do not (e.g. [77, 78]). This accumulation of evidence indicates that anhedonia is one phenotypic expression of the biological vulnerability to develop schizophrenia.

Though the use of laboratory stimuli has previously been criticized for its low ecological validity [79] the main strength is that such measures are less prone to cognitive-perceptual biases than self-report and may yield more valid results of in-the-moment hedonic capacity. Some behavioral studies have found diminished facial expressivity in individuals with social anhedonia (e.g. [80, 81]); whereas another study indicated that individuals with schizotypy display greater facial response to laboratory stimuli than controls, suggesting greater reactivity [82]. Both findings are nonetheless inconsistent with meta-analytic results from patients with schizophrenia reporting no difference in facial expressivity [83].

Another contrast with the schizophrenia literature [49] is that individuals with high levels of physical anhedonia rate pleasant and neutral stimuli as less positive than do individuals with low levels of physical anhedonia [82]. Finally, a group high in social anhedonia was rated more poorly than a low social anhedonia group on overall social skills in a laboratory social interaction paradigm [84]. This is in contrast to previous research showing physical and social anhedonia in patients with schizophrenia to be unrelated to social skills [20]. Paradoxically, behavioral results from laboratory studies tend to show a more pervasive pattern of hedonic deficit in individuals with schizotypy than in schizophrenia (see [46]). It has been suggested that the experience-expression incongruence in patients may not yet be present in subclinical individuals [80]. Studies directly comparing schizophrenia, prodromal, and schizotypic groups on behavioral measures of physical and social anhedonia may help clarify this apparent paradox.

The use of psychophysiological assessment allows examination of the potential discontinuity in response among self-report, arousal, and behavioral systems.

Whereas hedonic individuals show varying heart rate patterns for differently valenced stimuli, a college sample with high physical anhedonia showed no cardiac differentiation among positive, negative, and neutral stimuli. On the other hand, their skin conductance response and self-reported affect were comparable to that of controls [82]. However, a handful of studies have found hypo-responsive skin conductance in groups with high social and physical anhedonia (e.g. [85]; for a review, see [86]). Although the literature shows some mixed results, physical anhedonia appears to be generally associated with decreased autonomic response to stimuli.

It is commonly accepted that patients with schizophrenia have aberrations in the neural reward mechanism (e.g. [87]). Although neurological research on anhedonia in subclinical schizotypy has been limited, similar results emerge from the available literature. One group provided converging evidence from functional neuroimaging and voxel-based morphology study. They showed that functionally, physical anhedonia was associated with ventromedial prefrontal cortex activity: Blood Oxygenation Level Dependent (BOLD) response was positively correlated with processing of positive stimuli and negatively correlated with processing of negative stimuli. Structurally, physical anhedonia was associated with bilaterally reduced gray matter in the anterior caudate, a key structure in the neural reward system [88].

An fMRI study in a group with elevated ratings of physical anhedonia showed that, although self-reported psychosocial stress in response to a high-pressure mental arithmetic task was comparable to that of control and perceptual aberration groups, the physical anhedonia group had greater striatal and limbic deactivation. This is believed to reflect greater stress-reactivity and genetic vulnerability in physical anhedonia [89]. Overall, the results indicate the presence of neural correlates of diminished reward processing in anhedonia. This is consistent with reports from the schizophrenia literature of lower activation of pleasure centers in the brain in response to pleasant stimuli (e.g. [90]).

Studies have reported that physical and social anhedonia are associated with interview ratings of negative symptom. For example, Kwapil, Crump, & Pickup [91] reported that participants with elevated scores (standard scores of at least 1.96) on the Physical Anhedonia Scale ($n = 73$) and the Revised Social Anhedonia Scale ($n = 104$) exceeded control participants ($n = 178$) on interview ratings of negative and schizoid symptoms, and Kwapil et al. [7] reported that a combined anhedonia index based upon physical and social anhedonia correlated significantly with interview ratings of negative and schizoid symptoms in a sample of 430 young adults. However, these studies did not examine the association of anhedonia with individual classes of negative symptoms. We used the data from Kwapil et al. [7] to examine the association of physical and social anhedonia, as well as from the anhedonia index, with six individual classes of negative symptoms. The sample included 430 young adults (320 women, 110 men; mean age = 19.2, $SD = 1.4$) who completed the anhedonia scales and underwent structured diagnostic interviews including the Negative Symptom Manual. The Negative Symptom Manual provides a total score, as well as subscale scores for flattened affect, anhedonia, avolition/anergia, social withdrawal, alogia, and attentional deficits. Table 9.1 shows the bivariate correlations of the anhedonia measures with the interview ratings of negative symptoms.

Table 9.1 Correlations of questionnaire measures of anhedonia with interview ratings of negative symptoms (n = 430)

Negative symptom manual rating	Physical anhedonia	Social anhedonia	Combined anhedonia
Total score	**.35***	***.53****	***.52****
Avolition/anergia	.21*	**.30***	**.30***
Attentional deficits	.11	**.30***	.24*
Social withdrawal	.25*	***.53****	**.45***
Alogia	.19*	.29*	.28*
Flattened affect	**.32***	**.37***	**.41***
Anhedonia	**.31***	**.35***	**.39***

Medium effect sizes in bold, large effect sizes in bold and italics
*$p < .001$

Consistent with the characterization of anhedonia playing a central role in negative schizotypy, the physical, social, and combined anhedonia ratings had moderate to large associations with the overall interview rating of negative symptoms and with the anhedonia and flattened affect components. Not surprisingly, social anhedonia had especially elevated associations with the social withdrawal rating, but was also moderately associated with the cognitive deficit components of negative symptoms. Note that the interview rating of anhedonia was significantly correlated with the other five classes of negative symptoms with large effects for the associations with social withdrawal and flattened affect. Overall, the results are especially striking because they were found in a non-clinical sample of young adults.

9.7.2 Longitudinal Assessment of Schizotypic Anhedonia

The previously reviewed studies typically examined anhedonia within schizotypy and schizophrenia at cross-sectional assessments. However, longitudinal study is ultimately needed to examine the expression and role of anhedonia in the etiology and development of schizophrenia-spectrum psychopathology. Longitudinal studies are difficult to conduct because of the lengthy time investment and the cost and challenges associated with follow-up visits. Nonetheless, longitudinal research can yield direct information about risk factors and clinical prognosis, which can inform clinical prevention. Several psychometric high-risk studies have examined the predictive validity of anhedonia.

Chapman et al. [22] conducted a 10-year longitudinal study of 534 young adults identified by high scores on their schizotypy or psychosis screening scales. They used a high-risk groups approach in which extreme scorers on the scales were compared with a control group of low scoring participants. They indicated that physical anhedonia did not predict the development of schizophrenia or spectrum disorders at the 10-year follow-up. However, a combined magical ideation-social anhedonia group was found to be at particular heightened risk, with 21 % transitioning to psychotic disorders at the 10-year reassessment.

Kwapil et al. [92] replicated the deviance of this combined positive and negative schizotypy group in an independent longitudinal sample. Kwapil [38] examined the predictive validity of the Revised Social Anhedonia Scale partialling out the effects of positive schizotypy measures using the Chapmans' 10-year follow-up data. In this sample, 24 % of individuals with elevated social anhedonia reported schizophrenia-spectrum disorders at the 10-year follow-up compared to only 1 % of controls. Additionally, social anhedonia predicted elevated rates of psychotic-like, schizotypal, schizoid, and paranoid symptoms and poor functioning in the participants who had not transitioned into schizophrenia-spectrum disorders, indicating that the schizotypic features were not simply limited to the individuals who developed other schizophrenia-spectrum disorders.

However, the strongest support for the predictive validity of the physical and social anhedonia comes from a recent reanalysis of the Chapmans' longitudinal data [93]. They found that a combined dimensional rating of negative symptoms based upon scores on the Physical and Revised Social Anhedonia Scale significantly predicted schizophrenia-spectrum disorders at the 10-year follow-up over-and-above positive schizotypy and provided better prediction than group membership based upon the individual anhedonia scales. Furthermore, anhedonia was also associated with schizophrenia-spectrum symptoms and impairment in individuals who had not developed clinical disorders at the 10-year follow-up, consistent with a continuum model of schizotypy.

Gooding and colleagues also replicated these longitudinal findings. Gooding et al. [37] reported that 15 % of a group of high scorers on the Revised Social Anhedonia Scale developed schizophrenia-spectrum disorders at a 5-year reassessment compared to only 3 % of a positive schizotypy group and none of the control participants. Gooding et al. [94] reanalyzed this data and reported that the rate of spectrum disorders in the anhedonia group increased to 19 % when avoidant personality disorder was included in the definition of spectrum conditions.

These findings have been corroborated by a recent longitudinal study with an ultra high-risk group, showing social anhedonia and withdrawal at baseline predicted transition to psychosis at a 3-year follow-up [78]. On the other hand, a 1-year follow-up study with an ultra high-risk sample showed that, while a composite of 6 negative symptoms predicted transition to psychosis, none of the negative symptoms alone—anhedonia included—were predictive of conversion [77]. In a study following an at-risk prodromal group, half of participants developed a psychotic disorder 1 year later. Exploratory analyses indicated that marked social isolation was one of the prodromal symptoms found to predict conversion to psychosis [95].

Our laboratory conducted a 2.5-year longitudinal reassessment of 74 female and 28 male college students who were oversampled for physical and social anhedonia. The participants had a mean age of 19.4 years (SD = 2.8) at the initial assessment and 22.0 years (SD = 2.9) at the follow-up assessment. Participants completed the Physical and Revised Social Anhedonia Scales in mass screening sessions and underwent structured diagnostic interviews assessing schizophrenia-spectrum psychopathology, mood disorders, substance abuse, and impairment at the time of selection and at the follow-up assessment. Table 9.2 presents the correlations and

Table 9.2 Correlations and logistic regressions of measures at the initial and follow-up assessment (n = 102)

	Initial assessment anhedonia	Follow-up assessment anhedonia
Dependent variable	*r*	*r*
Global assessment of functioning	***–.55**********	**–.42*****
Psychotic-like experiences	.26**	.27**
Negative symptom manual	***.55**********	***.55**********
Schizotypal personality rating	**.46*****	**.32****
Schizoid personality rating	***.53**********	***.51**********
Paranoid personality rating	.29**	.25*
Impairment from alcohol use	–.04	.00
Impairment from drug use	.03	–.11

Binary logistic regressions

	Anhedonia		Anhedonia	
Dependent variable	Odds ratio	95 % CI	Odds ratio	95 % CI
Any schizophrenia-spectrum disorder	1.00	0.99–1.01	1.99	1.00–.4.00
Any mental health treatment	1.12	0.78–1.60	1.26	0.93–1.71
Major depressive episode	0.88	0.68–1.58	1.02	0.74–1.41

Medium effect sizes in bold, large effect sizes in bold and italics (correlations only)
*$p < .05$; **$p < .01$; ***$p < .001$

binary logistic regressions of anhedonia predicting interview ratings of functioning and psychopathology at the initial and follow-up assessments. As hypothesized, anhedonia significantly predicted impaired functioning and schizophrenia-spectrum symptoms at both assessments, but was unassociated with ratings of substance use or diagnoses of major depressive disorder. Strikingly, psychometrically assessed schizotypic anhedonia was cross-sectionally and longitudinally associated with interview ratings of negative and schizoid symptoms, but not with depressive disorders—nicely highlighting the differences between schizotypic and depressive anhedonia. Not surprisingly, rates of schizophrenia-spectrum disorders were low, consistent with the use of a college student sample. One participant met criteria for schizoid personality disorder at the initial assessment (as well as at the follow-up assessment). This participant had a combined physical and social anhedonia scale score at the time of selection that was five standard deviations above the mean. At the follow-up assessment, two other participants had developed psychotic disorders. However, the prediction of spectrum disorders at the follow-up by anhedonia fell short of statistical significance, $p = .051$. Anhedonia did not significantly predict the number of participants receiving any psychological treatment at either assessment. However, it did predict the number of new treatment cases at the follow-up, OR = 1.51 (95 % CI = 1.01–2.26), $p < .05$.

In sum, longitudinal data show that schizotypic anhedonia is predictive of the development of schizophrenia-spectrum disorders and symptoms. Given that anhedonia is defined as a component of negative schizotypy, the presence of social

and physical anhedonia in late adolescence or early adulthood represents early signs of schizotypic psychopathology and impairment and for some participants may represent early manifestations of the schizophrenia prodrome. Thus, it is not entirely surprising, but nonetheless important to demonstrate, that anhedonia predicts subsequent development of schizophrenia-spectrum disorders. Given this basic demonstration of the construct validity of schizotypic anhedonia, it will be essential to identify factors that exacerbate this risk and increase the likelihood of transitioning into schizophrenia-spectrum disorders, and protective factors that may dampen this risk. Note that consideration of the multidimensionality of schizotypy is essential for targeting risk factors. For example, cannabis is frequently cited as a risk factor for transition into psychosis (e.g., [96]). However, our findings repeatedly indicate that participants with negative schizotypy (characterized primarily by anhedonia) are not at elevated risk for using cannabis (and may in fact be at lower risk—especially in comparison to their positive schizotypy peers). This does not mean that we should not encourage participants with negative schizotypy to avoid cannabis, but rather that this may not be as important of a risk pathway as in positive schizotypy. We suggest that the compounding consequences of social withdrawal and the loss of the protective factors provided by healthy social relationships may be especially worth examining.

9.8 Assessing Anhedonia in Daily Life

Traditional laboratory and self-report studies provide important information about anhedonia and its role in schizophrenia-spectrum psychopathology. However, these studies often are unable to inform us about the experience and expression of anhedonia in daily life. Self-report or interview assessments typically inquire about general recollections across weeks or months regarding symptoms and impairment. However, these questions are subject to recall biases and may be influenced by the artificial setting of the study. Recent investigations have employed ESM to examine anhedonia in daily life. ESM is a within-day self-assessment technique in which participants are prompted at random intervals to complete brief questionnaires. ESM offers several advantages to traditional assessment procedures. Specifically, ESM: (1) repeatedly assesses participants in their normal daily environment, enhancing ecological validity; (2) assesses participants' experiences at the time of the signal, minimizing retrospective bias; and (3) allows for examination of the context of participants' experiences. Thus, this method provides a unique window for examining the real-world expression of anhedonia.

Our research group has conducted four ESM studies examining the expression of anhedonia in daily life. The first two studies, Brown et al. [34] and Kwapil et al. [33] were limited to the study of social anhedonia. However, Kwapil et al. [97] and Barrantes-Vidal et al. [98] examined the expression of our composite rating of physical and social anhedonia (negative schizotypy) and positive schizotypy in daily life. Kwapil et al. [97] examined the expression of anhedonia in the daily life of 412 undergraduate students. Participants were issued personal digital assistants that

signaled them eight times daily for 1 week to complete brief questionnaires regarding affect, thoughts, activities, and social contact. They completed an average of 42 questionnaires during the weeklong assessment. As hypothesized, anhedonia was associated with daily life reports of diminished positive affect, less pleasure from important events, and less time spent with others. Anhedonia was associated with greater social distance and greater preference to be alone when with others, and a diminished desire to be with others when alone. Finally, anhedonia was associated with diminished enjoyment of current activities. Thus anhedonia is characterized by a pattern of diminished pleasure from social and non-social activities, decreased social contact, and preference to be alone. Furthermore, the pattern of findings in daily life for anhedonia/negative symptoms was in sharp contrast to positive schizotypy, which was associated with affective dysregulation, social anxiety, and suspiciousness.

Barrantes-Vidal et al. [98] extended the work of Kwapil et al. [97] by examining the association of anhedonia with psychotic-like, paranoid, and negative symptoms in daily life in a sample of 206 Spanish college students who completed an average of 41 ESM questionnaires during the week. They reported that anhedonia was associated with diminished positive affect and positive appraisals of the current situation and current activities, but not with elevated negative affect or appraisals. They replicated Kwapil et al.'s [97] findings that anhedonia was associated with diminished social contact, interest, and closeness. Most striking, they found that anhedonia was associated with the negative symptom of reporting "no thoughts or emotions" in the moment and with the momentary experience of psychotic-like experiences. Furthermore, social stress in the moment was associated with increased psychotic-like symptoms for high anhedonic participants.

Converging evidence from various assessment methods and domains of research shows that anhedonia is present across the entire schizotypic continuum. Though recent data reveals that its underpinnings may be cognitive-behavioral in nature, as well as reflecting an experiential deficit in pleasure, anhedonia is nevertheless present in a range of individuals and associated with adverse outcomes. Cross-sectional studies have shown social and physical anhedonia to be linked with low positive affect and poor social, familial, and global functioning. Longitudinal studies have shown that social anhedonia greatly increases the risk of developing schizophrenia-spectrum disorders and symptoms across time. Recent improvements in assessment methods, such as new interview measures that distinguish between anticipatory and consummatory pleasure, have increased our knowledge about the expression of anhedonia. Cross-sectional studies simultaneously comparing groups along the schizotypic continuum, as well as additional longitudinal studies, could provide more precise information about the developmental course of anhedonia.

9.9 Conclusions and Future Directions

Ample evidence suggests that "some patients" with schizophrenia exhibit "some degree" of "some types" of anhedonia. Furthermore, anhedonia also seems to characterize the broader phenotype of schizotypy, albeit with the same provisos

and guarded language. We believe that anhedonia provides a useful example of the heterogeneity of schizotypy and schizophrenia and why we must consider, understand, and operationalize the underlying multidimensional structure of schizotypy if we are going to make headway in understanding etiology and developing effective treatments and prophylactic interventions. In fact, we would argue that anhedonia is a core deficit of the negative symptom dimension of schizotypy. Furthermore, it appears that this dimension is associated with unique underlying pathophysiology, symptoms, impairment, and treatment response. Studies that fail to consider this multidimensional structure risk producing misleading, uninterpretable, or irreproducible results. For example, studies that ask broad questions such as, is schizotypy [broadly defined] associated with substance abuse or openness to experience could find significant direct or inverse relationships, or no relationship at all, simply dependent upon the "flavor of schizotypy" in their sample. For example, we have found that positive schizotypy is strongly associated with substance use and with elevated openness. Our dimension of negative/anhedonic schizotypy is associated with low openness and sensation seeking, and usually unassociated with substance use.

Thus future study of the role of anhedonia in schizotypy and schizophrenia should consider careful operationalization, rigorous assessment, differentiation of schizotypic anhedonia from other pathological conditions and normal individual differences, and perhaps most importantly, understanding of processes and mechanisms underlying anhedonia and the larger heterogeneity of schizotypy and schizophrenia. Undoubtedly, elucidating underlying processes will involve genetic, neuroanatomical, and neurotransmitter mechanisms across a complex pattern of development. However, we also strongly urge consideration of environmental factors, especially early interpersonal factors such as trauma and attachment in considering the development of both social and non-social anhedonia. Along with considering the environmental factors contributing to the development of anhedonia, studies should consider how anhedonia plays out in the environment across the schizophrenia spectrum. This is especially concerning for nonclinical individuals with prominent social anhedonia who may avoid early detection and lose the benefits of a nurturing social environment. The anticipatory and consummatory pleasure distinction appears especially promising. However, we expect that the answer is not a simple either-or, but that different processes underlie these deficits and that there is considerable individual differences among patients regarding the degree to which they exhibit deficits in the anticipation of pleasure and the immediate experience of pleasure. Furthermore, it is important to keep in mind that depression is highly comorbid with schizophrenia-spectrum disorders and subclinical schizotypy and contributes another pathway to diminished pleasure that may further "muddy" the search for specific etiological pathways.

Finally, we believe that there are exciting prospects for novel assessments of anhedonia in schizotypy and schizophrenia. Self-report and interview-based assessments of anhedonia in schizotypy have been extensively developed. Based on the large literature using these tools reviewed here and elsewhere [7], self-report scales for assessing physical and social anhedonia have substantial evidence

for reliability and validity. The next step, then, is to develop innovative ways of capturing the expression of negative schizotypy that move beyond self-reports and structured interviews.

ESM strikes us as particularly promising for providing a detailed, nuanced look at what anhedonia, and more broadly negative schizotypy, looks like in everyday life. This chapter has reviewed work on the daily expression of anhedonia, and these studies have supported our description of the construct. So far, however, experience sampling work has only scratched the surface of the possibilities for daily-life assessment. For example, as of yet there are no event-contingent designs, which ask people to complete a survey when an event occurs, such as social interactions, pleasant and unpleasant experiences, and unusual thoughts. Such methods would afford highly detailed assessments of particular events of interest when they happen. In addition, it would be worthwhile to use extended sampling periods, such as one or more months, to examine trends in functioning over extended periods of time, rather than sampling a single typical week.

Another direction in assessment concerns the use of physiological methods. In our recent work, we have become interested in tools from autonomic psychophysiology for indexing how much effort people expend as they strive to achieve goals and incentives (e.g., [99, 100]). A large literature in the basic science of effort has established sympathetic and parasympathetic markers of engagement in the pursuit of rewards [101, 102], with a particular emphasis on measures of cardiac activity. This literature can thus be translated to the problem of negative schizotypy to yield physiological indicators of when people are trying harder to reach a goal versus withdrawing effort and failing to engage.

A final intriguing direction combines the self-report assessments found in conventional experience sampling with the physiological information gained by cardiac autonomic assessment. Advances in ambulatory physiological monitoring enable researchers to assess cardiac functioning as people go about their normal days [103]. By combining self-reports and physiological assessment, researchers can examine how biological markers of stress, motivation, and engagement change as people encounter the naturalistic goals and challenges in their normal environments. Such methods are on the frontier of schizotypy research, and they promise a new level of insight into how both biological and psychological aspects of anhedonia are expressed in everyday life.

References

1. Gooding DC, Iacono WG. Schizophrenia through the lens of a developmental psychopathology perspective. In: Cicchetti D, Cohen DJ, editors. Developmental psychopathology: risk, disorder, and adaptation, vol. 2. Oxford: Wiley; 1995. p. 535–80.
2. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J. 1987;295:681–2.
3. Claridge G. Schizotypy: implications for illness and health. New York: Oxford University Press; 1997.

4. Kwapil TR, Barrantes-Vidal N. Schizotypal personality disorder: an integrative review. In: Widiger TA, editor. The Oxford handbook of personality disorders. Oxford: Oxford University Press; 2012. p. 437–77.
5. Lenzenweger MF. Schizotypy and schizophrenia: the view from experimental psychopathology. New York: Guilford Press; 2010.
6. Meehl PE. Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. J Personal Disord. 1990;4:1–99.
7. Kwapil TR, Barrantes-Vidal N, Silvia PJ. The dimensional structure of the Wisconsin schizotypy scales: factor identification and construct validity. Schizophr Bull. 2008;34:444–57.
8. Vollema MG, van den Bosch RJ. The multidimensionality of schizotypy. Schizophr Bull. 1995;21:19–31.
9. Arndt S, Alliger RJ, Andreasen NC. The distinction of positive and negative symptoms: the failure of a two-dimensional model. Br J Psychiatry. 1991;158:317–22.
10. Lenzenweger MF, Dworkin RH. The dimensions of schizophrenia phenomenology: not one or two, at least three, perhaps four. Br J Psychiatry. 1996;168:432–40.
11. Liddle PF. The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. Br J Psychiatry. 1987;151:145–51.
12. Cicero DC, Kerns JG. Multidimensional factor structure of positive schizotypy. J Personal Disord. 2010;24:327–44.
13. Raine A, Reynolds C, Lencz T, et al. Cognitive-perceptual, interpersonal and disorganized features of schizotypal personality. Schizophr Bull. 1994;20:191–201.
14. Ritsner MS. Anhedonia of patients with schizophrenia and schizoaffective disorder is attributed to personality-related factors rather than to state-dependent clinical symptoms. Clin Schizophr Rel Psychoses. 2013;21:1–32.
15. Barrantes-Vidal N, Gross G, Sheinbaum T, et al. Positive and negative schizotypy are associated with prodromal and schizophrenia-spectrum symptoms. Schizophr Res. 2013;145:50–5.
16. Meehl PE. Schizotaxia, schizotypy, schizophrenia. Am Psychol. 1962;17:827–38.
17. Rado S. Psychoanalysis of behavior. New York: Grune & Stratton; 1956.
18. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169:364–73.
19. Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. J Abnorm Psychol. 1992;101:37–44.
20. Blanchard JJ, Bellack AS, Mueser KT. Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. J Abnorm Psychol. 1994;103:719–28.
21. Blanchard JJ, Mueser KT, Bellack AS. Anhedonia, positive and negative affect, and social functioning in schizophrenia. Schizophr Bull. 1998;24:413–24.
22. Chapman LJ, Chapman JP, Kwapil TR, et al. Putatively psychosis-prone subjects 10 years later. J Abnorm Psychol. 1994;103:171–83.
23. Schürhoff F, Szöke A, Bellivier F, et al. Anhedonia in schizophrenia: a distinct familial subtype? Schizophr Res. 2003;61:59–66.
24. Blanchard JL, Horan WP, Brown SA. Diagnostic differences in social anhedonia: a longitudinal study of schizophrenia and major depressive disorder. J Abnorm Psychol. 2001;110:363–71.
25. Loas G, Monestes J, Ingelaere A, et al. Stability and relationships between trait or state anhedonia and schizophrenic symptoms in schizophrenia: a 13-year follow-up study. Psychiatry Res. 2009;161:132–40.
26. Blanchard JJ, Kring AM, Horan WP, et al. Toward the next generation of negative symptom assessments: the collaboration to advance negative symptom assessment in schizophrenia. Schizophr Bull. 2011;37:291–9.
27. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32:259–73.
28. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:2.

29. Baumeister RF, Leary MR. The need to belong: desire for interpersonal attachments as a fundamental human motivation. Psychol Bull. 1995;117:497–529.
30. Leary MR, Kelly KM. Belonging motivation. In: Leary MR, Hoyle RH, editors. Handbook of individual differences in social behavior. New York: Guilford Press; 2009. p. 400–9.
31. Kwapil TR, Silvia PJ, Barrantes-Vidal N. Social anhedonia and solitude. In: Coplan RJ, Bowkers J, editors. A handbook of solitude: psychological perspectives on social isolation, social withdrawal, and being alone. Hoboken: Wiley-Blackwell; 2014.
32. Silvia PJ, Kwapil TR. Aberrant asociality: how individual differences in social anhedonia illuminate the need to belong. J Personal. 2011;79:1013–30.
33. Kwapil TR, Silvia PJ, Myin-Germeys I, et al. The social world of the socially anhedonic: exploring the daily ecology of asociality. J Res Pers. 2009;43:103–6.
34. Brown LH, Silvia PJ, Myin-Germeys I, et al. When the need to belong goes wrong: the expression of social anhedonia and social anxiety in daily life. Psychol Sci. 2007;18:778–82.
35. Leary MR, Herbst KC, McCrary F. Finding pleasure in solitary activities: desire for aloneness or disinterest in social contact? Personal Individ Differ. 2003;35:59–68.
36. Brown LH, Silvia PJ, Myin-Germeys I, et al. The relationship of social anxiety and social anhedonia to psychometrically identified schizotypy. J Soc Clin Psychol. 2008; 27:127–49.
37. Gooding DC, Tallent KA, Matts CW. Clinical status of at-risk individuals 5 years later: further validation of the psychometric high-risk strategy. J Abnorm Psychol. 2005;114:170–5.
38. Kwapil TR. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. J Abnorm Psychol. 1998;107:558–65.
39. Kraepelin E. Dementia praecox and paraphrenia. Edinburgh: Livingstone; 1913/1919.
40. Bleuler EP. Dementia praecox or the group of schizophrenias (Zinkin J, trans). New York: International Universities Press; 1911/1950.
41. Rado S. Dynamics and classification of disordered behaviour. Am J Psychiatry. 1953; 110:406–16.
42. Meehl PE. Primary and secondary hypohedonia. J Abnorm Psychol. 2001;110:188–93.
43. Horan WP, Blanchard JJ, Gangestad SW, et al. The psychometric detection of schizotypy: do putative schizotypy indicators identify the same latent class? J Abnorm Psychol. 2004;113:339–57.
44. Gard DE, Kring AM, Gard MG, et al. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:1–3.
45. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry. 1982;39:784–8.
46. Strauss GP, Keller WR, Buchanan RW, et al. Next-generation negative symptom assessment for clinical trials: validation of the brief negative symptom scale. Schizophr Res. 2012;142:88–92.
47. Bellack AS, Morrison RL, Wixted JT, et al. An analysis of social competence in schizophrenia. Br J Psychiatry J Ment Sci. 1990;156:809–18.
48. Cohen AS, Dinzeo TJ, Nienow TM, et al. Diminished emotionality and social functioning in schizophrenia. J Nerv Ment Dis. 2005;193:796–802.
49. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36:143–50.
50. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374–82.
51. Garnet K, Glick M, Edell W. Anhedonia and premorbid competence in young, nonpsychotic psychiatric inpatients. J Abnorm Psychol. 1993;102:580–3.
52. Katsanis J, Iacono WG, Beiser M, Lacey L. Clinical correlates of anhedonia and perceptual aberration in first-episode patients with schizophrenia and affective disorder. J Abnorm Psychol. 1992;101:184–91.

53. Eckblad ML, Chapman LJ, Chapman JP, et al. The revised social anhedonia scale. Unpublished test (copies available from T.R. Kwapil, Department of Psychology, University of North Carolina at Greensboro, P.O. Box 26170, Greensboro, NC, 27402–6170); 1982.
54. Meehl PE. Manual for use with checklist of schizotypic signs, No. PR-73-5. Minneapolis: University of Minnesota Research Laboratories of the Department of Psychiatry; 1964.
55. Andreasen NC. Scale for the assessment of negative symptoms (SANS). Iowa City: University of Iowa; 1983.
56. McGlashan TH, Miller TJ, Woods SW, et al. Structured interview for prodromal symptoms. New Haven: Yale University; 2001.
57. Yung AR, Yuen H, McGorry PD, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust N Z J Psychiatry. 2005;39:964–71.
58. Kwapil TR, Dickerson LA. Negative symptom manual. Unpublished interview manual; 2001.
59. Kring AM, Gur RE, Blanchard JJ, et al. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry. 2013;170:165–72.
60. Sayers SL, Curran PJ, Mueser KT. Factor structure and construct validity of the scale for the assessment of negative symptoms. Psychol Assess. 1996;8:269–80.
61. Kring AM, Neale JM. Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? J Abnorm Psychol. 1996;105:249–57.
62. Hoekert M, Kahn RS, Pijnenborg M, et al. Impaired recognition and expression of emotional prosody in schizophrenia: review and meta-analysis. Schizophr Res. 2007;96:135–45.
63. Gard DE, Gard MG, Kring AM, et al. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.
64. Kring AM, Caponigro J. Emotion in schizophrenia: where feeling meets thinking. Curr Dir Psychol Sci. 2010;19:255–9.
65. Strauss GP, Wilbur RC, Warren KR, et al. Anticipatory vs. consummatory pleasure: what is the nature of hedonic deficits in schizophrenia? Psychiatry Res. 2011;187:36–41.
66. Chan RCK, Wang Y, Huang J, et al. Anticipatory and consummatory components of the experience of pleasure in schizophrenia: cross cultural validation and extension. Psychiatry Res. 2010;175:181–3.
67. Buck B, Lysaker PH. Consummatory and anticipatory anhedonia in schizophrenia: stability, and associations with emotional distress and social function over six months. Psychiatry Res. 2013;205:30–5.
68. Martin EA, Becker TM, Cicero DC, et al. Differential associations between schizotypy facets and emotion traits. Psychiatry Res. 2011;187:94–9.
69. Chan RCK, Wang Y, Yan C, et al. A study of trait anhedonia in non-clinical Chinese samples: evidence from the Chapman Scales for Physical and Social Anhedonia. PLoS One. 2012;7:e34275.
70. Gooding D, Pflum M. The nature of diminished pleasure in individuals at risk for or affected by schizophrenia. Psychiatry Res. 2012;198:172–3.
71. Bailey B, West KY, Widiger TA, et al. The convergent and discriminant validity of the Chapman Scales. J Pers Assess. 1993;61:121–35.
72. Horan WP, Brown SA, Blanchard JJ. Social anhedonia and schizotypy: the contribution of individual differences in affective traits, stress, and coping. Psychiatry Res. 2007;149:147–56.
73. Velthorst E, Meijer C, G.R.O.U.P. Investigators. The association between social anhedonia, withdrawal and psychotic experiences in general and high-risk populations. Schizophr Res. 2012;138:2–3.
74. Emmerson LC, Miller SL, Blanchard JJ. Behavioral signs of schizoidia and schizotypy in the biological parents of social anhedonics. Behav Modif. 2009;33:452–73.
75. Docherty AR, Sponheim SR. Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. J Abnorm Psychol. 2008;117:788–98.
76. Kaczorowski JA, Salinger WL, Henrich VC, et al. Gene affecting dopamine metabolism underlies schizophrenia risk in young adults. Submitted for publication.

77. Piskulic D, Addington J, Cadenhead KS, et al. Negative symptoms in individuals at clinical high risk of psychosis. Psychiatry Res. 2012;196:220–4.
78. Velthorst E, Nieman DH, Becker HE, et al. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophr Res. 2009;109:1–3.
79. Blanchard JJ. Hedonic capacity: implications for understanding emotional and social functioning in schizophrenia. In: Flack Jr WF, Laird JD, editors. Emotions in psychopathology: theory and research. New York: Oxford University Press; 1998. p. 336–52.
80. Leung WW, Couture SM, Blanchard JJ, et al. Is social anhedonia related to emotional responsivity and expressivity? A laboratory study in women. Schizophr Res. 2010;124:1–3.
81. Kring AM, Alpert M, Neale JM, et al. A multimethod, multichannel assessment of affective flattening in schizophrenia. Psychiatry Res. 1994;54:211–22.
82. Fitzgibbons L, Simons RF. Affective response to color-slide stimuli in subjects with physical anhedonia: a three-systems analysis. Psychophysiology. 1992;29:613–20.
83. Berenbaum H, Snowhite R, Oltmanns TF. Anhedonia and emotional responses to affect evoking stimuli. Psychol Med. 1987;17:677–84.
84. Llerena K, Park SG, Couture SM, et al. Social anhedonia and affiliation: examining behavior and subjective reactions within a social interaction. Psychiatry Res. 2012;200:679–86.
85. Bernstein AS, Riedel JA. Psychophysiological response patterns in college students with high physical anhedonia: scores appear to reflect schizotypy rather than depression. Biol Psychiatry. 1987;22:829–47.
86. Raine A, Lencz T, Benishay DS. Schizotypal personality and skin conductance orienting. In: Raine A, Lencz T, Mednick SA, editors. Schizotypal personality. New York: Cambridge University Press; 1995. p. 219–49.
87. Stein L, Wise CD. Possible etiology of schizophrenia: progressive damage to the noradrenergic reward system by 6-hydroxydopamine. Science. 1971;171:1032–6.
88. Harvey PO, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry. 2007;12:767–75.
89. Soliman A, O'Driscoll GA, Pruessner J, et al. Limbic response to psychosocial stress in schizotypy: a functional magnetic resonance imaging study. Schizophr Res. 2011;131:184–91.
90. Crespo-Facorro B, Paradiso S, Andreasen NC, et al. Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. J Am Med Assoc. 2001;286:427–35.
91. Kwapil TR, Crump RA, Pickup DR. Assessment of psychosis proneness in African-American college students. J Clin Psychol. 2002;58:1601–14.
92. Kwapil TR, Miller MB, Zinser MC, et al. Magical ideation and social anhedonia as predictors of psychosis proneness: a partial replication. J Abnorm Psychol. 1997;106:491–5.
93. Kwapil TR, Gross GM, Silvia PJ, et al. Prediction of psychopathology and functional impairment by positive and negative schizotypy in the Chapmans' ten-year longitudinal study. J Abnorm Psychol. 2013;122:807–15.
94. Gooding DC, Tallent KA, Matts CW. Rates of avoidant, schizotypal, schizoid and paranoid personality disorders in psychometric high-risk groups at 5-year follow-up. Schizophr Res. 2007;94:1–3.
95. Mason O, Startup M, Halpin S, et al. Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. Schizophr Res. 2004;71:2–3.
96. Arseneault L, Cannon M, Poulton R, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. Br Med J. 2002;325:1212–3.
97. Kwapil TR, Brown LH, Silvia PJ, et al. The expression of positive and negative schizotypy in daily life: an experience sampling study. Psychol Med. 2012;42:2555–66.
98. Barrantes-Vidal N, Chun C, Myin-Germeys I, et al. Psychometric schizotypy predicts the experience of psychotic-like, paranoid, and negative symptom experiences in daily life. J Abnorm Psychol. 2013;122:1077–87.

99. Silvia PJ. Mirrors, masks, and motivation: implicit and explicit self-focused attention influence effort-related cardiovascular reactivity. Biol Psychol. 2012;90:192–201.
100. Silvia PJ, Eddington KM, Beaty RE, et al. Gritty people try harder: grit and effort-related cardiac autonomic activity during an active coping challenge. Int J Psychophysiol. 2013;88:200–5.
101. Brehm JW, Self E. The intensity of motivation. Annu Rev Psychol. 1989;40:109–31.
102. Gendolla GHE, Wright RA, Richter M. Effort intensity: some insights from the cardiovascular system. In: Ryan RM, editor. The Oxford handbook of human motivation. New York: Oxford University Press; 2012. p. 420–38.
103. Houtveen JH, de Geus EJC. Noninvasive psychophysiological ambulatory recordings: study design and analysis strategies. Eur Psychol. 2009;14:132–41.

Chapter 10
Anticipatory and Consummatory Anhedonia in Individuals with Schizotypal Traits

Raymond C.K. Chan, Chao Yan, Yi Wang, Qi-feng Yin, Simon S.Y. Lui, and Eric F.C. Cheung

Abstract Anhedonia is the reduced ability to experience pleasure emotion and has been considered a key symptom in schizophrenia spectrum disorders. However, little is known about the hedonic capacity and related neural basis for individuals prone to develop psychosis such as people with schizotypal personality traits. On the other hand, anhedonia is a complex, multidimensional construct that is important for social interaction and functioning in both healthy individuals and people with neuropsychiatric disorders. However, most measures of anhedonia are limited to clinical rating and self-report checklists that adopt a unitary concept. Increasing interest has emerged in the past decade to subdivide this construct into anticipatory and consummatory experience of pleasure. This book chapter will examine these two facets of anhedonia in individuals with schizotypal personality traits using a multi-pronged approach, including self-report questionnaires, computerized tests, and neuroscientific measures.

Keywords Anticipatory • Consummatory • Anhedonia • Schizotypal traits

R.C.K. Chan (✉) • C. Yan • Y. Wang
Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Beijing, China
e-mail: rckchan@psych.ac.cn

Q. Yin
Department of Psychology, Renmin University of China, Beijing, China

S.S.Y. Lui
Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Beijing, China

Castle Peak Hospital, Hong Kong Special Administrative Region, China

E.F.C. Cheung
Castle Peak Hospital, Hong Kong Special Administrative Region, China

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_10,

Abbreviations

DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
fMRI	Functional magnetic resonance imaging
SPD	Schizotypal Personality Disorder
TEPS	The Temporal Experience of Pleasure Scale
VBM	Voxel Based Morphometry

10.1 Introduction

Emotional impairments have been considered core features of negative symptoms of schizophrenia and one of the most critical determinants of functional outcome of this clinical group [1, 2]. Anhedonia is defined as the diminished ability to experience pleasure, whereas avolition is defined as the diminished motivation to seek and sustain in goal-directed behaviour driven by positive or desirable events or the possibility of these events happening [3, 4]. Negative symptoms in schizophrenia present great challenge to available treatments [5, 6] and have significant bearings on prognosis. The reason which could account for the difficulties in finding effective treatment is that the nature (especially the neural mechanism) of anhedonia in schizophrenia remains unclear. However, even though the clinical understanding of anhedonia in schizophrenia is not completely clear, it is commonly acknowledged that there is an "emotional paradox" observed in this clinical group. Patients with schizophrenia demonstrate intact pleasurable experience when they are presented with evocative stimuli in laboratory-based assessments when compared to their self-reported pleasure experience [7–11]. Moreover, the study of anhedonia has been extended to at-risk individuals before the development of the disorder such as individuals with schizotypal personality disorder (SPD) traits. In Meehl's [12] model of schizophrenia, he considers anhedonia as an important marker of genetic vulnerability for schizophrenia which can also be observed in individuals at risk of developing the illness such as those exhibiting SPD traits. Studying anhedonia in these medication-free individuals with SPD traits can help us understand the nature of hedonic capacity in patients with schizophrenia.

In an effort to address the complex nature of anhedonia in schizophrenia spectrum disorders, the present chapter summarizes up-to-date findings of anhedonia in individuals with SPD traits. We begin with the conceptualization of SPD and its relationship with schizophrenia spectrum disorders, and the current constructs of hedonic capacity. We emphasize how important the current view and conceptualization of hedonic capacity (or anhedonia) is in understanding the aforementioned emotion paradox observed in this clinical group. In particular, we focus on the two distinct components of pleasure experience, namely anticipatory and consummatory pleasure, and their relationships to the objective laboratory-based assessments of hedonic capacity in individuals with SPD traits.

10.2 Conceptualizaiton of SPD and Its Relationship with Schizophrenia Spectrum Disorders

Meehl [12] proposed that schizotaxia, a genetic liability, predisposes an individual to develop some form of disorganization termed schizotypal behaviours which in turn will form a predisposition to schizophrenia. However, he also pointed out that this genetic risk alone is not sufficient for the development of schizophrenia. This implies that individuals with schizotypal traits can have behavioural manifestations that range from nearly normal to clinically abnormal presentation. Since then, Paul Meehl's theory has evolved into two separate but related lines of research. The first one focuses on schizotypy traits that comprise cognitive slippage (mild associative loosening), anhedonia (pleasure-capacity deficit), ambivalence, and interpersonal aversiveness (social fear) [13, 14]. The second one focuses on the constellation of symptoms indicating the presence of schizotypy. The DSM-IV [15] adopts such a construct to diagnose SPD as part of the personality disorders on Axis II, which is characterized by positive (e.g., magical thinking, Ideas of reference) and negative (e.g., social withdrawal, anhedonia) symptoms [16]. However, more recent work suggests that SPD is better conceptualized as an attenuated form of schizophrenia [17]. SPD has also been considered to be one of the operational criteria for the schizophrenia prodrome [17]. An SPD diagnosis encompasses subclinical positive and negative symptoms of schizophrenia. The conversion rate of prodrome to full-blown psychosis is roughly between 25 and 45 % 1 year after the diagnosis of schizophrenia prodrome [18]. The prevalence of SPD in the general population is about 3 % (DSM-IV, 2000). Biological relatives of patients with schizophrenia have a higher prevalence of SPD [19]. Researchers have suggested a continuum concept of psychosis with SPD and schizophrenia lying on the extremes, ranging from nearly normal functioning to psychotic disorders [20]. Empirical evidence has also demonstrated that SPD traits are commonly distributed in the general population [21, 22].

In this chapter, we operationally define SPD traits as the traits generally covering the concepts of both Paul Meehl's theory of schizotypy and the DSM-IV-based construct of attenuated form of schizophrenia. However, it should be noted that the original conceptualization of schizotaxia or schizotypy proposed by Meehl [23] does not exactly match the DSM-IV diagnosis of schizotypal personality disorder. In Meehl's viewpoint, schizotypy refers to a latent personality organization and is essentially a broader construct linked to a developmental theory, whereas the SPD in DSM-IV is an atheoretical categorization or aggregation of a set of observable signs and symptoms. Moreover, individuals with SPD traits, like their clinical counterparts, may also demonstrate subtypes of behavioural manifestations, i.e., dominant with negative-like and positive-like symptoms. Lastly, we have included both clinically diagnosed SPD and psychometrically defined SPD in the discussion in the present chapter.

10.3 Current Construct of Hedonic Capacity and Its Underlying Neural Mechanisms

Anhedonia is commonly defined as the inability to experience pleasure and is a core feature of schizophrenia and depression [24, 25]. Traditionally it is conceptualized as a unitary construct of diminished momentary pleasure experience [26–31]. For example, Rado [32] posited that anhedonia is the inherited predisposition to schizophrenia as a result of the inability to experience pleasures and a lack of motive to engage in rewarding activities. It has then been incorporated into Meehl's construct of schizotypy [12, 23] and subsequent assessment of physical and social anhedonia in schizotypy [33]. However, although the current literature demonstrates a consistent pattern of emotional deficits in schizophrenia spectrum disorders, recent findings have highlighted the presence of an "emotional paradox" in patients with schizophrenia [7, 8, 34]. While patients with schizophrenia could report experiencing strong emotions (including pleasant emotion) in response to emotional material, they do not often report experiencing strong pleasant emotions in naturalistic situations [34]. These findings were not confounded by the corresponding cognitive and language disturbances that often accompany schizophrenia and convergent evidence indicates that these patients are able to provide reliable and valid reports of emotional experience [7, 9, 35].

The advance of neuroscience in both animal and human research now suggests that anhedonia is a multidimensional construct that comprises at least two components, namely consummatory and anticipatory pleasure [36–39]. Consummatory pleasure is the ability to experience momentary pleasure (i.e., the feeling of liking) when an individual is directly engaging in an enjoyable activity; whereas anticipatory pleasure is the ability to experience a motivated and goal-directed behaviour (i.e., the feeling of wanting) for a future pleasant event [40, 41]. Motivation is always accompanied by hedonic experience, especially anticipatory experience of pleasure (appetitive pleasure) [36, 37, 40, 41]. Berridge and Robinson [41, 42] argue that "wanting" (anticipatory) behaviour is equivalent to approach motivation and is closely associated with appetitive pleasure in animals. Knutson's anticipatory affect model further posits that the neural response of the nucleus accumbens correlated with anticipatory pleasure (arousal) predicts motivated behaviour in the future [36]. Studies on the dopamine system have shown that dopamine in the reward process is classically linked to the anticipatory experience of pleasure [43], and data suggest that the dopamine system also plays a motivational role [41]. Neuroanatomical hotspots have also been linked up with hedonic capacity [43, 44]. For example, the orbitofrontal and cingulate cortices as well as the insular cortices contribute to experiences of pleasure. Subcortical areas such as the dorsal and ventral striatum and the amygdala have also been implicated in the processing of positive emotional or reward stimuli. In particular, the orbitofrontal cortex takes up an important role in linking reward to hedonic experiences [45]. Patients with schizophrenia have been found to have hypoactivation at the ventral striatum and orbitofrontal cortex when compared with healthy controls, although it is still not clearly

known whether schizophrenia is associated with impaired reward valuation and motivation rather than a diminished processing of hedonic capacity [4, 9, 46].

The outstanding issue of hedonic capacity in general and anhedonia research in schizophrenia in particular is that the nature of the subjective experience of pleasure is still not fully understood. The study of anhedonia in schizophrenia is further complicated by the impact of clinical symptoms, medications, as well as the associated impairment of cognitive functioning and insight. Despite these challenges, the question of anhedonia in SPD can still be approached using a multi-pronged approach, utilizing findings from self-reported, behavioural and imaging work.

10.4 Self-Reported Anticipatory and Consummatory Pleasure in Individuals with SPD Traits

The current literature suggests that all but one self-reported measure of experiential pleasure were based on the unitary construct of pleasure. The Temporal Emotional Experience of Pleasure Scale (TEPS) [3] is an 18-item checklist that captures both the anticipatory (10 items) and consummatory (8 items) components of pleasure experience in schizophrenia research. Satisfactory construct validity, internal consistency, test-retest reliability and clinical discrimination have been demonstrated [3, 38, 47–49]. The TEPS can serve as an important tool to evaluate the subjective experience of individuals with SPD traits.

Martin et al. [50] were among the first few researchers to adopt the two-facet perspective of pleasure experience to study individuals with SPD traits. They first screened and recruited their potential participants using the Revised Social Anhedonia Scale [51] and Perceptual Aberration/Magical Ideation scale [52, 53]. Then they compared these two facets of experiential pleasure using the TEPS. Their findings showed that individuals with negative SPD traits (elevations in social anhedonia score) had significantly lower scores on both the anticipatory and consummatory subscales of the TEPS. However, no significant difference was found between individuals with positive SPD traits (elevations in magical ideation and perceptional aberrations) and healthy controls.

Gooding et al. [49] administered the TEPS to specifically examine the experience of pleasure in individuals with and without SPD traits using the TEPS. They further classified the participants into negative SPD traits and positive SPD traits, and healthy controls without these traits. Their results showed that only the subtype of SPD traits characterized by social anhedonia but not the subtype characterized by positive symptom-like behaviour reported deficits in both anticipatory and consummatory pleasure when compared with the individuals without SPD traits. These authors also found that working memory was differentially associated with the anticipatory and consummatory components of experiential pleasure. That is, significant association was only found between the consummatory components of the TEPS and working memory. These findings suggest that individual with negative SPD traits (socially

anhedonia) share similar diminished anticipatory and consummatory pleasure reported in patients with schizophrenia.

Shi et al. [54] screened out a sample of 1,039 college students from an extended pool of participants in a mentally at-risk study using the Schizotypal Personality Questionnaire [55, 56] and recruited 117 individuals with SPD traits and 116 individuals without SPD traits. They then classified their SPD sample into positive and negative SPD using cluster analysis. They found that individuals with negative SPD traits demonstrated significantly lower TEPS anticipatory subscore than healthy controls. However, the two groups did not differ significantly in terms of consummatory subscore and total TEPS score. In contrast, individuals with positive SPD traits had significantly higher anticipatory and consummatory subscores as well as total TEPS score than both negative SPD and healthy controls. These findings are consistent with those demonstrated in patients with schizophrenia. In particular, the negative SPD group reported diminished anticipatory pleasure but relatively intact consummatory pleasure compared to healthy controls. Interestingly, Shi et al. [54] also found that individuals with negative SPD traits showed the least emotional expression and reported the highest levels of problems with memory as well as other depressive symptoms compared to controls. The pattern seems to be reversed in individuals with positive SPD traits with heightened pleasure experience compared to healthy controls. However, there was no significant difference between the two groups of participants in terms of emotion expression. These findings have been cross-validated by another independent study [57] showing that SPD traits could be clustered into subtypes, and with the negative group reported the lowest emotional experience ability on both anticipatory and consummatory pleasure experience than the positive and low SPD groups.

Extending the line of continuum of psychosis proposed by van Os et al. [21], Chan et al. [48] demonstrated that anhedonia, as measured by the Chapman Scales for Physical and Social Anhedonia [51], could serve as an enduring trait similar to psychotic symptoms distributing along the non-clinical sample. Significant correlations were found between SPD traits, physical and social anhedonia. More importantly, the anticipatory and consummatory subscores as well as the total TEPS score were all inversely and significantly correlated with physical and social anhedonia. However, when the sample was split into individuals with and without SPD traits, individuals with SPD traits did not report diminished experiential anticipatory and consummatory pleasure as assessed by the TEPS. These findings may be due to the heterogeneity of SPD traits similar to that of schizophrenia patients. It is likely that only the negative subtype of SPD trait is associated with subjective pleasure experience impairment. Unfortunately, Chan et al. [48] did not report any subtype comparison in their study. The inconsistent findings might have also been due to the variability of the reported TEPS scores among different studies. Strauss et al. [58] suggest that it is likely that self-reported anticipatory and consummatory pleasure may be influenced by demographic differences (e.g., ages, gender, education, and ethnicity).

Taken together, the above findings suggest that individuals with SPD traits show a similar pattern of self-reported anticipatory and consummatory pleasure with patients

with schizophrenia. However, it is necessary to examine negative and positive SPD traits as separate entities to avoid confusion and misunderstanding in their emotional manifestations.

10.5 Experimental Tasks for Anticipatory and Consummatory Pleasure in Individuals with SPD Traits

Experimental studies of anhedonia in individuals with SPD traits were mainly limited to a unitary construct of anhedonia. The literature in this area suggests that individuals with SPD traits may experience a reduction in self-reported pleasure in response to experimental stimuli [59, 60] although there has also been studies showing no such difference [61]. Few studies have adopted an experimental paradigm to examine the anticipatory and consummatory components of pleasure experience in individuals with SPD traits. Yan et al. [62] conducted two experiments to examine specifically approach motivation based cognitive function and perceptual function in individuals with SPD traits, respectively. In their first experiments, they administered a memory probabilistic reward task based on signal detection theory to capture approach motivation. In this task, participants were first required to learn 15 pictures of sign language and were then asked to recognize the pictures that they had seen from 90 pictures comprising pictures that they had learned and not learned. Participants were informed that correct recognition of the pictures that they had learned would be accompanied by more reward. Three blocks with varied amount of reward (0, 5, 10 points) were administrated to each participant. They found that participants would increase their approach motivation along the increment of reward. Although demonstrating elevated level of anhedonia, individuals with SPD traits ($n = 20$) did not differ in their response bias (log b) when compared with individuals without SPD traits ($n = 20$) during the recognition phase, indicating that approach motivation may be intact in these individuals. In their second study, participants from another sample pool were asked to perform a perceptual probabilistic reward task. In each block of this task, participants were presented with two types of stimuli: a face with a long mouth and a face with a short mouth, and they were required to judge whether the mouth was long or not. The face with a long mouth was accompanied by more reward than the face with a short mouth. Feedback followed the participants' judgment. Each participant was asked to perform three blocks. They observed that individuals with SPD traits ($n = 24$) did not display attenuated approach motivation. On the contrary, they showed a trend of enhanced approach motivation compared to individuals without SPD traits ($n = 24$) ($p = 0.06$). Taken together, these two experiments suggest that individuals with SPD traits tend to report higher levels of anhedonia, especially experiential pleasure in anticipation of future events, than healthy controls. However, no impairment was found in the approach motivation in these individuals using either the

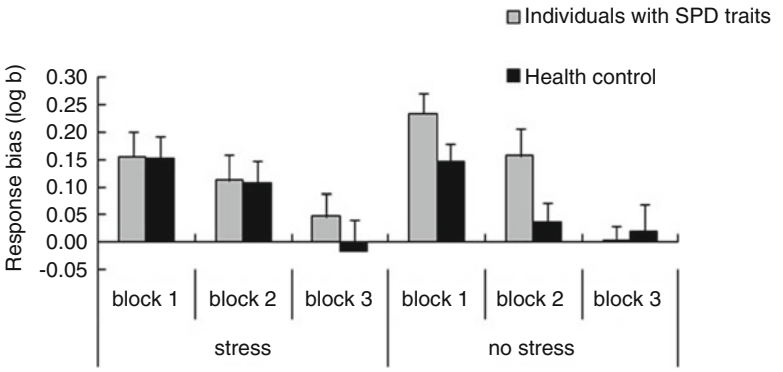

Fig. 10.1 The response bias in the individuals with SPD traits group and health control group from block 1 to block 3 under the stress condition and no stress condition

memory or the perceptual signal detection task. These authors postulated that the insignificant findings in approach motivation might be due to the fact that SPD individuals needed no additional effort to gain the reward similar to healthy controls in smoking motivation [63].

However, it is not known whether reward learning is stable or not over time and the effect of stress on reward response in these individuals. We adopted a probabilistic reward learning task developed by Bogdan and Pizzagalli [64] to a group of individuals with and without SPD traits. We modified this task by making the stimuli conditions transparent to the participants during the reward learning task, hence allowing the participants to make an informed discrimination between the two possible stimuli (reward asymmetry). This modified task has been successfully applied to discriminate patients with major depression from healthy controls [65]. However, our unpublished data on SPD showed that there was no significant difference in all parameters of this reward learning task between individuals with (n = 31) and without (n = 31) SPD traits. Figure 10.1 shows that the main effect of block was significant ($F(2, 59) = 19.316$, $p < 0.001$, partial $\eta 2 = 0.244$) with a diminished response bias over time (Block 1 > Block 2 > Block 3, all ps < 0.01). The interaction among condition, block and group was also significant ($F(2, 59) = 3.205$, $p < 0.044$, partial $\eta 2 = 0.051$). However, no other significant effects were found except for block effect in each group. When we further examined whether introducing stress would change the response bias in individuals with SPD traits, we found that there was only a trend of interaction between condition and block ($F(1, 60) = 3.661$, $p = 0.060$, partial $\eta 2 = 0.058$) (Fig. 10.2). Moreover, a check on the discriminability between individuals with and without SPD traits showed that there was only a main effect of Block ($F(2, 59) = 10.139$, $p < 0.001$, partial $\eta 2 = 0.145$) with a diminished response bias (Block 1 < Block 2, Block 1 < Block 3, all ps < 0.005). Other variables were all non-significant (all Fs < 3.876; all ps > 0.054). These findings suggest that individuals with SPD traits did not demonstrate any difficulties in maintaining positive affect to appetitive stimulus and possess intact ability to experience consummatory pleasure (Fig. 10.3).

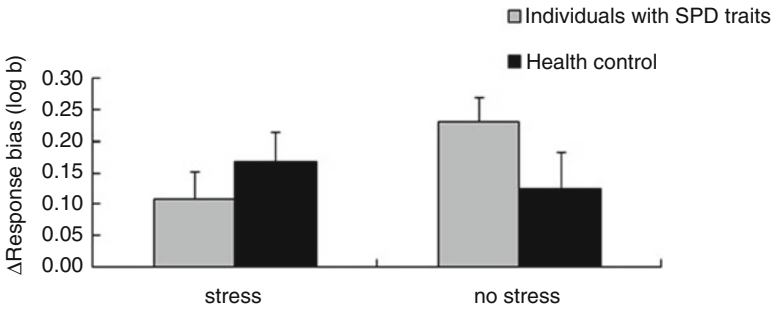

Fig. 10.2 The change of a response bias in the individuals with SPD traits and health control under the stress condition and no stress condition

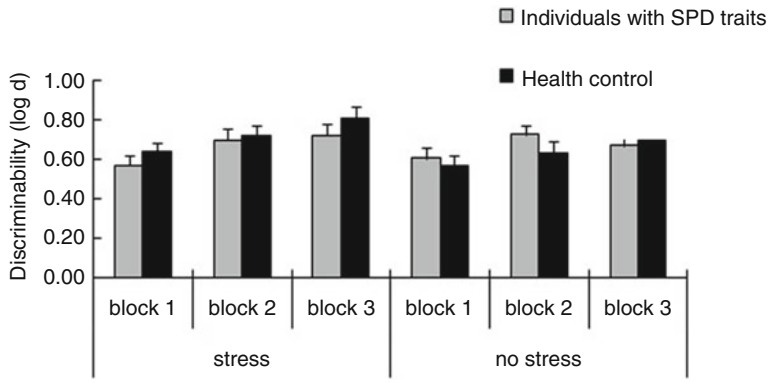

Fig. 10.3 The discriminability in the individuals with SPD traits group and health control group from block 1 to block 3 under the stress condition and no stress condition

Lui et al. [66] conducted two experiments to examine emotion-volition decoupling in patients with first-onset schizophrenia and healthy controls, as well as individuals with and without SPD traits. They adopted a task developed by Heerey and Gold [67] to examine the anticipation and consummation of experiential pleasure. They found that both patients with first-onset schizophrenia and individuals with SPD showed similar affective experiences as their controls but their experiences were significantly less predictive of their behaviour. This emotion-volition decoupling was more impaired in anticipatory than in consummatory pleasure experience for patients with schizophrenia. These findings suggest that emotion-volition decoupling can be demonstrated in patients with few negative symptoms in the early course of schizophrenia and in individuals with SPD traits. However, the latter seems to show a milder form of impairments when compared with the clinical group.

Strauss et al. [68] examined specifically both state and trait anhedonia between patients with schizophrenia, individuals with psychometric schizotypy, and healthy controls. They administered the Positive and Negative Affect Schedule (PANAS) [69]

to examine the trait affect in these participants and found that individuals with schizotypy did not show significant differences from patients. However, for state affect, which was assessed by a mood-induction task that asked participants to evaluate their affective state (pleasant and unpleasant, separately) followed by seeing neutral/good/bad affective images, individuals with schizotypy reported lower pleasant ratings on each conditions than the other three groups, but no significant difference was found on unpleasant emotion ratings. They also showed that the negative subscale scores in schizotypy were negatively correlated with pleasant emotion ratings, whereas blunted affect was found to be inversely associated with pleasant ratings in patients with schizophrenia. These findings suggest that there might be another paradox in the schizophrenia spectrum in that for state anhedonia, individuals with schizotypy demonstrated diminished pleasure, whereas schizophrenia patients did not.

10.6 Neuroimaging Findings of Anhedonia in Individuals with SPD Traits

Substantial evidence from structural brain imaging studies indicates that individuals with SPD traits, particularly clinically diagnosed individuals with SPD, often exhibit a wide range of brain abnormalities including a reduction in grey matter volume in the temporal lobe, the frontal lobe, the parietal lobe, the basal ganglia [70] and the posterior cingulate cortex [71]. However, most of these studies focused on positive-like symptoms rather than negative symptoms. More recently, Asami et al. [72] adopted the voxel-based morphometry method to examine 54 clinically diagnosed SPD individuals and 54 healthy controls and found that there was a significant reduction in grey matter volume in individuals with SPD in the left superior temporal gyrus and widespread frontal, frontolimbic and parietal regions compared to healthy controls. More importantly, reduction in grey matter volume in these regions was significantly correlated with negative symptoms. However, it should be noted that neither a unitary construct nor a two-facet construct of anhedonia was specifically examined in this clinically diagnosed SPD sample.

Harvey et al. [73] were among the first to examine the enduring trait of anhedonia using both structural and functional imaging methods in a group of college students. The optimized Voxel Based Morphometric (VBM) analysis was adopted for structural images preprocessing and the structural correlates of trait anhedonia, assessed by the Chapman Physical Anhedonia Scale [33], was examined by regression analysis. The results showed that the grey matter volume of bilateral anterior caudate was inversely correlated with trait anhedonia. In the same study, they also examined brain activity during the viewing of positive pictures compared to neutral pictures and its relationship with trait anhedonia. Positive associations between trait anhedonia and brain activity of the ventromedial prefrontal cortex, the middle and superior found during the processing of positive information. These findings suggest a specific

kind of vulnerability for the development of affective disorders and suggest that trait anhedonia may be linked to a volumetric reduction in the basal ganglia and to a prefrontal functional abnormality during hedonic processing. However, it should be noted that the authors did not attempt to discriminate individuals with SPD traits from those without SPD traits. These authors did not find any significant inverse association between trait anhedonia severity and functional activation in subcortical regions. These might be due to the fact that the authors did not use a selection method to divide the participants into those with SPD and without SPD traits. Moreover, anhedonia was only defined by the physical domain of the Chapman Physical Anhedonia Scale [33] and did not take into the consideration of the social domain, and more importantly, the two-facet component of anhedonia. Future research should adopt a reward-based paradigm that could specifically characterize the subtle relationship between the structural and functional correlates of anhedonia in different contexts.

Empirical findings on neural network associated with pleasure may provide insight into the study of anhedonia in individuals with SPD traits. For example, individuals with anhedonia in social interaction have been found to have less neural activity in facial expression discrimination regions such as the medial prefrontal cortex, the right superior temporal gyrus, and the left somatosensory cortex [74]. Interpersonal relationship of individuals with SPD traits has been particularly shown to correlate with reduced accuracy on the facial expression recognition task [75]. However, very few studies have been conducted to examine the neural activities of individuals with SPD traits in a social interaction situation. Huang et al. [76] developed a dyadic conversation paradigm to examine dynamic happy facial expression processing in different social interaction contexts in individuals with and without SPD traits. Their findings showed that bilateral activation of the prefrontal cortex during the contrast of happiness appearing and disappearing. More regions such as the right parahippocampal gyrus and the right insula were activated when contrasting the "praise"-"blame" cues. Individuals with SPD traits were found to exhibit less deactivation to the happiness disappearing faces than healthy controls in the rostral anterior cingulate. These SPD individuals also showed more deactivation than healthy controls in the left prefrontal cortex and the rostral superior temporal gryus with "blame" cues. However, the two groups did not differ in the contrast of incongruent and congruent conditions. If we merged the data from the two groups, we found two cortical regions (the right superior frontal gyrus and the left inferior occipital gyrus) which were sensitive to the incongruence between dynamic facial expression and social interaction context. When we re-analyzed the data with the TEPS score retrospectively, we found that the beta value of activation in the right superior frontal gyrus in the happiness appearing of blame context was significantly correlated with TEPS total score while the left inferior occipital gyrus was not. This might suggest that the right superior frontal region was involved in both processing the context-face incongruence and pleasure experience. Taken together, these findings suggest individuals with SPD traits have different neural inhibition mechanisms when processing the happiness disappearing stimuli with "blame" cues.

Recently, in addition to the conventional univariate analysis, novel multivariate approaches for the analysis of fMRI data are emerging. Unlike the univariate approach detecting the averaged activation differences in the brain [77], multivariate approach can detect fine-grained changes in neural representations and reflect more information in neural activation pattern than mean activation [78–80]. In Modinos et al.'s recent study, the Community Assessment of Psychic Experiences questionnaire [81] was used to identify participants with psychosis-proneness/SPD [82]. Each participant was required to view the neutral and negative valenced pictures from the International Affective Pictures System during scanning. Multivariate pattern analysis was employed to distinguish individuals with SPD traits from those without SPD traits during negative emotion processing. A unique pattern of activation was found between these two groups in the amygdala, the insula, the anterior cingulate cortex, the orbital frontal cortex, and the medial prefrontal cortex, while the conventional univariate analysis could not detect such differences. Our unpublished imaging data further suggest an altered medial orbitofrontal activation pattern during the experience of consummatory pleasure in individuals with SPD traits. Specifically, individuals with SPD traits could not differentiate the activation pattern of consummatory pleasure from consummatory negative emotion at the medial orbitofrontal cortex.

In summary, anhedonia is the reduced capacity to experience pleasure and is one of the negative symptoms in schizophrenia. Anhedonia is also one of the main symptoms confounding the functional outcome of patients with schizophrenia. Reduced hedonic capacity can also be measured as an enduring trait in non-clinical subjects. Such altered hedonic capacity is likely the result of a basic neuropsychophysiological dysfunction and a vulnerability marker that potentially precedes and contributes to the liability of developing psychotic disorders. It is crucial to the psychopathology of schizophrenia spectrum disorders. However, most previous studies were limited by recruiting only patients with clinically diagnosed psychotic disorders, behavioural rating of anhedonia, and the adoption of a unitary concept of anhedonia. Currently, no study in the literature has examined the neural basis of anhedonia in individuals with SPD traits, and little is known about the relationship between motivation and anhedonia.

10.7 Conclusions and Future Directions

Anhedonia is a symptom manifestation not only observed in patients with schizophrenia but also can be observed in individuals at-risk of psychosis as well as individuals with SPD traits. Studying anhedonia in individuals with SPD traits may provide better understanding of the problem because these individuals are not influenced by the course of illness and medication effects. However, this kind of study is surprisingly rare. One the one hand, the limited literature suggests that individuals with SPD traits exhibit a similar pattern of self-reported anticipatory and consummatory pleasure to patients with schizophrenia. On the other hand, it is surprising

that the study of anhedonia is no simpler than patients with schizophrenia. Although most of the self-reported findings suggest that these individuals demonstrate impairment in anticipatory and consummatory pleasure as compared to healthy controls, some suggest it is the reverse. The picture is even more complicated when findings from laboratory-based studies were taken into consideration. A large proportion of empirical findings suggest that individuals with SPD traits do not show impairment in pleasure. Taken as a whole, it seems that there is another emotion paradox, namely the state anhedonia paradox, in this at-risk group [83]. That is, by definition, it is paradoxical in the sense that schizophrenia is much more severe in virtually every illness-related aspect as compared with individuals with SPD traits. Cohen et al. [83] argue that this situation does not always apply to the whole spectrum of the disorder. However, the underlying mechanism is largely unknown. Therefore future study should focus more on this state anhedonia paradox.

It is noteworthy that Strauss and Gold [58] postulate that observed anhedonia may not be merely due to diminished experiential pleasure but also the belief system endorsed by patients with schizophrenia. According to these authors, there are three components interacting with one another in influencing the corresponding anhedonia observed in these clinical patients. These components include (1) low pleasure beliefs and a lack of prospective or retrospective overestimation of positive emotion; (2) reduced pleasure-seeking behaviour, and (3) elevated negative symptoms. However, this speculation is totally based on empirical findings from patients with schizophrenia. Given the state-anhedonia-paradox mentioned above, it is not fully known whether this speculation is applicable to individuals with SPD traits. Nevertheless, our unpublished findings on time perspective scale [84] revealed that individuals with SPD traits reported significantly lower score in past positive but higher scores in past negative as well as present fatalistic perspectives than healthy controls. Given such a negative past experience and uncertain current situation, individuals with SPD traits were found to be scoring significantly higher on present hedonistic perspective. These preliminary findings suggest that individuals with SPD traits may possess a set of cognitive style or belief system that may determine their observed hedonic behaviour. However, further systematic research is needed to verify this interesting paradox observed across the spectrum of schizophrenia. It is also necessary to examine negative and positive SPD traits as separate entities to avoid confusion and misunderstanding in their emotional manifestations.

The aforementioned studies of the two-facet experiential pleasure construct were all cross-sectional in design. No longitudinal study has been undertaken to specifically track the changes of anticipatory and consummatory experiential pleasure over time and their predictive validity in individuals with SPD traits. However, empirical findings using the Chapman Scales of Physical and Social Anhedonia [33] indicate that individuals characterized by social anhedonia were associated with elevated SPD traits and psychotic-like experiences [35, 85, 86]. It will be interesting to examine whether the anticipatory and consummatory components would change similarly or differentially over time in these individuals. In particular, it will be important to identify whether there is any predictive validity of the changes of these two facets of experiential pleasure from prodrome to full-blown psychosis.

The advance of neuroimaging technologies may provide better ways to investigate the underlying neural mechanism of anhedonia in individuals with SPD traits. Neuroimaging allows us to examine the neural substrates and their connectivity with specific areas. A related potential implication of neuroimaging technologies is to pave the way for the possibility of non-invasive way treatment for anhedonia, which is currently considered an enduring feature of schizophrenia. For example, meta-analyses of the effects of repetitive transcranial magnetic stimulation have reported medium to large effect size in improving negative symptoms of schizophrenia [87, 88]. The application of neuroimaging has been extended recently from being used as an evaluation tool to an intervention tool such as real-time imaging neurofeedback [89, 90]. There have been initial reports of success in helping patients to regulate negative emotions such as pain perception [91]. Given its promising effect of manipulating a specific brain region, it is possible that real-time imaging neurofeedback may also allow us to examine how mental strategy can regulate the hotspots of hedonic capacity such as the orbitofrontal cortex, the rostral anterior cingulate cortex and the insula.

On the other hand, Favrod et al. [92] adopted an innovative cognitive-sensory intervention to improve the anticipatory experiential pleasure in five patients with anhedonia as measured by the TEPS. These individuals were trained to enter a state of relaxation to anticipate pleasure from potential enjoyable activities and to experience the sensation of the pleasure in their bodies. The intervention has been effective in improving the anticipatory pleasure subscore of the TEPS, but did not have an effect on the consummatory pleasure subscore. Despite the preliminary nature of the study, these findings suggest that cognitive-sensory interventions may be specific to anticipatory experiential pleasure through multimodalities simulation. This kind of approach together with real-time imaging neurofeedback may have advantages over conventional medical interventions especially for individuals with SPD traits who are not clinically diagnosed patients.

Taken together, the existing literature suggests that anhedonia is not limited to patients with established schizophrenia but also extends to individuals prone to psychosis such as those with SPD traits. However, the study of anhedonia in individuals with SPD traits remains preliminary. There are a number of unresolved issues in this area and its relationship with schizophrenia spectrum disorders remains unclear. Nevertheless, a potentially fruitful avenue is the use of the two-facet construct (i.e., anticipatory and consummatory) of pleasure experience and a combination of hedonic capacity measures to provide a comprehensive approach to anhedonia evaluation in individuals with SPD traits. These will facilitate a clearer understanding on whether anhedonia may serve as a vulnerability maker for schizophrenia and contribute to the development of potential intervention for this deficit.

Acknowledgments This research received support from a grant from the National Science Fund China Young Investigator Award (81088001); the National Key Technologies R&D Program (2012BAI36B01); and the "Strategic Priority Research Program (B)" of the Chinese Academy of Sciences (XDB02030002).

References

1. Herbener ES, Harrow M, Hill SK. Change in the relationship between anhedonia and functional deficits over a 20-year period in individuals with schizophrenia. Schizophr Res. 2005;75:97–105.
2. Kirkpatrick B, Fenton WS, Carpenter WTJ, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006;32:214–9.
3. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:253–60.
4. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull. 2010;36:359–69.
5. Silver H, Chertkow Y, Weinreb O, Danovich L, Youdim M. Multifunctional pharmacotherapy: what can we learn from study of selective serotonin reuptake inhibitor augmentation of antipsychotics in negative-symptom schizophrenia? Neurotherapeutics. 2009;6(1):86–93.
6. Lewis SW, Barnes TRE, Davids L, Murray RM, Dunn G, Hayhurst KP, Markwick A, Lloyd H, Jones PB. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull. 2006;32(4):715–23.
7. Horan PH, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. Schizophr Bull. 2006;32:259–73.
8. Cohen A, Minor K. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36:143–50.
9. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. Schizophr Bull. 2008;34(5):819–34.
10. Cohen AS, Najolia GM, Brown LA, Minor KS. The state-trait disjunction of anhedonia in schizophrenia: potential affective, cognitive and social-based mechanisms. Clin Psychol Rev. 2011;31(3):440–8.
11. Yan C, Cao Y, Zhang Y, Song LL, Cheung EF, Chan RC. Trait and state positive emotional experience in schizophrenia: a meta-analysis. PLoS One. 2012;7:e40672.
12. Meehl PE. Schizotaxia, schizotypy, schizophrenia. Am Psychol. 1962;17:827–38.
13. Lenzenweger MF. Psychometric high-risk paradigm, perceptual aberrations, and schizotypy: an update. Schizophr Bull. 1994;20(1):121–35.
14. Chapman LJ, Chapman JP, Kwapil TR, Eckblad M, Zinser MC. Putatively psychosis-prone subjects 10-years later. J Abnorm Psychol. 1994;103(2):171–83.
15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.
16. First MB, Spitzer RL, Gibbon M, Williams JBW, Benjamin L. Structured clinical interview for DSM-IV axis II personality disorders (SCID-II, version 2.0). New York: NY State Psychiatric Institute; 1994.
17. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. Schizophr Bull. 2009;35(5):894–908.
18. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res. 2003;60(1):21–32.
19. Tienari P, Wynne LC, Laksy K, Moring J, Nieminen P, Sorri A, et al. Genetic boundaries of the schizophrenia spectrum: evidence from the Finnish Adoptive Family Study of Schizophrenia. Am J Psychiatry. 2003;160:1587–94.
20. Johns LC, van Os J. The continuity of psychotic experiences in the general population. Clin Psychol Rev. 2001;21(8):1125–41.
21. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis

proneness-persistence-impairment model of psychotic disorder. Psychol Med. 2009;39(2): 179–95.
22. Chan RCK, Li X, Lai M, Li H, Wang Y, Cui J, Deng Y, Raine A. Exploratory study on the base-rate paranoid ideation in a non-clinical Chinese sample. Psychiatry Res. 2011;185(1–2): 254–60.
23. Meehl PE. Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. J Personal Disord. 1990;4:1–99.
24. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:22.
25. Romney DM, Candido CL. Anhedonia in depression and schizophrenia: a reexamination. J Nerv Ment Dis. 2001;189:735–40.
26. Katsanis J, Iacono WG, Beiser M. Anhedonia and perceptual aberration in first-episode psychotic patients and their relatives. J Abnorm Psychol. 1990;99:202–6.
27. Clementz BA, Grove WM, Katsanis J, Iacono WG. Psychometric detection of schizotypy: perceptual aberration and physical anhedonia in relatives of schizophrenics. J Abnorm Psychol. 1991;100:607–12.
28. Grove WM, Lebow BS, Clementz BA, Cerri A, Medus C, Iacono WG. Familial prevalence and coaggregation of schizotypy indicators: a multitrait family study. J Abnorm Psychol. 1991;100:115–21.
29. Blanchard JJ, Collins LM, Aghevil M, Leung WW, Cohen AS. Social anhedonia and schizotypy in a community sample: the Maryland longitudinal study of schizotypy. Schizophr Bull. 1998;37(3):587–602.
30. Lubin B, Van Whitlock R, Zuckerman M. Affect traits in differential diagnosis of anxiety, depressive, and schizophrenic disorders using the multiple affect adjective check list-revised. Assessment. 1998;5:309–19.
31. Loas G, Boyer P, Legrand A. Anhedonia in the deficit syndrome of schizophrenia. Psychopathology. 1999;32:207–19.
32. Rado S. Psychoanalysis of behavior; collected papers. New York: Grune and Stratton; 1956.
33. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85(4):399–407.
34. Kring AM. Emotion in schizophrenia: old mystery, new understanding? Curr Dir Psychol Sci. 1999;8(5):160–3.
35. Blanchard JJ, Mueser KT, Bellack AS. Anhedonia, positive and negative affect, and social functioning in schizophrenia. Schizophr Bull. 1998;24:413–24.
36. Knutson B, Greer SM. Anticipatory affect: neural correlates and consequences for choice. Philos Trans R Soc Lond B Biol Sci. 2008;363(1511):3771–86.
37. Kringelbach ML, Bridge KC. Towards a functional neuroanatomy of pleasure and happiness. Trends Cogn Sci. 2009;13(11):479–87.
38. Gard DE, Gard-Germans M, Kring AM, Oliver JP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Personal. 2006;40:1086–102.
39. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55.
40. Klein D. Depression and anhedonia. In: Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1984. p. 1–14.
41. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev. 1998;28:309–69.
42. Bridge KC, Robinson TE. Parsing reward. Trends Neurosci. 2003;26:507–13.
43. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35(1):68–77.
44. Kringelbach ML. The hedonic brain: a functional neuroanatomy of human pleasure. In: Kringelbach ML, Bridge KC, editors. Pleasures of the brain. Oxford: Oxford University Press; 2010. p. 202–21.

45. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci. 2005;6:691–702.
46. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull. 2008;34(5):835–47.
47. Chan RCK, Wang Y, Huang J, Shi Y, Wang Y, Hong X, Ma Z, Li Z, Lai MK, Kring AM. Anticipatory and consummatory components of the experience of pleasure in schizophrenia: cross-cultural validation and extension. Psychiatry Res. 2010;175:181–3.
48. Chan RCK, Shi YF, Lai MK, Wang YN, Wang Y, Kring AM. The Temporal Experience of Pleasure Scale (TEPS): exploration and confirmation of factor structure in a healthy Chinese sample. PLoS One. 2012;7(4):e35352.
49. Gooding DC, Pflum MJ. The nature of diminished pleasure in individuals at risk for or affected by schizophrenia. Psychiatry Res. 2012;198:172–3.
50. Martin EA, Becker TM, Cicero DC, Cocherty AR, Kerns JG. Differential associations between schizotypy facets and emotion traits. Psychiatry Res. 2011;187:94–9.
51. Eckblad ML, Chapman LJ, Chapman JP, Mishlove M. The revised social anhedonia scale. 1982.
52. Chapman LJ, Chapman JP, Raulin ML. Body-image aberration in schizophrenia. J Abnorm Psychol. 1978;87(4):399–407.
53. Eckblad M, Chapman LJ. Magical ideation as an indicator of schizotypy. J Consult Clin Psychol. 1983;51(2):215–25.
54. Shi YF, Wang Y, Cao XY, Wang Y, Wang YN, Zong JG, Xu T, Tse VWS, Hsi XL, Stone WS, Lui SSY, Cheung EFC, Chan RCK. Experience of pleasure and emotional expression in individuals with schizotypal personality features. PLoS One. 2012;7(5):e34147.
55. Raine A. The Schizotypal Personality Questionnaire (SPQ): a measure of schizotypal personality based on DSM-III-R criteria. Schizophr Bull. 1991;17:555–64.
56. Chen WJ, Hsiao CK, Lin CCH. Schizotypy in community samples: the three-factor structure and correlation with sustained attention. J Abnorm Psychol. 1997;106:649–54.
57. Wang Y, Neumann D, Shum DHK, Chan RCK. A cross-validation study of clustering of schizotypy using a non-clinical Chinese sample. Psychiatry Res. 2012;1(30):55–8.
58. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169(4):364–73.
59. Cohen AS, Iglesias B, Minor KS. The neurocognitive underpinnings of diminished expressivity in schizotypy: what the voice reveals. Schizophr Res. 2009;109:38–45.
60. Kerns JG, Docherty AR, Martin EA. Social and physical anhedonia and valence and arousal aspects of emotional experience. J Abnorm Psychol. 2008;117(4):735–46.
61. Gooding DC, Davidso RJ, Putnam KM, Tallent KA. Normative emotion-modulated startle response in individuals at risk for schizophrenia-spectrum disorders. Schizophr Res. 2002;57:109–20.
62. Yan C, Liu WH, Cao Y, Chan RCK. Self-report pleasure experience and motivation in individuals with schizotypal personality disorders proneness. East Asian Arch Psychiatry. 2011;21:115–22.
63. Joseph S, Manafi E, Lakovaki AM, Cooper R. Personality, smoking motivation, and self-efficacy to quit. Personal Individ Diff. 2003;34:749–58.
64. Bogdan R, Pizzagalli DS. Acute stress reduces reward responsiveness: implications for depression. Biol Psychiatry. 2006;60:1147–54.
65. Liu WH, Chan RCK, Wang LZ, Huang J, Cheung EFC, Gong QY, Gollan JK. Deficits in sustaining reward responses in subsyndromal and syndromal major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:1045–52.
66. Lui SSY, Shi YF, Li Z, Liu ACY, Chan CKY, Leung MMW, Chui WWH, Tsang CCM, Wang Y, Yan C, Heerey EA, Cheung EFC, Chan RCK. Affective experience and motivated behaviour in schizophrenia spectrum disorders: Convergent evidence from clinical and non-clinical samples. Submitted.
67. Heerey EA, Gold JM. Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. J Abnorm Psychol. 2007;116:268–78.

68. Strauss GP, Gold JM. Response to Gooding and Plfum, "The nature of diminished pleasure in individuals at risk for or affected by schizophrenia" Anticipatory and consummatory pleasure deficits across the schizophrenia spectrum. Psychiatry Res. 2012;198:174–5.
69. Watson D, Tellegen A. Toward a consensual structure of mood. Psychol Bull. 1985;98:219–35.
70. Dickey CC, McCarley RW, Shenton ME. The brain in schizotypal personality disorder: a review of structural MRI and CT findings. Harv Rev Psychiatry. 2002;10(1):1–15.
71. Modinos G, Mechelli A, Ormel J, Groenewold NA, Aleman A, McGuire PK. Schizotypy and brain structure: a voxel-based morphometry study. Psychol Med. 2010;40:1423–31.
72. Asami T, Whitford TJ, Bouix S, Dickey CC, Niznikiewicz M, Shenton ME, Voglmaier MM, McCarley RW. Globally and locally reduced MRI gray matter volumes in neuroleptic-naïve men with schizotypal personality disorder: association with negative symptoms. JAMA Psychiatry. 2013;70(4):361–72.
73. Harvey PO, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry. 2007;12:767–75.
74. Germine LT, Garrido L, Bruce L, Hooker C. Social anhedonia is associated with neural abnormalities during face emotion processing. Neuroimage. 2011;58:935–45.
75. Abbott GR, Green MJ. Facial affect recognition and schizotypal personality characteristics. Early Interv Psychiatry. 2013;7:58–63.
76. Huang J, Wang Y, Jin Z, Di X, Yang T, Gur RC, Gur RE, Shum DHK, Cheung EFC, Chan RCK. Happy facial expression processing with different social interaction cues: an fMRI study of individuals with schizotypal personality traits. Prog Neuropsychopharmacol Biol Psychiatry. 2013;44:108–17.
77. Friston KJ, Frith CD, Turner R, Frackowiak RS. Characterizing evoked hemodynamics with fMRI. Neuroimage. 1995;2:157–65.
78. Haxby JV. Multivariate pattern analysis of fMRI: the early beginnings. Neuroimage. 2012;62:852–5.
79. Kamitani Y, Tong F. Decoding the visual and subjective contents of the human brain. Nat Neurosci. 2005;8:679–85.
80. Kriegeskorte N, Goebel R, Bandettini P. Information-based functional brain mapping. Proc Natl Acad Sci U S A. 2006;103:3863–8.
81. Stefanis NC, Hanssen M, Smirnis NK, Avramopoulos DA, Evdokimidis IK, Stefanis CN, Verdoux H, Van Os J. Evidence that three dimensions of psychosis have a distribution in the general population. Psychol Med. 2002;32:347–58.
82. Modinos G, Pettersson-Yeo W, Allen P, McGuire PK, Aleman A, Mechelli A. Multivariate pattern classification reveals differential brain activation during emotional processing in individuals with psychosis proneness. Neuroimage. 2012;59(3):3033–41.
83. Cohen A, Callaway DA, Larsen JT, Strauss GP. On "risk" and reward: investigating anhedonia in psychometrically defined schizotypy and schizophrenia. J Abnorm Psychol. 2012;121(2):407–15.
84. Zimbardo PG, Boyd JN. Putting time in perspective: a valid, reliable individual-differences metric. J Pers Soc Psychol. 1999;77(6):1271–88.
85. Kwapil TR. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. J Abnorm Psychol. 1998;107:558–65.
86. Gooding DC, Tallent KA, Matts CW. Clinical status of at risk individuals 5 years later: further validation of the psychometric high-risk strategy. J Abnorm Psychol. 2005;114:170–5.
87. Dlabac-de Lange JJ, Knegtering R, Aleman A. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis. J Clin Psychiatry. 2010;71(4):411–8.
88. Freitas C, Gregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. Schizophr Res. 2009;108:11–24.
89. deCharms RC. Applications of real-time fMRI. Nat Rev Neurosci. 2008;9(9):720–9.

90. Sulzer J, Haller S, Scharnowski F, Weiskopf N, Birbaumer N, Blefari ML, Bruehl AB, Cohen LG, deCharms RC, Gassert R, Goebel R, Herwig U, LaConte S, Linden D, Luft A, Seifritz E, Sitaram R. Real-tem fMRI neurofeedback: progress and challenges. NeuroImage. 2013. doi:10.1016/j.neuroimage.2013.03.033.
91. deCharms RC, Maeda F, Glover GH, Ludlow D, Pauly JM, Soneji D, Gabrieli JDE, Mackey SC. Control over brain activation and pain learned by using real-time functional MRI. Proc Natl Acad Sci U S A. 2005;102(51):18626.
92. Favrod J, Giuliani F, Ernst F, Bonsack C. Anticipatory pleasure skills training: a new intervention to reduce anhedonia in schizophrenia. Perspect Psychiatr Care. 2010;46:171–81.

Chapter 11
Anhedonia and Risk of Suicide: An Overview

Gwenolé Loas

Abstract The studies of the relationship between anhedonia and risk of suicide have led to conflicting results. The aim of the present paper is to review the different studies and to propose a conceptual model of anhedonia allowing to understand the different role of anhedonia in the risk of suicide.

Keywords Anhedonia • Suicide • Depression • Schizophrenia

Abbreviations

BDI	Beck Depression Inventory
PAS	Physical Anhedonia Scale
SADS	Schedule for affective disorders and schizophrenia
SAS	Social Anhedonia Scale
SCID	Structured Clinical Interview for diagnosis

11.1 Introduction

Anhedonia, the lowered ability to experience pleasure, constitutes either a symptom that characterizes various psychiatric disorders or a trait characterizing the personality [1]. When anhedonia is a symptom of a particular psychiatric disorder its

G. Loas (✉)
University Department of Psychiatry, Hôpital Erasme and ULB,
route de Lennik 808, B-1070 Bruxelles, Belgium
e-mail: gwenole.loas@erasme.ulb.ac.be

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_11,

duration can be the same that the duration of the disorder. When anhedonia is a trait it can have a long-term stability.

Several studies have suggested that anhedonia is associated with an elevated risk of suicide but other studies, paradoxically, have suggested that anhedonia could be associated with a lower risk of suicide.

In the present overview we present the different studies and discus the reasons explaining the discrepancy found in the literature. Then we proposed a model explaining the different roles of anhedonia on the risk of suicide.

11.2 Anhedonia and Elevated Risk of Suicide

Seven cross-sectional studies have reported in psychiatric patients significant correlations or associations between anhedonia scales and items rating suicide risk (Table 11.1).

Robins and Alessi [2] have studied depressive symptoms and suicidal behaviour in 64 adolescent psychiatric patients using a structured interview and the schedule for affective disorders and schizophrenia (SADS). Forty-nine patients had mood disorders. The SADS assessed suicidal tendencies, expressed intent to die, number of previous gestures or attempts, and the lethality of the most recent attempt. Pearson's correlations by each of the four suicide items and each of 38 SADS items were calculated. Anhedonia was significantly associated with suicidal tendencies, seriousness of intent and medical lethality.

Table 11.1 Relationships between anhedonia and risk of suicide

	Number	Diagnosis	Study	Measure	Association
Robins and Alessi [2]	49	Mood disorders	C	SADS	+
Nordström et al. [3]	32	Parasuicide	P	PAS	+
Loas and Boyer [4]	61	Major depression	C	PAS	+
Nock and Kazdin [5]	175	Psychiatric subjects	C	CDS	+
Kelly et al. [6]	97	Schizophrenia	C	SCID	+
Loas et al. [7]	150	Schizophrenia	P	PAS	+
Agrawal et al. [8]	1,041	Healthy	C	Ad hoc Q	+
	1,428	Heroin-dep			
Fawcett et al. [9]	954	Major aff disorders	P	SADS	+
Oei et al. [10]	46	Depression	C	PAS, SAS	+
Watson and Kucala [11]	39	Psychiatric subjects	P	Watson anh scale	–
Fenton et al. [12]	187	Schizophrenia	P		–
Loas et al. [14]	224	Healthy	C	PAS	
Loas et al. [15]	103	Parasuicide	C	PAS	+
Loas et al. [16]	103	Parasuicide	P	PAS	–
Etain et al. [17]	350	Euthymic bipolar	C	PAS	

BDI Beck Depression Inventory, *CDS* Children depression scale, *PAS* Physical Anhedonia Scale, *SADS* Schedule for affective disorders and schizophrenia, *SAS* Social Anhedonia Scale, *SCID* Structured Clinical Interview for diagnosis, *C* cross sectional study, *P* prospective study

One study [3] has compared 32 suicide attempters and 32 sex and age-matched controls on several personality characteristics including anhedonia rated by the PAS. The suicide attempters were interviewed 6–7 weeks after the suicide attempt. Suicide attempters had higher scores on the PAS than the control ($p = .01$). If this study the depression was not controlled although suicide attempters were more depressed than the controls.

Loas and Boyer [4] in a sample of 61 major depressed subjects reported significant correlation between the suicide item of the Hamilton depression rating scale and the total score of the revised Physical Anhedonia Scale (PAS).

Nock and Kazdin [5] have examined the role of affective factors in the occurrence of sucidal ideation, suicide attempts ad suicidal intent in 175 child and young adolescent aged from 6 to 13 years. The most frequent diagnosis was conduct disorder ($N = 85$). The authors used the Children's depression scale, the Scale for suicidal ideation, the Scale for suicidal intent for the rating of affective factors and risk of suicide, respectively. The Children's depression scale is divided into two subscales measuring depressed mood and anhedonia. Anhedonia subscale of the Children's depression scale was significantly correlated with the Scale for suicidal ideation, the Suicidal intent scale and current suicide attempt. After for controlling depressed mood the correlations remained significant except for the Suicidal intent scale.

Kelly et al. [6] have compared the psychiatric symptom of schizophrenic subjects who have died by suicide to those who have died by other means of death. The psychological autopsy method was used to assess the clinical characteristics of deceases subjects. Ninety-seven subjects were included in the study. The best informant was contacted within 6–12 weeks of the death. A semi-structured interview based upon the Structured Clinical Interview for diagnosis (SCID) was used. Using this interview and a review of all available medical records the Diagnostic evaluation after death was completed. Significant difference of anhedonia was found (20 % in the suicide group, 4 % in the non-suicide group). Significant higher rates of depressive and positive symptoms were also found in the suicide group comparatively to the non-suicide group in psychiatric subjects.

One study [7] has compared the initial characteristic of two groups of deceased schizophrenic subjects followed during 14 years. Among 150 schizophrenic patients followed during 14 years 8 patients deceased from suicide and 17 from other causes. The two groups were compared for clinical variables and scores on different rating scales. Suicide subjects had higher scores on the social withdrawal item of the BDI, measuring depressive anhedonia, than the scores of subjects deceased from other cause. Lower rates of "negative subjects" characterized suicide subjects and there was no significant difference of the total score of the PAS.

Agrawal et al. [8] in a genetic association study in large samples of healthy or heroin-dependent subjects have reported elevated rates (20.4 % for both samples) of suicide attempt in subjects presenting anhedonia and major depressive disorders comparatively with those with neither anhedonia nor major depressive disorder (0 and 1.4 %). Moreover in participants with anhedonia and without major depressive disorder the rates of suicide attempts were 8.4 and 8.3 %. In this study

anhedonia was rated using an ad hoc questionnaire measuring experience pleasure from daily activities for the last 1 or 2 weeks.

The seven preceding studies suggest only an association between anhedonia and risk of suicide and only prospective studies can test the relation of causality between anhedonia and risk of suicide.

One prospective study [9] in 954 psychiatric patients with major affective disorders found that anhedonia, rated by the SADS, was associated with suicide within 1 year.

One study [10] has suggested in a group of 46 depressed subjects that anhedonia, rated by the Physical and Social anhedonia scales, suicidal ideation and non-suppression in the dexamethasone test characterized a subgroup of 10 subjects. Moreover this subgroup was not identified with subgroups on any diagnosis from the DSM-III. The diagnoses according to DSM-III were major depression (n = 6) dysthymic disorder (n = 2) or atypical depression (n = 2).

11.3 Anhedonia and Low Risk of Suicide

Watson and Kucala in 1978 [11] have compared the score on the Watson anhedonia scale of 39 psychiatric subjects who later deceased by suicide, by natural causes or remained alive. Lower scores on the anhedonia scale characterized subjects who committed suicide comparatively with the scores of subjects who deceased by natural causes. Unfortunately, the authors did not mention the diagnoses of the psychiatric subjects.

A 19-year follow-up study [12] examined the relationships of symptoms, illness subtypes, and suicidal behaviors among patients with schizophrenia or schizophrenia spectrum disorders. Patients who later committed suicide had a significantly lower negative symptom severity at index admission than patients without suicidal behaviors. However, the paranoid schizophrenia subtype was associated with an elevated risk (12 %) and the deficit subtype according to Carpenter's criteria was associated with a lower risk of suicide (1.5 %). Taken into account that the deficit subtype is characterized by anhedonia [13] comparatively to the non-deficit subtype of schizophrenia, it could be suggested that low risk of suicide in deficit schizophrenia could be partly explained by anhedonia.

Two other studies in healthy subjects or parasuicide subjects have found no relationship between anhedonia and suicide.

In 224 healthy subjects the authors [14] did not found significant correlation between the current suicidal ideation item of the Beck depression inventory (BDI) and the PAS.

In a previous study [3] comparing anhedonia rated by the PAS in suicide attempters and controls the authors reported higher PAS scores in suicide attempters but the level of depression was not controlled. To take into account this limitation of the study a survey [15] has compared 73 depressed suicide attempters, 30 non-depressed suicide attempters and 104 sex and age-matched controls on the PAS. Depressed suicide attempters had significantly higher scores on the PAS than

controls and non-depressed suicide attempters. There was no significant difference between non-depressed suicide attempters and controls. This study suggests that anhedonia was a symptom of depression in suicide attempters and not a stable trait. The sample of the 106 suicide attempters was followed during 6.5 years [16].

6.7 % of the suicide attempters deceased by suicide during the follow-up. Cox regression analyses revealed that high proportion of men and low anhedonia were associated with decrease of the survival time. There was not effect of depression as assessed by the BDI.

One study [17] has tested the hypothesis that physical anhedonia could be an endophenotype in bipolar affective disorder. Using the cutoff score of the PAS the authors assigned euthymic bipolar patients to anhedonic or hedonic subgoups. The two groups did not differ on personal history of suicide attempt (violent or not).

11.4 How to Explain the Discrepancy of the Literature?

Firstly, the role of anhedonia in the risk of suicide is related to different characteristics of this dimension. The characteristics that must be into account are the level of anhedonia (severe or not severe), the stability of anhedonia (acute or stable dimension) and the measure used.

Concerning the measures the authors used either non specific rating scales or specific rating scales. The Social and Physical Chapman scales rates trait-anhedonia although non specific rating scales (e.g. SADS, ad hoc questionnaire) rates rather state and depressive anhedonia.

When anhedonia is severe and constitutes a state and notably a depressive symptom then anhedonia is a risk factor of suicide. Fawcett et al. [18] have proposed four hypothetical pathways leading to suicide in clinical depression. Among the four pathways the authors distinguished severe anhedonia that characterized only 15 % of subjects hospitalized for major depression [18] and was associated with suicide within 1 year [19].

It is interesting to note that anhedonia as a depressive symptom is also associated with the risk of death whatever the causes in older persons or in medical patients as suggested by two prospective studies [19, 20].

When anhedonia is not related to depression and constitute a trait then anhedonia is either unrelated to risk of suicide or associated with a low risk of suicide.

In other words acute anhedonia notably related to depression could be a short-term risk factor of suicide although chronic anhedonia could be either non-related to the suicide risk or even could be a long-term protective factor of suicide.

When anhedonia is chronic the subjects become less sensitive to pleasure of the life and thus are less sensitive to frustrations when the search of pleasure is not satisfied.

Secondly, the distinction between consummatory and anticipatory anhedonia [21] is not taken into account although these two anhedonias could play different role in the risk of suicide.

Klein [22] has suggested that deficit in consummatory pleasure could characterize endogenomorphic depression, a subtype of depression associated with elevated risk of suicide.

Specific rating scales measuring anticipatory and consummatory are now available [21] but unfortunately any study has explored the link between these anhedonia and the risk of suicide.

References

1. Loas G, Pierson A. Anhedonia in psychiatry: a review. Ann Med Psychol (Paris). 1989;147(7):705–17.
2. Robbins DR, Alessi NE. Depressive symptoms and suicidal behavior in adolescents. Am J Psychiatry. 1985;142(5):588–92.
3. Nordström P, Schalling D, Asberg M. Temperamental vulnerability in attempted suicide. Acta Psychiatr Scand. 1995;92(2):155–60.
4. Loas G, Boyer P. Relationships between anhedonia and depressive symptoms in major depressive disorder. Eur Psychiatry. 1993;8:51–2.
5. Nock MK, Kazdin AE. Examination of affective, cognitive, and behavioral factors and suicide-related outcomes in children and young adolescents. J Clin Child Adolesc Psychol. 2002;31(1):48–58.
6. Kelly DL, Shim JC, Feldman SM, Yu Y, Conley RR. Lifetime psychiatric symptoms in persons with schizophrenia who died by suicide compared to other means of death. J Psychiatr Res. 2004;38:531–6.
7. Loas G, Azi A, Noisette C, Legrand A, Yon V. Fourteen-year prospective follow-up study of positive and negative symptoms in chronic schizophrenic patients dying from suicide compared to other causes of death. Psychopathology. 2009;42(3):185–9.
8. Agrawal A, Nelson EC, Littlefield AK, Bucholz KK, Degenhardt L, Henders AK, Madden PA, Martin NG, Montgomery GW, Pergadia ML, Sher KJ, Heath AC, Lynskey MT. Cannabinoid receptor genotype moderation of the effects of childhood physical abuse on anhedonia and depression. Arch Gen Psychiatry. 2012;69(7):732–40.
9. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R. Time-related predictors of suicide in major affective disorder. Am J Psychiatry. 1990;147(9):1189–94.
10. Oei TI, Verhoeven WM, Westenberg HG, Zwart FM, van Ree JM. Anhedonia, suicide ideation and dexamethasone nonsuppression in depressed patients. J Psychiatr Res. 1990;24(1):25–35.
11. Watson CG, Kucala T. Anhedonia and death. Psychol Rep. 1978;43:1120–2.
12. Fenton WS, Mc Glashan TH, Victor BJ, Blyler CR. Symptoms, subtype, and suicidality in patients with schizophrenia spectrum disorders. Am J Psychiatry. 1997;154:199–204.
13. Loas G, Noisette C, Legrand A, Boyer P. Anhedonia, depression and the deficit syndrome of schizophrenia. Acta Psychiatr Scand. 1996;94:477–9.
14. Loas G, Fremaux D, Gayant C, Boyer P. Anhedonia, depression, and suicidal ideation. Percept Mot Skills. 1995;80(3 Pt 1):978.
15. Loas G, Perot JM, Chignague JF, Trespalacios H, Delahousse J. Parasuicide, anhedonia, and depression. Compr Psychiatry. 2000;41(5):369–72.
16. Loas G. Anhedonia and suicide: a 6.5-yr. follow-up study of patients hospitalised for a suicide attempt. Psychol Rep. 2007;100(1):183–90.
17. Etain B, Roy I, Henry C, Rousseva A, Schürhoff F, Leboyer M, Bellivier F. No evidence for physical anhedonia as a candidate symptom or an endophenotype in bipolar affective disorder. Bipolar Disord. 2007;9(7):706–12.

18. Fawcett J, Busch K.A, Jacobs D., Kravitz H.M, Foog L. Suicide: a four-pathway clinical-biochemical model. Ann N Y Acad Sci. (1997);836:288–301, Neurobiology of suicide, the: from the bench to the clinic.
19. Furlanetto LM, von Ammon Cavanaugh S, Bueno JR, Creech SD, Powell LH. Association between depressive symptoms and mortality in medical inpatients. Psychosomatics. 2000;41(5):426–32.
20. Covinsky KE, Cenzer IS, Yaffe K, O'Brien S, Blazer DG. Dysphoria and anhedonia as risk factors for disability or death in older persons: implications for the assessment of geriatric depression. Am J Geriatr Psychiatry. 2013; in press.
21. Gard DE, Germans MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.
22. Klein DF. Depression and anhedonia. In: Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA Publishing Corporation; 1987. p. 1–14.

Part III
Anhedonia in Neurological and Physical Disorders

Chapter 12
Anhedonia and Epilepsy

Marco Mula

Abstract Mood and anxiety disorders represent the most frequent psychiatric comorbidity in patients with epilepsy and reasons for such a close link are both biological and psychosocial. On one hand, epilepsy is a chronic disorder that brings about a number of social limitations (e.g. driving license, job opportunities etc.) and social discriminations leading to demoralization, poor self-esteem and phobic avoidance. On the other hand, the biological contribution to this association is given by neuroanatomical and neurochemical principles such as the involvement of the mesiotemporal structures in temporal lobe epilepsy.

The issue of phenomenology of depression has been matter of debate for a long time. A number of authors pointed out that atypical features characterize depression in epilepsy and such atypical symptoms are poorly captured by conventional classificatory systems such as DSM. In general terms, the psychopathological spectrum of depression in epilepsy is likely to be large. On one hand, it is reasonable to hypothesize that patients with epilepsy can experience forms of mood disorders identical to those of patients without epilepsy. On the other hand, it is equally reasonable to assume that the underlying brain pathology can influence the final phenomenology of mood disorder symptoms making less evident some aspects or emphasizing others. A number of variables may account for such atypical features such as peri-ictal manifestations, the high comorbidity between mood and anxiety disorders (up to 73 %), the underlying neurologic condition and the psychotropic effect of AEDs.

In this chapter, the relationship between epilepsy and mood disorders is discussed with special attention to anhedonia, discussing phenomenology and pathophysiology in the context of epilepsy.

M. Mula, M.D., Ph.D. (✉)
Division of Neurology Trinity Hospital, Borgomanero, Italy
e-mail: marcomula@yahoo.it

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_12,

Keywords Epilepsy • Anhedonia • Depression • Antiepileptic drugs • Interictal dysphoric disorder

Abbreviations

AEDs	Antiepileptic drugs
IDD	Interictal dysphoric disorder
DSM	Diagnostic and statistical manual of mental disorders
ICD	International classification of diseases

12.1 Introduction

Epilepsy is one of the most common neurological disorders, affecting about 50 million people around the world [1]. However, it is not a single entity, encompassing many different conditions with many different causes. Nevertheless, all these forms share the same degree of stigmatization and psychosocial burden [2]. In fact, a number of epidemiological studies have pointed out that any epilepsy syndrome, even those relatively uncomplicated, brings a multitude of complications that can be somatic, developmental, cognitive, behavioral and psychiatric [3, 4]. Such complications have a multifactorial origin, being related to the epilepsy itself, to specific characteristics of the individual patient and to the long-term treatment with antiepileptic drugs (AEDs).

Mood disorders represent an example of such a multifactorial and complex relationship [5]. In fact, epilepsy is a chronic disorder that brings about a number of social limitations (e.g. driving license, job opportunities etc.) and discriminations leading to demoralization, poor self-esteem and phobic avoidance. Nevertheless, the biological contribution to the association between epilepsy and depression is given by neuroanatomical and neurochemical principles such as the involvement of the mesiotemporal structures [6] and the psychotropic effect of AEDs [7].

12.2 Epidemiology of Depression in Epilepsy

Community-based studies report prevalence rates for depressive disorders in the region of 20–22 % [8, 9]. In selected samples, such as tertiary referral centers or surgery programs, the prevalence is even higher and raising up to 50 % [10, 11]. Such differences partially reflect the severity of the seizure disorder [12, 13]. However, epidemiological studies point out that the relationship between epilepsy and depression is not necessarily unidirectional, namely that some patients may present a mood disorder before the emergence of the seizure disorder [14].

The bidirectional relationship between epilepsy and depression may be related to a number of variables. Not least, a shared neurobiology that seems to be operant in both conditions [15].

12.3 Phenomenology of Depression in Epilepsy

During the last 20 years, the issue of phenomenology of depression in epilepsy has been matter of debate mainly because it has relevant implications in terms of treatment and prognosis. According to some authors, comorbid mood disorders are often characterized by atypical features, which are poorly reflected by conventional classificatory systems such as DSM and ICD [16–18]. In particular, classic endogenous-type depressive symptoms, such as feelings of guilt, "*Gefühl der Gefühllosigkeit*", and a circadian pattern of symptom severity are rarely reported [19]. However, other studies clearly show that it is possible to apply standardized criteria of DSM in a not negligible proportion of patients [20, 21].

Pre-modern psychiatrists, such as Kraepelin and Bleuler, observed that patients with epilepsy could develop a pleomorphic pattern of depressive symptoms intermixed with euphoric moods, irritability, fear and anxiety as well as anergia, pain and insomnia [22, 23]. This concept has been revitalized during the twentieth century by Blumer [24] who coined the term interictal dysphoric disorder (IDD) to refer to this type of somatoform-depressive disorder claimed as typical of patients with epilepsy. According to Blumer, IDD is characterized by eight key symptoms, grouped in three major categories, namely labile depressive symptoms (depressive mood, anergia, pain, and insomnia), labile affective symptoms (fear, anxiety), and supposedly "specific" symptoms (paroxysmal irritability, and euphoric moods). The latter group, in particular, identifies a peculiar symptom cluster of IDD that is reflected by the term "dysphoria" that mirrors the original definition of Kraepelin "*Verstimmungszustand*", emphasizing the periodicity of mood changes and the presence of outbursts of irritability and aggressive behavior. Such dysphoric episodes are described as occurring without external triggers and without clouding of consciousness, beginning and ending rapidly and recurring fairly regularly in a uniform manner (every few days to every few months and lasting a few hours up to 2 days). Since its introduction, the concept of IDD has been matter of debate. A cross-sectional study conducted in two epilepsy centers in Europe report prevalence rates of 17 % [25], raising up to 27 % [26] and 57 % [27] in selected samples, such as severe seizure disorders and surgery patients.

Notably, the concept of the IDD, theorized by Blumer, goes beyond the mood disorder per se, encompassing a spectrum of conditions which embraces a mood disorder with fleeting symptoms, a more severe syndrome with transient psychotic features till an even more debilitating disorder with prolonged psychotic states. In fact, according to Blumer's view, the schizophrenia-like psychoses of epilepsy [28] can be considered as a severe IDD with prominent psychotic features. Such a hypothesis is clearly influenced by the Kraepelinian view of the relationship between mood disorders and schizophrenia.

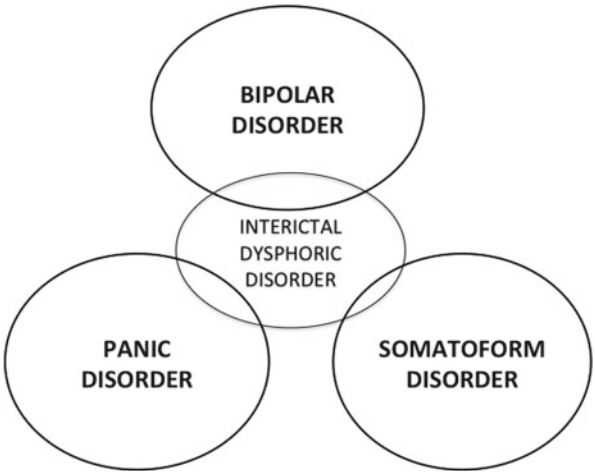

Fig. 12.1 The clinical spectrum of the interictal dysphoric disorder

In general terms, it is reasonable to hypothesize that the IDD observed today might have features different from those described by premodern psychiatry. For example, depressed mood and anergia may be much more evident than before because antiepileptic medications attenuate dysphoria and mood instability. Along these lines, different authors highlighted the chronic course of this state of moderate neurotic depression with symptom-free intervals typical of epilepsy, referring to a dimension very close to dysthymia [5, 29]. However, a detailed description of the clinical phenomenology of the IDD, using the operative definition of Blumer, has shown several commonalities with a specific subset of cyclothymic subjects, where depressive periods and labile-angry-irritable moods dominate the clinical picture [25]. This is in keeping with the original observation that patients with IDD benefit from a combined therapy of AEDs and antidepressant drugs [30], a combination extensively used in psychiatry in bipolar depression. Nevertheless, a validation of the concept of IDD against DSM criteria has shown that comorbid anxiety (especially generalized anxiety disorder) [25] and somatoform symptoms [31] represent important elements in the phenomenology of IDD. It is, therefore, evident, that the psychopathological characteristics of this syndrome overlap with a variety of clinical entities seen in clinical psychiatric practice (Fig. 12.1).

Finally, another relevant issue relates to the specificity of IDD with epilepsy. According to Blumer, IDD represents the most frequently seen comorbidity among patients with seizure disorders, being unique for this neurological condition [30]. A cross-sectional study in patients with epilepsy and migraine shows similar prevalence rates in both conditions, disfavoring the hypothesis that IDD is typical only of patients with epilepsy. However, it has to be acknowledged that Blumer points out that IDD can be occasionally seen in the absence of clinical seizures, in patients with brain lesions (with or without an abnormal EEG) [32]. Epilepsy and migraine

share a number of elements in terms of pathophysiology [33]. Therefore, further studies are needed to clarify whether IDD is an organic affective syndrome of neurological patients or is generally associated to chronically ill populations.

12.4 The Issue of Peri-ictal Mood Symptoms

A number of atypical and pleomorphic features of mood disorders in epilepsy are related to peri-ictal symptoms [34], namely a number of behavioral manifestations that occur around the ictus, either preceding or following. This point has relevant implications in terms of diagnosis, prognosis and treatment, emphasizing the need to dissect out peri-ictal manifestations from interictal ones. In fact, such symptoms are almost indistinguishable from interictal ones, apart from duration and the close relation with seizure occurrence and cannot be detected by rating scales or questionnaires [35].

Peri-ictal symptoms are usually classified according to their temporal relationship with seizures (Fig. 12.2). Pre-ictal symptoms are very rarely reported by patients, if not specifically questioned, and poorly investigated by clinicians. However, around one-third of patients with partial seizures report premonitory symptoms, usually preceding secondary generalized tonic-clonic seizures [4]. Among pre-ictal symptoms, behavioral changes are those most frequently experienced [36]. Prodromal moods of depression or irritability may occur hours to days before a seizure and are often relieved by the convulsion [37]. In a cross-sectional study in tertiary referral centers in Europe, around 13 % of patients experience irritability, dysphoria or depressed mood preceding seizures [34].

As for pre-ictal symptoms, post-ictal mood changes are rarely recognized in clinical practice. A case series of presurgical patients reports a 18 % prevalence of patients having post-ictally at least five symptoms of depression lasting more than 24 h [38]. Anhedonia, in particular, is the most frequently reported post-ictal

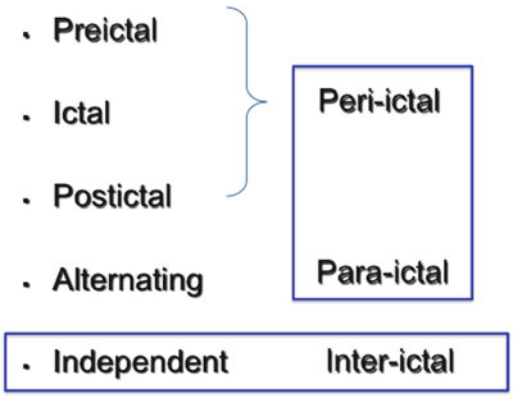

Fig. 12.2 Classification of peri-ictal symptoms in epilepsy

mood symptoms, about 33 % [38]. This quite interesting since that, as discussed before, anhedonia is rarely reported interictally.

Manic and hypomanic symptoms are also reported during the post-ictal phase. It has been reported that around 22 % of patients may present manic symptoms often with associated hallucinations or delusions [38]. Post-ictal mania seems to have a distinct position among psychiatric manifestations observed in the post-ictal period. Compared to post-ictal psychoses, post-ictal mania has a longer duration, a high frequency of recurrence, an old age at onset and is associated with EEG frontal discharges involving the non-dominant hemisphere [39]. Post-ictal anxiety is reported by 45 % of patients [38]. The median duration of symptoms ranges from 6 to 24 h but in one third of cases, post-ictal anxiety may last 24 h or longer.

12.5 Conclusions

Mood disorders in epilepsy present a number of atypical manifestations probably related to the neurobiology of the underlying neurological condition. However, anhedonia present a typical spectrum of presentation, being more frequently reported post-ictally than interictally. Further investigations in this subset of patients may shed light into the neurobiology of anhedonia, confirming the role of epilepsy as a privileged neurobiological model for the understanding of behavior and emotions.

References

1. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011;77:1005–12.
2. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav. 2008;12:540–6.
3. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. Epilepsia. 2012;53:1282–93.
4. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand. 2004;110:207–20.
5. Kanner AM, Balabanov A. Depression and epilepsy: how closely related are they? Neurology. 2002;58:S27–39.
6. Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res. 2000;39:121–5.
7. Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. Drug Saf. 2007;30:555–67.
8. Edeh J, Toone BK. Antiepileptic therapy, folate deficiency, and psychiatric morbidity: a general practice survey. Epilepsia. 1985;26:434–40.
9. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007;48:2336–44.
10. Victoroff JI, Benson F, Grafton ST, Engel Jr J, Mazziotta JC. Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates. Arch Neurol. 1994;51:155–63.

11. Ring HA, Moriarty J, Trimble MR. A prospective study of the early postsurgical psychiatric associations of epilepsy surgery. J Neurol Neurosurg Psychiatry. 1998;64:601–4.
12. Jacoby A. Psychosocial functioning in people with epilepsy in remission and the outcomes of antiepileptic drug withdrawal [electronic resource]. Tyne: University of Newcastle upon Tyne; 1995.
13. O'Donoghue MF, Goodridge DM, Redhead K, Sander JW, Duncan JS. Assessing the psychosocial consequences of epilepsy: a community-based study. Br J Gen Pract. 1999;49:211–4.
14. Hesdorffer DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. Ann Neurol. 2000;47:246–9.
15. Kanner AM. Depression and epilepsy: a bidirectional relation? Epilepsia. 2011;52 Suppl 1:21–7.
16. Kanner AM, Kozak AM, Frey M. The use of sertraline in patients with epilepsy: is it safe? Epilepsy Behav. 2000;1:100–5.
17. Mendez MF, Cummings JL, Benson DF. Depression in epilepsy. Significance and phenomenology. Arch Neurol. 1986;43:766–70.
18. Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: a proposal by the ILAE commission on psychobiology of epilepsy. Epilepsy Behav. 2007;10:349–53.
19. Mula M, Schmitz B. Depression in epilepsy: mechanisms and therapeutic approach. Ther Adv Neurol Disord. 2009;2:337–44.
20. Jones JE, Bell B, Fine J, Rutecki P, Seidenberg M, Hermann B. A controlled prospective investigation of psychiatric comorbidity in temporal lobe epilepsy. Epilepsia. 2007;48:2357–60.
21. Jones JE, Hermann BP, Barry JJ, Gilliam F, Kanner AM, Meador KJ. Clinical assessment of Axis I psychiatric morbidity in chronic epilepsy: a multicenter investigation. J Neuropsychiatry Clin Neurosci. 2005;17:172–9.
22. Kraepelin E, Diefendorf AR. Clinical psychiatry (1907). Delmar: Scholars' Facsimiles and Reprints; 1981.
23. Bleuler E. Textbook of psychiatry. New York: The Macmillan Co; 1924.
24. Blumer D. Dysphoric disorders and paroxysmal affects: recognition and treatment of epilepsy-related psychiatric disorders. Harv Rev Psychiatry. 2000;8:8–17.
25. Mula M, Jauch R, Cavanna A, Collimedaglia L, Barbagli D, Gaus V, Kretz R, Viana M, Tota G, Israel H, Reuter U, Martus P, Cantello R, Monaco F, Schmitz B. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. Epilepsia. 2008;49:650–6.
26. Hellwig S, Mamalis P, Feige B, Schulze-Bonhage A, van Elst LT. Psychiatric comorbidity in patients with pharmacoresistant focal epilepsy and psychiatric outcome after epilepsy surgery. Epilepsy Behav. 2012;23:272–9.
27. Blumer D, Wakhlu S, Davies K, Hermann B. Psychiatric outcome of temporal lobectomy for epilepsy: incidence and treatment of psychiatric complications. Epilepsia. 1998;39:478–86.
28. Trimble MR. The psychoses of epilepsy. New York: Raven Press; 1991.
29. Himmelhoch J. Major mood disorders related to epileptic changes. In: Blumer D, editor. Psychiatric aspects of epilepsy. Washington, DC: American Psychiatric Press; 1984. p. 271–94.
30. Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. Epilepsy Behav. 2004;5:826–40.
31. Blumer D, Herzog AG, Himmelhoch J, Salgueiro CA, Ling FW. To what extent do premenstrual and interictal dysphoric disorder overlap? Significance for therapy. J Affect Disord. 1998;48:215–25.
32. Blumer D, Heilbronn M, Himmelhoch J. Indications for carbamazepine in mental illness: atypical psychiatric disorder or temporal lobe syndrome? Compr Psychiatry. 1988;29:108–22.
33. Post RM, Silberstein SD. Shared mechanisms in affective illness, epilepsy, and migraine. Neurology. 1994;44:S37–47.
34. Mula M, Jauch R, Cavanna A, Gaus V, Kretz R, Collimedaglia L, Barbagli D, Cantello R, Monaco F, Schmitz B. Interictal dysphoric disorder and periictal dysphoric symptoms in patients with epilepsy. Epilepsia. 2010;51:1139–45.

35. Mula M, Schmitz B, Jauch R, Cavanna A, Cantello R, Monaco F, Trimble MR. On the prevalence of bipolar disorder in epilepsy. Epilepsy Behav. 2008;13:658–61.
36. Scaramelli A, Braga P, Avellanal A, Bogacz A, Camejo C, Rega I, Messano T, Arciere B. Prodromal symptoms in epileptic patients: clinical characterization of the pre-ictal phase. Seizure. 2009;18:246–50.
37. Blanchet P, Frommer GP. Mood change preceding epileptic seizures. J Nerv Ment Dis. 1986;174:471–6.
38. Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. Neurology. 2004;62:708–13.
39. Nishida T, Kudo T, Inoue Y, Nakamura F, Yoshimura M, Matsuda K, Yagi K, Fujiwara T. Postictal mania versus postictal psychosis: differences in clinical features, epileptogenic zone, and brain functional changes during postictal period. Epilepsia. 2006;47:2104–14.

Chapter 13
Anhedonia in Parkinson's Disease and Other Movement Disorders

Gianfranco Spalletta, Francesca Assogna, Carlo Caltagirone, and Albert F.G. Leentjens

Abstract Anhedonia, defined as lowered ability to experience physical or social pleasure, is a frequent symptom in patients with Parkinson's disease (PD). In this population, most studies report an association of anhedonia with neuropsychiatric disorders and syndromes such as depression, apathy and cognitive decline. Reports on the relationship between anhedonia and severity of motor symptoms in PD are inconclusive. The presence of anhedonia is diagnosed on the basis of history and mental status examination; its severity can be assessed by available rating scales. Several studies described anhedonia as strictly associated to depression in PD and probably related to degeneration of mesolimbic and mesocortical dopamine projections, thus contributing directly to the high incidence of depression and consequently of anhedonia in PD patients. This is supported by the observation that inhibition of dopamine system via D_2 receptor antagonists can be accompanied by reduced motivation, drive and spontaneity, and dysphoria.

G. Spalletta (✉) • F. Assogna
Neuropsychiatry Laboratory, I.R.C.C.S. Santa Lucia Foundation,
Via Ardeatina, 306 – 00179 Rome, Italy
e-mail: g.spalletta@hsantalucia.it

C. Caltagirone
Department of Neuroscience, University "Tor Vergata", Rome, Italy

Department of Clinical and Behavioral Neurology, I.R.C.C.S. Santa Lucia Foundation,
Via Ardeatina, 306 – 00179 Rome, Italy

A.F.G. Leentjens
Department of Psychiatry, Maastricht University Medical Centre,
P.O. Box 5800, 6202AZ Maastricht, The Netherlands
e-mail: a.leentjens@maastrichtuniversity.nl

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_13,

In contrast to PD, data on anhedonia in other movement disorders are still scarce.

Future research should be directed to a better understanding of the etiology and pathophysiology of anhedonia in order to be able to identify and provide new strategies for treatment of this neuropsychiatric phenomenon.

Keywords Parkinson's disease • Movement disorders • Anhedonia • Motor symptoms • Non-motor symptoms • Cognitive deficits • Apathy • Depression

Abbreviations

DBS-STN	Deep brain stimulation of the subthalamic nucleus
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR	The fourth revised edition of the DSM
ICD-10	International Classification of Diseases
PD	Parkinson's disease

13.1 Introduction

Parkinson's disease (PD) is generally considered a multidimensional neuropsychiatric disease with a broad spectrum of symptoms. Following the Queens Square Brain Bank diagnostic criteria, motor symptoms such as tremor, rigidity, hypokinesia, and postural instability are essential for a diagnosis of PD [1]. In addition to motor symptoms, psychopathological symptoms often accompany, and sometimes precede, the disease [2–4]. Depression, anxiety, apathy, psychosis, and cognitive dysfunction all occur frequently in PD [2], while it is known that both depression and anxiety may precede the onset of motor symptoms [5–7].

The pathophysiology of PD is widespread and multisystemic, involving several brain structures. Braak et al. [8] proposed a staging system for this pathophysiology based on the presence of intraneuronal α synucleine deposits, known as Lewy bodies. Different cerebral regions that are part of different functional neuro-anatomic circuits and different neurotransmitter systems, are affected sequentially. In the first stages, the olfactory tract and lower brainstem regions are affected; then, the pathology proceeds upwards to the midbrain, and next to the basal forebrain and cerebral cortex. In this sequence, the substantia nigra, which is thought to be associated with the motor symptoms of PD, is affected in mid-stage disease. The diversity of systems affected, and the fact that some of these systems are affected before involvement of the substantia nigra, may explain the diversity of symptoms as well as the fact that some of the non-motor symptoms may precede motor symptoms.

Anhedonia is a non-motor phenomenon defined as lowered ability to experience physical or social pleasure. It is generally considered a symptom rather than a disorder. In fact, anhedonia is a key symptom of various psychiatric illnesses,

including depression, which is the most frequent neuropsychiatric disorder observed in PD [2], apathy [9], abstinence or intoxication with several substances of abuse [10–12] and a negative symptom of schizophrenia [13–15]. Altered hedonic capacity is probably due to a basic neuropsychophysiological dysfunction. It is a marker of vulnerability that potentially precedes and contributes to the likelihood of developing psychiatric disorders [16]. Moreover, mood related symptoms, including anhedonia and apathy, also occur frequently in a variety of movement disorders other than PD, such as Lewy bodies dementia, Huntington's disease, progressive supranuclear palsy, multisystem atrophy, corticobasal degeneration, essential tremor, tics and dystonia [17–22]. Unfortunately, there is still a lack of data on anhedonia in these movement disorders.

Although anhedonia is often confused with depression or apathy, it differs from these different non-motor symptoms in term of mechanisms, therapeutic approaches, and prognosis. In this chapter we will try to clarify the concept of anhedonia in the context of movement disorders in order to determine whether it is a symptom of depression and apathy or, rather, a specific phenomenon, independent from other behavioral characteristics. Furthermore, we will illustrate the clinical assessment of anhedonia and rating scales used to measure hedonic tone. Finally, we will explain the link among anhedonia, motor symptoms and cognitive deficits in movement disorders and discuss the pathophysiology and potential pro-dopaminergic treatment of anhedonia. Correct recognition of anhedonia in patients with these disorders could lead to better treatment of the diseases and their clinical features leading to improved quality of life.

13.2 Conceptual Issues and Phenomenology

The term "anhedonia" comes from the Greek ἀν (an = "without") and ἡδονή (hēdonē = "pleasure"), and refers to a group of clinical phenomena whose common denominator is the complaint of incapacity to experience pleasure. At the end of the nineteenth century, anhedonia was first defined by Ribot [23] as loss of the capacity to feel pleasure. Anhedonia has been included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) series since 1980 [24] and in the International Classification of Diseases (ICD) since 1992 [25]. In both textbooks, it is considered a symptom of depression and schizophrenia, although it is unclear whether the mental states involved are the same in both cases. Finally, the fourth revised edition of the DSM (DSM-IV-TR) [26] defines anhedonia as diminished interest or pleasure in response to stimuli previously perceived as rewarding in a pre-morbid state.

More commonly, anhedonia is defined as the inability to experience pleasure or to get the accustomed satisfaction from everyday events or objects [27]. Sometimes a distinction into social and physical anhedonia is made, whereby physical anhedonia refers to the inability to experience pleasure from physical activities (including such activities as sporting or eating), while social anhedonia refers to the inability to experience pleasure from social encounters or relationships. Although this

distinction may be useful from a phenomenological point of view, there is as yet no pathophysiological evidence to support such division.

Several authors have recently proposed a more circumscribed definition of anhedonia centered on the distinction between anticipatory and consummatory pleasures [14]. Anticipatory pleasure is the pleasure that a subject experiences at the thought of a future event while consummatory pleasure reflects the pleasure that a subject experiences while he is engaged in an enjoyable activity. Anticipatory and consummatory pleasures correspond respectively to the neuroscientist concepts of liking and wanting in relation to reward. Moreover, some studies have strongly suggested that dopamine could be involved in the anticipatory experience of pleasure, whereas other neurotransmitters, such as opioids, could be involved in the consummatory experience of pleasure [28].

As previously mentioned, anhedonia is considered a symptom that can be present in various disorders, such as major depressive disorder, schizophrenia or schizophrenia spectrum disorders, dementia, or apathy [29]. In patients with movement disorders, symptoms of depression, such as apathy and anhedonia, may overlap with primary symptoms, thus making it more difficult to recognize secondary psychiatric symptoms. Flattening of the positive component of affect in anhedonia may lead to diminished facial expression of positive emotions and be confused with the hypomimia of PD or progressive supranuclear palsy. Moreover, anhedonia in PD may occur as a stand-alone symptom, but it mostly occurs as part of other syndromes, especially apathy and depressive disorder. In a recent review, all but one included studies reported that anhedonia was related to the presence of other psychiatric symptoms [30]. This issue was specifically addressed by Weintraub et al. [31]. In their study it was shown that PD patients showed no anhedonia in response to positive life events when compared with healthy controls. This was interpreted as evidence that anhedonia was not associated with PD as such, but instead must be due to other comorbidities, such as apathy or depression [31]. These findings are not surprising, since anhedonia is part of the proposed diagnostic criteria for apathy, as well as part of the criteria for major and minor depressive disorders of the DSM-IV-TR.

13.3 Clinical Assessment of Anhedonia

The fact that anhedonia is considered a *symptom* implies that it is improbable, or even impossible, to make a categorical (syndromal) diagnosis of anhedonia. The presence of anhedonia is defined on the basis of history and mental status examination. Unfortunately, there is no diagnostic test that can confirm the presence of this symptom on the basis of biological evidence. Patients themselves, or their spouse or caregiver, may reveal that they have difficulty in experiencing pleasure from activities that the person found pleasurable in the past. Sometimes this lack of pleasure is evident from observation as well. When anhedonia is present, it is fundamental to check for additional psychiatric comorbidity, especially the presence of apathy and

depression, for differential diagnosis. These two syndromal diagnoses based too on history and mental state examination.

In the case of apathy, it is usually not the patient that complains of apathy, but the spouse or caretaker. They observe that the patient is passive, disinterested, with a flattened affect. The patient may be inactive and spend a big part of the day sitting on the couch doing nothing, but typically he denies being bored. Usually, the patient's partner will suffer more from his inactivity than the patient himself. Moreover, the partner will report that the patient may need stimulation to perform everyday activities, involving grooming among other things. Often apathy is being mistaken for depression, which is understandable given the similarity of many of its symptoms. However, when the patient is questioned, he denies feeling sad and denies not being able to enjoy things. This enables the clinician to differentiate apathy from depression. In case of apathy, mental status examination will reveal reduced motivation, reduced activity, mental and physical slowing, poverty of thoughts, affective flattening and disinterest. A syndromal diagnosis of apathy can be made on the basis of proposed diagnostic criteria in case of apathy, and the DSM-IV criteria are used in case of depression [32]. The severity of anhedonia as a symptom, or of the syndromes of apathy and depression can be rated by specific rating scales mentioned (see below).

The syndromal diagnosis of depression is also made on the basis of history taking and mental state examination, and should meet the diagnostic criteria laid down in the DSM-IV [33]. A good starting point for history taking is to probe the two core symptoms of depression: depressed mood, and diminished interest or pleasure. If the patient admits to at least one of these two symptoms, a more detailed history should be carried out to reveal other symptoms of depression. One should not avoid asking for symptoms that may potentially be embarrassing for the patient or his spouse or caregiver, such as suicidal thoughts or plans. Such questions are essential for a proper appraisal of the potential risk involved in depression. Mental state examination may reveal mood symptoms, such as sadness, loss of interest, affective flattening and feelings of guilt, cognitive symptoms, including loss of concentration and mental slowing (relative to a previous level of functioning), and physical symptoms, such as loss of facial expression, slowing of movements, weight loss, insomnia and others.

13.4 Anhedonia Rating Scales

Two scales are available for the measurement of anhedonia, the Snaith-Hamilton Pleasure Scale [34] and the Chapman Scales for Physical and Social Anhedonia [35]. In patients with movement disorders, the Snaith-Hamilton Pleasure Scale is probably most widely used in spite of the fact that there are no validation studies in this group specifically. It is a self-rated instrument that consists of 14 statements that patients can agree or disagree to on a four-point Likert scale. Thus, the scale assesses the presence and severity of one single symptom using a number of items. It was

developed with the aim of producing a shorter and simpler scale for the measurement of anhedonia that is unlikely to be affected by social class, sex, age, dietary habits and nationality. In patients not suffering from PD, it has good face validity, internal consistency, item-total correlation, and test–retest correlation. There is some overlap between the items and symptoms of parkinsonism. This may lead to the inflation of scores in movement disorders patients if the cut-off score is not adjusted for these confounders.

The scale has been used by several authors to assess the level of anhedonia in PD patients and to evaluate the effect of (pharmacological) treatment of motor symptoms of PD on hedonic symptoms. It has proven to be sensitive to changes in hedonic tone.

The Chapman Scales for Physical and Social Anhedonia are probably the most widely used instruments to measure anhedonia in patients with psychiatric disorders, such as schizophrenia and depressive disorder. The original scale consists of 88 true/false questions, divided over two subscales: a subscale for physical anhedonia consisting of 40 items and one for social anhedonia consisting of 48 items. Higher scores indicate more severe anhedonia, except in the Italian translation, which is reversely scored with higher scores indicating less severe anhedonia. The scale for physical anhedonia was later revised to include 61 items and is often used independently from the social anhedonia scale. The time frame is not well defined. This scale was thought to lack face validity as it includes aspects of social withdrawal, loss of interest, lack of motivation, and other features that are currently considered part of the larger concept of "apathy" and not of pure anhedonia. In addition, many items are sensitive to personal opinions, preferences, and habits. Nevertheless, it has good internal consistency and item-total correlation. The scale was used in one study with PD patients. In this study, the researchers highlighted the shortcomings and impracticability of the scale.

Anhedonia is also assessed as a subdimension of various apathy and depression rating scales. A discussion of the many apathy and depression rating scales goes beyond the scope of the chapter and the reader is referred to the respective reviews of Movement Disorder Society task forces, that specifically review and critique these scales for use in PD patients [29, 36].

13.5 Epidemiology

Few studies assessed the prevalence of anhedonia as a symptom in movement disorders. In these studies, the presence of anhedonia is commonly defined using a cut-off score on an anhedonia rating scale. Based on this definition, 10–46 % of all PD patients suffer from anhedonia [2, 37–39].

Anhedonia is mostly studied in the context of apathy and depression. Until recently, apathy was ill defined, and usually diagnosed on the basis of an above threshold score on an apathy rating scale. Not surprisingly, these studies reported a wide range of frequencies of apathy in PD patients, varying from 17 % to 70 %,

depending on the population characteristics and the assessment procedure used [40–42]. Recently, consensus diagnostic criteria have been formulated that define apathy as a syndrome of deficient motivation, characterized by lack of motivation associated with deficits in three different domains: reduced spontaneous motor behavior, reduced spontaneous thoughts and cognition, and reduced emotional responsiveness [32]. This latter criterion includes both affective flattening and anhedonia. Following the diagnostic criteria, 17 % of PD patients suffered from apathy, with 52 % of patients showing reduced emotional responsiveness [43].

As mentioned above, the gold standard for the diagnosis of depressive syndromes are the criteria of the DSM-IV-TR [33]. For a major depressive episode, the presence of at least five out of nine specified symptoms are required, of which either reduced mood, or markedly diminished pleasure or interest is obligatory. This second criterion is ambiguous because it includes aspects of both anhedonia (diminished pleasure) as well as apathy (loss of interest), thus making it impossible to make a distinction between the two when making a depression diagnosis. A systematic review of prevalence studies of depressive syndromes in PD patients reported an average prevalence of 17 % for major depressive disorder, 22 % for minor depression and 13 % for dysthymia [44]. Clinically relevant depressive symptoms without a formal diagnosis of depressive disorder were reported in 35 % of patients [44]. Lemke et al. [38] reported that anhedonia occurs in 80 % of depressed PD patients.

13.6 Anhedonia and Psychiatric Symptoms

Prospective studies identifying risk factors for the development of anhedonia in PD patients are lacking, and all evidence on the etiology and associations of anhedonia with affective, motor and cognitive symptoms are based on cross-sectional studies.

Most, but not all, clinical studies found that anhedonia was closely related to depression or apathy and that in PD it could be considered a symptom of psychiatric disorders [31] (see Table 13.1). In particular, anhedonia has been identified as a frequent symptom of depression in PD [38, 39, 45, 49, 53, 56, 62, 63], and seems to be more severe in patients with more depressive symptoms.

Spalletta et al. [61] showed that patients with diagnosis of major depressive disorder were more anhedonic than those with minor depressive disorder, who were in turn more anhedonic than PD patients without depression. Similarly, most, but not all studies, report that anhedonia is associated with apathy in patients with PD [41, 43].

Zahodne et al. [59] tried to characterize depression in PD patients in terms of components, including negative affect, apathy and anhedonia. In a factor analysis these factors were highly correlated and overlapped. Moreover, these three components were significantly associated with depressive status but the strongest unique association with depressive episode status was exhibited by negative affect, followed by apathy and anhedonia. Apathy was most associated with global psychological disturbance in PD, while anhedonia was least discriminating of a depressive episode.

Table 13.1 Anhedonia and psychiatric symptoms in movement disorders

Author (year)	Sample (n)	Anhedonia assessment	Anhedonia vs. psychiatric symptoms
Fibiger (1984) [45]	Not available	Not available	Anhedonia: cardinal feature of clinical depression
Cantello et al. (1989) [46]	dPD = 13; NODEP PD = 11; dCS = 14; CS = 12	Fawcett and Clark Pleasure Scale	Anhedonia: main features of PD patients with major depression
Fleminger (1991) [47]	PD = 30 (LHP = 13; RHP = 17)	Three items added to the 21 items of the BDI (MBDI)	LHP: higher scores on all measures of depression and greatest increase in MBDI compared with RHP The total group: MBDI items selectively raised in only one patient. Thus, depression experienced by PD patients is atypical, with relatively little anhedonia
Rockwell et al. (2000) [48]	LBD = 26; AD = 26	Structured interviews	Higher level of anhedonia in LBD than AD patients
Pluk and Brown (2002) [41]	PD = 45 (PD-HA = 17; PD-LA = 28); Osteoarthritis patients = 17	SHAPS	PD vs. Osteoarthritis: significant differences on the SHAPS only when measured on a binary scale and with a cut-off ≥3 Osteoarthritis group: no one anhedonic PD group: 3 anhedonic PD-HA more anhedonic than PD-LA
Reichman et al. (2003) [39]	PD = 626	SHAPS-D	Prevalence of anhedonia: 45.7 % Significant correlation between the SHAPS-D scores and the SPES depression items
Isella et al. (2003) [37]	PD = 25; HC = 25	Physical Anhedonia Scale	Prevalence of anhedonia: 40 % in PD No significant correlations among anhedonia, depression and apathy
Lemke et al. (2005, 2006) [38, 49]	PD = 626 (dPD = 138; NODEP = 488); HC = 50	SHAPS-D	Prevalence of anhedonia: 45.7 % in PD and 79.7 % in dPD Significant correlation between anhedonia and depression
Weintraub et al. (2006) [31]	PD = 24; HC = 23	Lawton Positive and Negative rating scale	When present in PD, anhedonia is a symptom of neuropsychiatric disorders
Lieberman (2006) [50]	PD = 206	NPI	Anhedonia is more frequent in depressed PD and in demented PD patients

(continued)

Table 13.1 (continued)

Author (year)	Sample (n)	Anhedonia assessment	Anhedonia vs. psychiatric symptoms
Ehrt et al. (2006) [51]	PD = 145; dCS = 100	MADRS item on anhedonia	PD patients experienced a specific profile of depressive symptoms characterize by less anhedonia than dCS
Miller et al. (2007) [19]	PD = 354; ET = 53; Dystonia = 83	Item 4 of BDI	No significant between-groups differences in anhedonia
Zheng et al. (2009) [52]	PD = 131 (dPD = 27; sdPD = 71; NODEP = 33)	HDRS	Anhedonia is one of the most common symptoms in dPD (85.2 %), sdPD (88.7 %) and NODEP (60.6 %). It is concomitant with PD, it is not caused by mood disorders and it is not specific to the diagnosis of depression in PD
Santangelo et al. (2009a) [53]	PD = 125 (dPD = 65; NODEP = 60)	SHAPS	Anhedonia significantly associated with depression; dPD scored significantly higher on the HDRS and the SHAPS compared with NODEP
Santangelo et al. (2009b) [54]	PD = 939; VP = 68; MSA = 28; PSP = 27; LBD = 14	SHAPS	Anhedonia significantly correlated with depression (HDRS) in PD patients; LBD patients had a much higher anhedonic score that patients with other diagnosis Significant impact of apathy and depression on anhedonia in the total group
Pouladi et al. (2009) [55]	Animal model of HD	The sucrose intake test	HD animals displayed anhedonic behavior
Schrag et al. (2010) [21]	PSP = 188; MSA = 286	HADS	PSP patients were more anhedonic than those with MSA
Kaji and Hirata (2011) [56]	PD = 50	SHAPS-J	Anhedonia is present in 74 % of PD patients: anhedonia alone was present in 29 % of PD, anhedonia and depression in 4 % of PD, anhedonia, apathy and depression in 13 % of PD, and anhedonia and apathy in 29 % of PD A strong correlation was found between apathy and anhedonia
Fujiwara et al. (2011) [57]	PD = 100 (dPD = 46; NODEP = 54); HC = 111	SHAPS-J	Prevalence of anhedonia: 10 % in PD; anehdonic PD scored significantly higher on the SRQ-D than non-anhedonic PD; dPD scored significantly higher on the SHAPS-J

(continued)

Table 13.1 (continued)

Author (year)	Sample (n)	Anhedonia assessment	Anhedonia vs. psychiatric symptoms
Miura et al. (2012) [58]	PD = 86	SHAPS-J	Prevalence of anhedonia: 16.3 % in PD
Zahodne et al. (2012) [59]	PD = 95	SHAPS TEPS (TEPS-ANT/TEPS-CONS)	Possibility of statistically separating the 3 depression components in PD: negative affect, apathy and anhedonia. All 3 components were significantly associated with depression status. Anhedonia was least discriminating of a depressive episode, support ing the idea that anhedonia is not very prominent in PD depression
Di Giuda et al. (2012) [17]	PD = 21; Dystonia = 14; ET = 15; HC = 17	SHAPS	No significant differences in anhedonia between patients and HC
Zahodne et al. (2013) [60]	PD = 95	SHAPS TEPS (TEPS-ANT/TEPS-CONS)	Cognitive dimension of apathy, dysphoria, negative affect, and anxiety may better identify PD patients at risk for more global psychological dysfunction in comparison to anhedonia or affective flattening
Spalletta et al. (2013) [61]	PD = 254	SHAPS	MDD PD were more anhedonic than those with MIND and NODEP. Anhedonia prevalence was significantly higher in MDD patients (12.5 %) than MIND patients (7.2 %) or NODEP (1.5 %) Reduced hedonic tone was predicted from increased depression severity only in patients with MDD and NODEP, but not in MIND subgroup

AD Alzheimer disease, *BDI* Beck Depression Inventory, *CS* control subjects, *dCS* depressed control subjects, *dPD* PD patients with depression, *ET* essential tremor, *HADS* Hospital Anxiety and Depression Scale, *HC* healthy controls, *HD* Huntington's disease, *HDRS* Hamilton Depression Rating Scale, *LBD* Lewy bodies dementia, *LHP* PD patients with worse signs of PD on the left side, *MADRS* Montgomery-Asberg Depression Rating Scale, *MDD* major depressive disorder, *MIND* minor depressive disorder, *MSA* multisystem atrophy, *NODEP* PD without depression, *NPI* Modification of Cumming's Neuropsychiatric Inventory, *PD* Parkinson's disease, *PD-HA* PD patients with high apathy, *PD-LA* PD patients with low apathy, *PSP* progressive supranuclear palsy, *RHP* PD patients with worse signs of PD on the right side, *sdPD* PD with sub-threshold depression, *SHAPS-D* Snaith-Hamilton Pleasure Scale-German version, *SHAPS-J* Snaith-Hamilton Pleasure Scale-Japanese version, *SPES* Short Parkinson's Evaluation Scale, *SRQ-D* Self-Rating Questionnaire of Depression, *VP* vascular parkinsonism

Yet a minority of authors are of the opinion that anhedonia is not specifically associated with depression. Isella et al. [37] found no relationship among anhedonia, depression, and apathy. Others stress the fact that in PD patients anhedonia may be experienced in absence of depression [64]. Another study [52] reported a high presence of anhedonia in non-depressed PD patients.

To test Fibiger's hypothesis that anhedonia is a fundamental symptom of depression resulting from dopamine depletion, Fleminger [47] measured depression and anhedonia in PD patients with worse signs of disease on the left side of the body and those with worse signs on the right side of the body. In general, they found that depression experienced by PD patients was atypical, characterized by relatively little anhedonia, evident negative view of self, and prominent symptoms of anxiety. In line with this, Ehrt et al. [51] reported that PD patients experienced a specific profile of depressive symptoms characterized by less anhedonia than elderly depressed patients without PD.

Data on anhedonia in others movement disorders than PD are scarce. One study investigated anhedonia in patients with Lewy bodies dementia, and reported a higher level of anhedonia (56 %) in these patients compared to patients with Alzheimer disease (25 %) [48]. In another study [19], the prevalence of anhedonia was 60 % in patients with PD, essential tremor and dystonia, without between group differences in occurrence. In line with this, Di Giuda et al. [17] showed that patients with PD, essential tremor and dystonia did not differ in levels of anhedonia in comparison to healthy controls.

Santangelo et al. [54] explored anhedonia in patients with PD and in patients with different types of parkinsonism. They reported more severe anhedonia in patients with Lewy bodies dementia than in those with PD or other forms of parkinsonism, including vascular parkinsonism, multisystem atrophy, and progressive supranuclear palsy [34, 53].

In conclusion, in patients with PD, anhedonia seems to be related to neuropsychiatric symptoms, particularly depression. In other movement disorders, only few studies have assessed anhedonia.

13.7 Anhedonia and Motor Symptoms

The relationship between anhedonia and motor symptoms, which are the characteristic diagnostic feature of movement disorders, is still not very clear. Some studies found a relationship between these two symptoms whereas others did not (see Table 13.2). In particular, Bermanzohn and Siris [66] suggested a link between akinesia and anhedonia in people with parkinsonism and suggested that the common denominator is probably the reduced dopamine turnover in the brain. In line with this, Reichmann et al. [39] observed a significant association between anhedonia and psychomotor retardation. Similarly, Lemke et al. [38] reported that patients in the early stages of PD (Hoehn & Yahr stage ≤ 2) suffered from anhedonia less often than patients in more advanced stages (Hoehn & Yahr stage >2). They also reported that

Table 13.2 Anhedonia and motor symptoms in movement disorders

Author (year)	Sample (n)	Anhedonia assessment	Anhedonia vs. motor symptoms
Reichman et al. (2003) [39]	PD = 626	SHAPS-D	Significant relationship between anhedonia and psychomotor retardation as measured by the SPES
Isella et al. (2003) [37]	PD = 25; HC = 25	Physical Anhedonia Scale	No significant correlations between anhedonia and motor symptoms (UPDRS-III score)
Lemke et al. (2005) [38]	PD = 626 (dPD = 138; NODEP = 488); HC = 50	SHAPS-D	Significant correlation between anhedonia and motor disability; PD patients in earlier stages of the disease (Hoehn and Yahr $\leq$ 2) had anhedonia less often than PD patients in more advanced stages (Hoehn and Yahr > 2), and with more motor deficits (SPES motor status)
Witt et al. (2006) [65]	PD-DBS STN = 15	SHAPS-D	Significant correlation only between motor changes due to medication and changes in the BDI score. No correlation between the SHAPS-D scores and motor changes
Santangelo et al. (2009b) [54]	PD = 939; VP = 68; MSA = 28; PSP = 27; LBD = 14	SHAPS	No significant correlations between anhedonia, disease duration, disease severity, and motor disability (UPDRS-III score)
Fujiwara et al. (2011) [57]	PD = 100; HC = 111	SHAPS-J	No significant differences were identified between PD with anhedonia and PD with normal hedonic tone in duration of disease and Hoehn-Yahr stage
Miura et al. (2012) [58]	PD = 86	SHAPS-J	Significant positive effect of disease severity on anhedonia

dPD PD patients with depression, *HC* healthy controls, *LBD* Lewy bodies dementia, *MSA* multi-system atrophy, *NODEP* PD without depression, *PD* Parkinson's disease, *PSP* progressive supra-nuclear palsy, *SHAPS-D* Snaith-Hamilton Pleasure Scale-German version, *SHAPS-J* Snaith-Hamilton Pleasure Scale-Japanese version, *SPES* Short Parkinson's Evaluation Scale, *UPDRS-III* Unified Parkinson's Disease Rating Scale-part III, *VP* vascular parkinsonism

patients suffering from anhedonia showed more motor deficits, restrictions in daily living activities, and depression than patients without anhedonia. Miura et al. [58] also found that disease severity is one of the predictors of anhedonia, influencing positively the Snaith-Hamilton Rating Scale score.

By contrast, Fujiwara et al. [57] reported that, although PD patients with anhedonia tended to have a longer duration of disease and a higher Hoehn & Yahr stage [67], no significant differences were identified between PD patients with anhedonia and PD patients with normal hedonic tone. Isella et al. [37] reported no significant correlation among motor symptoms, disease duration, and physical anhedonia in PD patients.

In a sample of PD patients who had undergone deep brain stimulation of the subthalamic nucleus (DBS-STN), Witt et al. [65] reported a significant correlation between motor changes due to medication and changes in depression severity induced by medication but they did not find any correlation between anhedonia and motor symptoms.

There is only one study that addressed the relationship between anhedonia and motor symptoms in movement disorders other than PD. Santangelo et al. [53] reported that anhedonia was not affected by disease duration, disease severity, and motor disability in a mixed sample of patients including patients with PD, progressive supranuclear palsy, vascular parkinsonism, multisystem atrophy and Lewy bodies dementia.

Taken together these findings may support the hypothesis that reduced hedonic tone is not a simple reaction to motor disability due to the illness but rather a non-motor symptom of movement disorders.

13.8 Anhedonia and Cognitive Deficits

Anhedonia is mostly part of apathy and depression; thus it is unlikely that there would be no association between anhedonia and cognitive performance, since the association of cognitive dysfunction with these syndromes is well established [40, 41, 53, 68–70]. Apathy is also considered a predictor of cognitive decline and dementia in PD patients [40], whereas dementia and cognitive decline are predictors of incident apathy [71]. Moreover, apathy is associated with deficits in executive functions, more severe depressive symptoms, and a decreased quality of life [40, 41, 72, 73]. Depression is associated with worse motor function, more severe limitations in activities of daily living [74–77] and a lower quality of life [74, 75]. Furthermore, memory, concentration, and attention impairment are some of the depressive symptoms.

Santangelo et al. [53] analyzed anhedonia as symptom of major depressive disorder and reported significant correlations between anhedonia and cognitive functions (see Table 13.3). Depressed patients without apathy or anhedonia scored significantly worse than depressed patients with apathy or anhedonia on frontal and visuoconstructional tasks. The authors also stratified depressed PD patients

Table 13.3 Anhedonia and cognitive deficits in movement disorders

Author (year)	Sample (n)	Anhedonia assessment	Anhedonia vs. cognitive deficits
Isella et al. (2003) [37]	PD = 25; HC = 25	Physical Anhedonia Scale	No significant correlations between physical anhedonia, global cognitive status (MDRS and spatial span), and frontal functions (Letter and Category Verbal Fluency Tests and EXIT)
Santangelo et al. (2009a) [53]	PD = 125 (dPD = 65; NODEP = 60)	SHAPS	dPD with anhedonia and apathy (n = 11) scored worse on the FAB and the CT than NODEP (n = 50) dPD with anhedonia (n = 8) scored worse on the CT than NODEP
Santangelo et al. (2009b) [54]	PD = 939; VP = 68; MSA = 28; PSP = 27; LBD = 14	SHAPS	Significant correlations among anhedonia and FAB in PD, VP and PSP patients Significant correlations between anhedonia and MMSE only in PD patients
Spalletta et al. (2013) [61]	PD = 254	SHAPS	SHAPS score was significantly correlated with RDR, CRO, and SWCT interference time in MDD patients. In NODEP patients, SHAPS score was significantly correlated with SWCT word reading time and SWCT color naming time. No significant correlations between SHAPS and neuropsychological scores were found in MIND subgroup Predictors of hedonic tone differed in patients with different mood disorders: RDR scores in MDD patients and SWCT word reading time in NODEP patients

CRO Copy of the Rey-Osterrieth picture, *CT* Copying Task, *dPD* PD patients with depression, *EXIT* Executive Interview, *FAB* Frontal Assessment Battery, *HC* healthy controls, *LBD* Lewy bodies dementia, *MDD* major depressive disorder, *MDRS* Mattis Dementia Rating Scale, *MIND* minor depressive disorder, *MMSE* Mini Mental State Examination, *MSA* multisystem atrophy, *NODEP* PD without depression, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy, *RDR* Rey's 15-word test – Delayed Recall, *SHAPS* Snaith-Hamilton Pleasure Scale, *SWCT* Stroop Word-Color Test, *VP* vascular parkinsonism

according to the occurrence of clinically relevant anhedonia and apathy. They found that PD patients with anhedonia performed worse than non-depressed PD patients without anhedonia or apathy on the copying task, whereas PD patients with apathy and anhedonia performed worse than the non-depressed group on the frontal and the copying tasks. Therefore, anhedonia/apathy symptoms were associated with more severe impairment of visuoconstructional and frontal functions.

Spalletta et al. [61] reported significant correlations between anhedonia and neuropsychological test scores in PD patients with major depressive disorder and PD patients without depression, but not in those with minor depressive disorder. In particular, anhedonia was significantly correlated with long-term verbal memory, complex constructional praxis, and attention shifting and control in patients with major depressive disorder. In non-depressed patients, anhedonia was correlated with simple attention. Thus, cognitive findings appear to be able to discriminate between PD patients with comorbid major depressive disorder and those without depression, indicating that cognition may be a useful marker of anhedonia in more homogeneous PD subpopulations.

By contrast, Isella et al. [37] found no significant correlations between physical anhedonia and the neuropsychological variables investigated; only one frontal task, the Executive Interview [78], showed a trend towards a statistically significant correlation with anhedonia.

In the only study [53] investigating the relationship between anhedonia and cognitive functions in a variety of movement disorders, a large group of patients were evaluated for global cognitive level and for frontal functions. Significant correlations emerged between anhedonia and frontal functions in patients with PD, vascular PD, and progressive supranuclear palsy [34, 53]. However, anhedonia and global cognitive level were significantly correlated only in PD patients. Moreover, a higher severity of anhedonia was found in demented compared to non-demented patients.

In conclusion, studies on both PD and other movement disorders support the hypothesis of the involvement of frontal and prefrontal circuits in anhedonia. However, results are sometime conflicting also because the multifaceted phenomenology (different mood disorders, apathy, illness stage, etc.) associated with anhedonia. Thus, a comprehensive assessment of all dimensions of PD must be performed for accurate conclusions.

13.9 Pathophysiology and Pro-dopaminergic Treatment of Anhedonia

Harvey et al. [16] investigated the brain correlates of anhedonia in nonclinical subjects using structural and functional magnetic resonance imaging techniques and showed that its severity was inversely correlated with anterior caudate volume but was positively related to ventromedial prefrontal cortex activity during the processing of pictures with positive emotional content. These findings suggest that anhedonia may be related to reduced volume of the basal ganglia and to abnormal prefrontal functioning during hedonic processing. It has also been postulated that experiencing joy and pleasure, in patients with a mixture of psychiatric diagnosis, depends on dopaminergic reward mechanisms in the limbic system that are thought to be the basis of motivation, drive, and activation [79].

In PD patients, neuropathological [80], pharmacological [46, 81], and functional imaging [82] data suggest that degeneration of the dopaminergic system not only involves brain motor structures (including the basal ganglia) but also brain emotional structures of the limbic system [83]. Therefore, the degenerative processes of PD may affect dopaminergic reward mechanisms and lead to anhedonia, loss of motivation, avolition, and apathy [45, 84–90]. This hypothesis has also been confirmed in research on animal models [91], which suggests that anhedonia may be a complication of PD [30]. Cantello et al. [46] conducted an experimental study into the role of dopamine in anhedonia and depression in PD patients. In particular, they studied the euphoric response to intravenous methylphenidate comparing PD patients with major depressive disorder with non-depressed PD patients, as well as with non-parkinsonian subjects suffering from major depressive disorder, and a group of controls with no central nervous system or psychiatric disease. They reported that PD patients with major depressive disorder had a significant lack of sensitivity to the euphorizing effects of methylphenidate, compared to the other groups. This result was interpreted as dysfunction of reward-related dopamine systems in PD patients with major depressive disorder.

Studies showing that performance-sparing doses of neuroleptic drugs attenuate lever-pressing and running for food reward in hungry rats suggest that dopamine D_2 receptor antagonists selectively blunt the rewarding impact of food and other hedonic stimuli and induce anhedonia [92]. In humans, inhibition of the dopamine system via D_2 receptor antagonists can be accompanied by a reduction in motivation, drive, spontaneity, and dysphoria [93]. Dopamine has come to be identified as a central neurotransmitter in the reward system and it is associated with several symptoms (i.e. anhedonia, apathy, and dysphoria) commonly found in neuropsychiatric disorders, such as depression in PD [85, 93, 94]. These symptoms may be caused by a functional deficit of dopaminergic transmission in the dopaminergic reward system, which ascends from the mesencephalon to the ventral striatum (nucleus accumbens). The high incidence of dysphoria and depression in PD patients suggests that damage of mesocorticolimbic dopamine projections may cause these symptoms [45]. However, recent evidence shows that anhedonia emerges not only from a depletion of dopamine but from combined lesions of dopaminergic, noradrenergic and serotonergic systems [95, 96]. Moreover, μ opioid and endocannabinoid receptors in nucleus accumbens and ventral pallidum mediate hedonic perception of rewards, and activation of these receptors enhances the affective response for highly palatable rewards, such as sucrose [97]. Activation of GABA-A receptors in the nucleus accumbens is also known to regulate the affective response to sucrose [98]. Human neuroimaging studies suggest that subjective evaluations of pleasure are also mediated by the orbitofrontal cortex [99], although it is unclear whether the orbitofrontal cortex mediates the perception of pleasure or rather codes for pleasure (e.g. by assessing relative reward value). Activity of the ventral striatum and orbitofrontal cortex is decreased in anhedonic individuals with major depressive disorder [100].

Returning to the crucial role of dopamine neurotransmitter in determining anhedonia, research conducted on animals indicates that dopamine is associated with

prediction or anticipation and motivation to obtain rewards [101]. Although in humans administration of addictive drugs that increase synaptic dopamine levels leads to feelings of euphoria [102], it is unclear whether this dopamine release mediates hedonic arousal. It is well established that dopamine projections from the ventral tegmental area to ventral striatum fire in response to unpredicted rewards [103]. Successively, dopaminergic neurons fire in response to cues that predict rewards. Thus, it has been hypothesized that one role of dopamine is to transfer positive incentive value from the reward to the cue that predicts the reward [104]. On the other hand, when predicted rewards are not presented, dopamine firing is blunted [103]. Therefore, ventral striatal dopamine regulates the prediction and anticipation of rewards, and two mechanisms may be responsible for basic reinforcement learning [105].

Summarizing, various regions of the limbic system, especially ventral striatal dopaminergic systems, are implemented in the anticipatory (appetitive) positive affective state. Dopaminergic independent mechanisms, utilizing opiate and GABA receptors in the ventral striatum, amygdala and orbitofrontal cortex, are important in elaborating consummatory (sensory pleasure) positive states. Therefore, the distinction between anticipatory and consummatory anhedonia could have a strong value in PD. In fact, it could be suggested that anticipatory anhedonia could characterize PD patients while consummatory anhedonia could characterize PD patients with melancholic depression.

There is evidence that supports a positive effect of dopaminergic antiparkinsonian treatment on tracts of anhedonia (see Table 13.4). Several studies [38, 39, 49, 65, 106, 107] showed that the prevalence of anhedonia and depression is significantly reduced during treatment with pramipexole, which seems to have a preferential action for D_3 versus D_2 receptors in the mesolimbic system and the prefrontal cortex. In fact, Reichmann et al. [39] found that pramipexole had beneficial effects on anhedonia, depression, and motor dysfunctions. Similarly, Lemke et al. [38, 49] reported that pramipexole, as add-on treatment to levodopa, reduced the frequency of anhedonia in two observational open studies that included large samples of levodopa responsive PD patients. Anhedonia was present in 286 (45.7 %) PD patients at the start of the study and in 160 (25.5 %) after 9 weeks of treatment. During the study period, the prevalence of anhedonia significantly decreased from 74.3 to 45.3 % in moderate to severely depressed PD patients, and from 34.6 to 18.3 % in non-depressed PD patients. These data were also confirmed by results found in animal models, that showed the efficacy of pramipexole on anhedonia and depression [110, 111]. In a large sample of PD patients with insufficient effect of treatment with non-pramipexole dopamine agonists [106] was described the effect of both direct or abrupt and overlapping switching to pramipexole. The authors reported that after 4–8 weeks of pramipexole treatment scores on depression and anhedonia scales improved equally in both groups. Thus, the authors confirmed their previous findings [39] of an antianhedonic and antidepressant effect of pramipexole. In accordance, another study [107] conducted to assess the effect of pramipexole on depressive symptoms, especially on the subjective experience of anhedonia and feelings of emptiness, revealed that the effects of pramipexole and ropinirole on

Table 13.4 Anhedonia and pro-dopaminergic therapy

Author (year)	Sample (n)	Anhedonia assessment	Impact of dopaminergic therapy on anhedonia
Reichman et al. (2003) [39]	PD = 626	SHAPS-D	Positive effects of pramipexole on anhedonia, depression, and motor symptoms
Lemke et al. (2005, 2006) [38, 49]	PD = 626 (dPD = 138; NODEP = 488); HC = 50	SHAPS-D	Positive effects of pramipexole on anhedonia, depression, and motor symptoms
Witt et al. (2006) [65]	PD-DBS STN = 15	SHAPS-D	Significant effect of medication (levodopa) on hedonic tone
Reichmann et al. (2006) [106]	PD = 485	Visual Analogue Scales	Positive effects of pramipexole after 4–8 weeks on anhedonia, depression, and motor symptoms
Lemke (2008) [107]	Unavailable	Unavailable	Pramipexole had antidepressant, anxiolytic, and antianhedonic properties
Fujiwara et al. (2011) [57]	PD = 100; CS = 111	SHAPS-J	Pramipexole had an antianhedonic effect. The frequency of anhedonia was 0 % in patients treated and 13 % in those not treated with pramipexole
Miura et al. (2012) [58]	PD = 86	SHAPS-J	Pramipexole improved anhedonia while entacapone increased anhedonia
Drijgers et al. (2012) [108]	PD = 23; HC = 23	SHAPS	Significant improvement on anhedonia, respect to baseline, was found after the challenge with MTP, but not after the challenge with pramipexole or placebo
Chaudhuri et al. (2013) [109]	PD = 267 (178 rotigotine, 89 placebo)	NMSS	Significant improvement on anhedonia after treatment with rotigotine

CS control subjects, *dPD* PD patients with depression, *HC* healthy controls, *MTP* methylphenidate, *NMSS* Non-Motor Symptoms Scale, *NODEP* PD without depression, *PD* Parkinson's disease, *PD-DBS STN* PD with Deep Brain Stimulation of subthalamic nucleus, *SHAPS-D* Snaith-Hamilton Pleasure Scale-German version, *SHAPS-J* Snaith-Hamilton Pleasure Scale-Japanese version

cortico-frontal D_2 and particularly D_3 receptors seem to have antidepressant, anxiolitic, and antianhedonic properties.

There is also evidence that depressive symptoms improve equally with dopaminergic therapy and DBS-STN; conversely, hedonic tone improves only with

administration of levodopa. Most emotional changes do not correlate with changes in motor performance, indicating they are not reactive responses but are specific to the treatment [65]. The authors explains the different effects of levodopa and DBS-STN on depressive symptoms and anhedonia in terms of the different physiological mechanisms of the two methods: levodopa restores the phasic activity of the midbrain dopamine neurons, which is necessary for the identification of primary rewards, whereas DBS-STN is supposed to suppress the pathological neuronal activity of the parkinsonian subthalamic nucleus. The limbic territory of the subthalamic nucleus is indirectly connected with the anterior cingulate cortex, which shows hypometabolism in depressed patients suffering from PD. Although both levodopa and DBS-STN bring about significant activation of the anterior cingulated cortex, the effect of levodopa is more diffuse and involves additional mesolimbic-cortical pathways projecting from the ventral tegmental area to the limbic parts of the basal forebrain. Therefore, dopaminergic medication is likely more effective, which may explain the dissociation of the effects of DBS-STN and levodopa on mood and hedonic tone. DBS-STN seems to partly mimic the psychotropic effects of levodopa but does not fully replicate the motivational effects of dopaminergic stimulation. Also, Kondo [112] proposed to reduce anhedonic symptoms stimulating the reward system through the administration of dopaminergic drugs, such as levodopa and dopamine agonists (in particular D_3 agonists). The underlying assumption is that patients return to be more active and therefore are able to perform their activities of daily living. However, this therapy can have adverse effects or can lead to a dopamine dysregulation syndrome characterized by a state of excitation which in turn could lead to the development of an impulse compulsive disorder (pathological gambling, compulsive shopping, hypersexuality, etc.) [113]. Thus, dopaminergic therapy would ensure the release of a large amount of dopamine and, in many cases, could determine a state of stimulation of dopamine receptors. One of the main drugs leading to this effect is pramipexole, as mentioned above, that is able to improve the motivational state in PD patients with anhedonic tone [49]. Supporting these data, Fujiwara et al. [57] compared the frequency of anhedonia between groups treated with different antiparkinsonian agents. A significant difference was observed only for pramipexole and specifically the frequency of anhedonia was 0 % in patients treated and 13 % in those not treated with pramipexole. Also Miura et al. [58] showed that pramipexole significantly reduced anhedonia, while entacapone and disease severity increased anhedonia.

Finally, in a recent randomized controlled trial [109] has been shown that rotigotine-treated patients improved in mood/apathy domain of the Non-Motor Symptoms Scale [114]. In particular, a positive effect was found on items of "lost interest in doing things", "lost interest in surroundings", "seems sad or depressed" and "difficulty experiencing pleasure". On the other hand, in a double-blind randomized placebo controlled study the authors analyzed the effects of: (i) a direct dopaminergic challenge with the D_2 receptor agonist pramipexole, (ii) an indirect challenge with the dopamine reuptake inhibitor methylphenidate, and (iii) placebo, on mood, motivation and cognition in PD patients and healthy controls. They found that at baseline, when the assessment was done prior to administration of the drug,

no significant differences between PD patients and healthy controls existed in hedonic tone. However, anhedonia improvement was found after the challenge with methylphenidate, but not after the challenge with pramipexole or placebo. In healthy controls there were no effects [108].

In conclusion, dopaminergic stimulation might be considered as a strategy for the treatment of both motor and non-motor symptoms in PD, particularly on depression and anhedonia [115]. However, additional dopaminergic therapy in patients who show sufficient control over motor symptoms may increase the risk of inducing adverse effects, such as lower limb edema, daytime drowsiness, valvular disease of the heart, psychiatric symptoms, and dyskinesia. Unfortunately, there are no data on the impact of pro-dopaminergic treatment on anhedonia in other movement disorders.

13.10 Conclusions and Future Directions

Anhedonia is a frequent symptom in patients with PD, while only limited data are available for other movement disorders. In particular, the majority of authors identified anhedonia as a symptom of depression in PD and other movement disorders. On the other hand, a minority of studies found no relationship between anhedonia and depression [37] or described anhedonia as independent from mood disorder [52, 56, 64] or least discriminant for a depressive episode [51, 59, 60]. In patients with major depressive disorder, anhedonia is correlated with increased activity in the ventromedial prefrontal cortex and reduced activity in the amygdala [100] and reduced volume of anterior caudate [116]. Similarly, fatigue and psychomotor symptoms are associated with frontal and caudate abnormalities in depression [117, 118]. Major depressive disorder, in particular the melancholic subtype, which is characterized by anhedonia and psychomotor retardation, seems to be related not only to serotonergic but also to dopaminergic dysfunctions [119]. Moreover, mesolimbic and mesocortical dopamine projections appear to be involved in the reward system and also in depression phenomenology [45]. Therefore, as these projections have been shown to degenerate in movement disorders, particularly PD, they might contribute directly to the high incidence of depression, and thus of anhedonia [85].

Dopamine agonists may have a positive effect on anhedonia [38, 39, 49, 106, 107], which supports the hypothesis that inhibition of dopamine system via D_2 receptor antagonists can be accompanied by reduced motivation, drive, spontaneity, and dysphoria.

As to the role of cognitive status in anhedonia, some studies [53, 61] support the hypothesis of involvement in patterns of frontal and prefrontal dopamine circuits, suggesting that frontal lobe dysfunctions may contribute to increase the severity of anhedonia.

Another issue of debate concerns the possible relationships among anhedonia, motor deficits, duration of illness and activities of daily living in PD patients and other movement disorders, but data are still inconsistent and do not allow any

conclusions [37–39, 54, 65]. This inconsistency can be attributed to several various factors: (a) the different scales used to measure anhedonia severity (Snaith-Hamilton Pleasure Scale, Chapman Scales for Physical and Social Anhedonia, items of depression scales); (b) the use of small samples which may have affected results, increasing negative findings; (c) the inadequate diagnosis of depressive disorders using depression rating scales instead of diagnostic interviews; and (d) the concomitant use of antiparkinsonian therapy.

In conclusion, from a clinical point of view the characterization of anhedonia (either physical or social) is important because it has negative effects on the activities of daily living, motor performance, and quality of life [29, 39]. Therefore, future studies aimed at investigating the relationship between anhedonia and other clinical features are required, particularly in the context of movement disorders other than PD.

Several questions remain unresolved and could be addressed by using better definition of anhedonia that distinguishes consummatory and anticipatory anhedonia. While anticipatory anhedonia may be present in both depressed and non-depressed PD patients, consummatory anhedonia may be characteristic of depressed PD patients only. The relationship between apathy and anhedonia could be explained by the anticipatory component of anhedonia that could be treated by dopamine therapy. Anticipatory *hyper*hedonia may be associated to impulse control disorders, which may also occur in PD. In view of the strong relationship between anticipatory anhedonia and dopamine deficits, anticipatory anhedonia may characterize non-PD subjects prone to develop an impulse control disorder. One hypothesis could be that patients with essential tremor and anhedonia, particularly anticipatory anhedonia, could be at a higher risk of developing PD that patients with essential tremor without anhedonia. Thus, the exploration of hedonic deficits in movement disorders may also have heuristic value for predicting disease progression, prevention of side effects of treatment with levodopa or a dopamine agonist, and the identification of vulnerability factors for movement disorders.

References

1. de Rijk MC, Rocca WA, Anderson DW, et al. A population perspective on diagnostic criteria for Parkinson's disease. Neurology. 1997;48(5):1277–81.
2. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009;24(11):1641–9.
3. Leentjens AFG. Epidemiology of psychiatric symptoms in Parkinson's disease. Adv Biol Psychiatry. 2012;27:1–12.
4. Wolters EC. Dopaminomimetic psychosis in Parkinson's disease patients: diagnosis and treatment. Neurology. 1999;52(7 Suppl 3):S10–3.
5. Leentjens AF, Van den Akker M, Metsemakers JF, etal. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord. 2003;18(4):414–8.
6. Schuurman AG, van den Akker M, Ensinck KT, et al. Increased risk of Parkinson's disease after depression: a retrospective cohort study. Neurology. 2002;58(10):1501–4.

7. Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case–control study. Mov Disord. 2000;15(4):669–77.
8. Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197–211.
9. Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci. 1991;3(3):243–54.
10. Kitanaka J, Kitanaka N, Takemura M. Neurochemical consequences of dysphoric state during amphetamine withdrawal in animal models: a review. Neurochem Res. 2008;33(1): 204–19.
11. Stevens A, Peschk I, Schwarz J. Implicit learning, executive function and hedonic activity in chronic polydrug abusers, currently abstinent polydrug abusers and controls. Addiction. 2007;102(6):937–46.
12. Vacca G, Ahn S, Phillips AG. Effects of short-term abstinence from escalating doses of D-amphetamine on drug and sucrose-evoked dopamine efflux in the rat nucleus accumbens. Neuropsychopharmacology. 2007;32(4):932–9.
13. Cohen AS, Leung WW, Saperstein AM, et al. Neuropsychological functioning and social anhedonia: results from a community high-risk study. Schizophr Res. 2006;85(1–3): 132–41.
14. Gard DE, Kring AM, Gard MG, et al. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93(1–3):253–60.
15. Winograd-Gurvich C, Fitzgerald PB, Georgiou-Karistianis N, et al. Negative symptoms: a review of schizophrenia, melancholic depression and Parkinson's disease. Brain Res Bull. 2006;70(4–6):312–21.
16. Harvey PO, Pruessner J, Czechowska Y, et al. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry. 2007;12(8):703, 767–75.
17. Di Giuda D, Camardese G, Bentivoglio AR, et al. Dopaminergic dysfunction and psychiatric symptoms in movement disorders: a 123I-FP-CIT SPECT study. Eur J Nucl Med Mol Imaging. 2012;39(12):1937–48.
18. Kim WH, Lee YS, Jung SH, et al. Major depressive disorder preceding the onset of progressive supranuclear palsy. Psychiatry Invest. 2009;6(2):112–4.
19. Miller KM, Okun MS, Fernandez HF, et al. Depression symptoms in movement disorders: comparing Parkinson's disease, dystonia, and essential tremor. Mov Disord. 2007;22(5): 666–72.
20. Paulsen JS, Nehl C, Hoth KF, et al. Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci. 2005;17(4):496–502.
21. Schrag A, Sheikh S, Quinn NP, et al. A comparison of depression, anxiety, and health status in patients with progressive supranuclear palsy and multiple system atrophy. Mov Disord. 2010;25(8):1077–81.
22. Vaccarino AL, Sills T, Anderson KE, et al. Assessment of depression, anxiety and apathy in prodromal and early Huntington disease. PLoS Curr. 2011;3:RRN1242.
23. Ribot TH. The psychology of emotions. London: W Scott Pub. Co.; New York: C. Scribner's; 1903.
24. APA. Diagnostic and statistical manual of mental disorders. 3rd ed. (DSM-III) Washington, DC: APA; 1980.
25. WHO. The ICD–10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: WHO; 1992.
26. APA. Diagnostic and statistical manual of mental disorders 4th text revised (DSM-IV-TR). Washington, DC: APA; 2000.
27. Sims A. Symptoms in the mind. London: Balliere Tindall; 1988.
28. Loas G, Krystkowiak P, Godefroy O. Anhedonia in Parkinson's disease: an overview. J Neuropsychiatry Clin Neurosci. 2012;24(4):444–51.
29. Leentjens AFG, Dujardin K, Marsh L, et al. Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2008;23(14):2004–14.

30. Assogna F, Cravello L, Caltagirone C, et al. Anhedonia in Parkinson's disease: a systematic review of the literature. Mov Disord. 2011;26(10):1825–34.
31. Weintraub D, Cary MS, Stern MB, et al. Daily affect in Parkinson disease is responsive to life events and motor symptoms. Am J Geriatr Psychiatry. 2006;14(2):161–8.
32. Robert P, Onyike CU, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry. 2009;24(2): 98–104.
33. APA. Diagnostic and statistical manual of mental disorder. 4th ed. (DSM-IV) Washington, DC: APA; 1994.
34. Snaith RP, Hamilton M, Morley S, et al. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995;167(1):99–103.
35. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85(4):374–82.
36. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2007;22(8):1077–92.
37. Isella V, Iurlaro S, Piolti R, et al. Physical anhedonia in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2003;74(9):1308–11.
38. Lemke MR, Brecht HM, Koester J, et al. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. J Neuropsychiatry Clin Neurosci. 2005;17(2):214–20.
39. Reichmann H, Brecht MH, Koster J, et al. Pramipexole in routine clinical practice: a prospective observational trial in Parkinson's disease. CNS Drugs. 2003;17(13):965–73.
40. Dujardin K, Sockeel P, Devos D, et al. Characteristics of apathy in Parkinson's disease. Mov Disord. 2007;22(6):778–84.
41. Pluck GC, Brown RG. Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002;73(6):636–42.
42. Starkstein SE, Merello M, Jorge R, et al. The syndromal validity and nosological position of apathy in Parkinson's disease. Mov Disord. 2009;24(8):1211–6.
43. Drijgers RL, Dujardin K, Reijnders JS, et al. Validation of diagnostic criteria for apathy in Parkinson's disease. Parkinsonism Relat Disord. 2010;16(10):656–60.
44. Reijnders JS, Ehrt U, Weber WE, et al. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23(2):183–9; quiz 313.
45. Fibiger HC. The neurobiological substrates of depression in Parkinson's disease: a hypothesis. Can J Neurol Sci. 1984;11(1 Suppl):105–7.
46. Cantello R, Aguggia M, Gilli M, et al. Major depression in Parkinson's disease and the mood response to intravenous methylphenidate: possible role of the "hedonic" dopamine synapse. J Neurol Neurosurg Psychiatry. 1989;52(6):724–31.
47. Fleminger S. Left-sided Parkinson's disease is associated with greater anxiety and depression. Psychol Med. 1991;21(3):629–38.
48. Rockwell E, Choure J, Galasko D, et al. Psychopathology at initial diagnosis in dementia with Lewy bodies versus Alzheimer disease: comparison of matched groups with autopsy-confirmed diagnoses. Int J Geriatr Psychiatry. 2000;15(9):819–23.
49. Lemke MR, Brecht HM, Koester J, et al. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. J Neurol Sci. 2006;248(1–2):266–70.
50. Lieberman A. Are dementia and depression in Parkinson's disease related? J Neurol Sci. 2006;248:138–42.
51. Ehrt U, Bronnick K, Leentjens AF, et al. Depressive symptom profile in Parkinson's disease: a comparison with depression in elderly patients without Parkinson's disease. Int J Geriatr Psychiatry. 2006;21(3):252–8.
52. Zheng J, Sun S, Qiao X, et al. Depression in patients with Parkinson's disease and the associated features. J Huazhong Univ Sci Technolog Med Sci. 2009;29(6):725–8.
53. Santangelo G, Vitale C, Trojano L, et al. Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. J Neurol. 2009;256(4):632–8.

54. Santangelo G, Morgante L, Savica R, et al. Anhedonia and cognitive impairment in Parkinson's disease: Italian validation of the Snaith-Hamilton Pleasure Scale and its application in the clinical routine practice during the PRIAMO study. Parkinsonism Relat Disord. 2009;15(8):576–81.
55. Pouladi MA, Graham RK, Karasinska JM, et al. Prevention of depressive behaviour in the YAC 128 mouse model of Huntington disease by mutation at residue 586 of huntingtin. Brain. 2009;132:919–32.
56. Kaji Y, Hirata K. Apathy and anhedonia in Parkinson's disease. ISRN Neurol. 2011;2011:219427.
57. Fujiwara S, Kimura F, Hosokawa T, et al. Anhedonia in Japanese patients with Parkinson's disease. Geriatr Gerontol Int. 2011;11(3):275–81.
58. Miura S, Kida H, Nakajima J, et al. Anhedonia in Japanese patients with Parkinson's disease: analysis using the Snaith-Hamilton Pleasure Scale. Clin Neurol Neurosurg. 2012;114(4):352–5.
59. Zahodne LB, Marsiske M, Okun MS, et al. Components of depression in Parkinson disease. J Geriatr Psychiatry Neurol. 2012;25(3):131–7.
60. Zahodne LB, Marsiske M, Bowers D. A latent class analysis of psychological disturbance in Parkinson's disease. Int J Geriatr Psychiatry. 2013;28:1054–60. doi:10.1002/gps.3927.
61. Spalletta G, Fagioli S, Meco G, et al. Hedonic tone and its mood and cognitive correlates in Parkinson's disease. Depress Anxiety. 2013;30(1):85–91.
62. Snaith RP. Identifying depression: the significance of anhedonia. Hosp Pract (Off Ed). 1993;28(9A):55–60.
63. Taylor AE, Saint-Cyr JA. Depression in Parkinson's disease: reconciling physiological and psychological perspectives. J Neuropsychiatry Clin Neurosci. 1990;2(1):92–8.
64. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol. 2008;15 Suppl 1:14–20.
65. Witt K, Daniels C, Herzog J, et al. Differential effects of L-dopa and subthalamic stimulation on depressive symptoms and hedonic tone in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2006;18(3):397–401.
66. Bermanzohn PC, Siris SG. Akinesia: a syndrome common to parkinsonism, retarded depression, and negative symptoms of schizophrenia. Compr Psychiatry. 1992;33(4):221–32.
67. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17(5):427–42.
68. Aarsland D, Bronnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. J Neurol Neurosurg Psychiatry. 2009;80(8):928–30.
69. Oguru M, Tachibana H, Toda K, et al. Apathy and depression in Parkinson disease. J Geriatr Psychiatry Neurol. 2010;23(1):35–41.
70. Troster AI, Stalp LD, Paolo AM, et al. Neuropsychological impairment in Parkinson's disease with and without depression. Arch Neurol. 1995;52(12):1164–9.
71. Pedersen KF, Alves G, Aarsland D, etal. Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. J Neurol Neurosurg Psychiatry. 2009;80(11):1279–82.
72. Holroyd S, Currie LJ, Wooten GF. Depression is associated with impairment of ADL, not motor function in Parkinson disease. Neurology. 2005;64(12):2134–5.
73. Liu CY, Wang SJ, Fuh JL, et al. The correlation of depression with functional activity in Parkinson's disease. J Neurol. 1997;244(8):493–8.
74. Global Parkinson's Disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord. 2002;17(1):60–7.
75. Hobson P, Holden A, Meara J. Measuring the impact of Parkinson's disease with the Parkinson's Disease Quality of Life questionnaire. Age Ageing. 1999;28(4):341–6.
76. Ravina B, Camicioli R, Como PG, et al. The impact of depressive symptoms in early Parkinson disease. Neurology. 2007;69(4):342–7.

77. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry. 2000;69(3):308–12.
78. Royall DR, Mahurin RK, Gray KF. Bedside assessment of executive cognitive impairment: the executive interview. J Am Geriatr Soc. 1992;40(12):1221–6.
79. Heinz A, Schmidt LG, Reischies FM. Anhedonia in schizophrenic, depressed, or alcohol-dependent patients–neurobiological correlates. Pharmacopsychiatry. 1994;27 Suppl 1:7–10.
80. Uhl GR, Hedreen JC, Price DL. Parkinson's disease: loss of neurons from the ventral tegmental area contralateral to therapeutic surgical lesions. Neurology. 1985;35(8):1215–8.
81. Javoy-Agid F, Agid Y. Is the mesocortical dopaminergic system involved in Parkinson disease? Neurology. 1980;30(12):1326–30.
82. Kunig G, Leenders KL, Martin-Solch C, et al. Reduced reward processing in the brains of Parkinsonian patients. Neuroreport. 2000;11(17):3681–7.
83. Braak H, Braak E. Pathoanatomy of Parkinson's disease. J Neurol. 2000;247 Suppl 2:II3–10.
84. Bench CJ, Friston KJ, Brown RG, et al. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. Psychol Med. 1993;23(3):579–90.
85. Bressan RA, Crippa JA. The role of dopamine in reward and pleasure behaviour–review of data from preclinical research. Acta Psychiatr Scand. 2005;111 Suppl 427:14–21. doi:10.1111/j.1600-0447.2005.00540.x.
86. Grafton ST. Contributions of functional imaging to understanding parkinsonian symptoms. Curr Opin Neurobiol. 2004;14(6):715–9.
87. Heinz A, Dufeu P, Kuhn S, et al. Psychopathological and behavioral correlates of dopaminergic sensitivity in alcohol-dependent patients. Arch Gen Psychiatry. 1996;53(12):1123–8.
88. Knable MB, Jones DW, Coppola R, et al. Lateralized differences in iodine-123-IBZM uptake in the basal ganglia in asymmetric Parkinson's disease. J Nucl Med. 1995;36(7):1216–25.
89. Malhi GS, Parker GB, Greenwood J. Structural and functional models of depression: from sub-types to substrates. Acta Psychiatr Scand. 2005;111(2):94–105.
90. Pizzagalli DA, Oakes TR, Fox AS, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatry. 2004;9(4):325, 393–405.
91. Carey RJ. An examination of parkinsonian versus anhedonia contributions to self-stimulation impairments induced by dopamine dysfunction. Behav Brain Res. 1986;22(2):117–25.
92. Wise RA, Spindler J, deWit H, et al. Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food. Science. 1978;201(4352):262–4.
93. Voruganti L, Awad AG. Neuroleptic dysphoria: towards a new synthesis. Psychopharmacology (Berl). 2004;171(2):121–32.
94. Scharfetter C. General psychopathology: an introduction. Cambridge: Cambridge University Press; 1980.
95. Delaville C, Chetrit J, Abdallah K, et al. Emerging dysfunctions consequent to combined monoaminergic depletions in Parkinsonism. Neurobiol Dis. 2012;45(2):763–73.
96. Rampersaud N, Harkavyi A, Giordano G, et al. Exendin-4 reverts behavioural and neurochemical dysfunction in a pre-motor rodent model of Parkinson's disease with noradrenergic deficit. Br J Pharmacol. 2012;167(7):1467–79.
97. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008;199(3):457–80.
98. Faure A, Richard JM, Berridge KC. Desire and dread from the nucleus accumbens: cortical glutamate and subcortical GABA differentially generate motivation and hedonic impact in the rat. PLoS One. 2010;5(6):e11223.
99. Rolls ET, Kringelbach ML, de Araujo IE. Different representations of pleasant and unpleasant odours in the human brain. Eur J Neurosci. 2003;18(3):695–703.
100. Keedwell PA, Andrew C, Williams SC, et al. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005;58(11):843–53.

101. Salamone JD, Correa M, Mingote S, et al. Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. J Pharmacol Exp Ther. 2003;305(1):1–8.
102. Volkow ND, Wang GJ, Fischman MW, et al. Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature. 1997;386(6627):827–30.
103. Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol. 1998;80(1): 1–27.
104. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998;28(3):309–69.
105. Hazy TE, Frank MJ, O'Reilly RC. Neural mechanisms of acquired phasic dopamine responses in learning. Neurosci Biobehav Rev. 2010;34(5):701–20.
106. Reichmann H, Odin P, Brecht HM, et al. Changing dopamine agonist treatment in Parkinson's disease: experiences with switching to pramipexole. J Neural Transm Suppl. 2006;71: 17–25.
107. Lemke MR. Depressive symptoms in Parkinson's disease. Eur J Neurol. 2008;15 Suppl 1:21–5.
108. Drijgers RL, Verhey FR, Tissingh G, et al. The role of the dopaminergic system in mood, motivation and cognition in Parkinson's disease: a double blind randomized placebo-controlled experimental challenge with pramipexole and methylphenidate. J Neurol Sci. 2012;320(1–2):121–6.
109. Chaudhuri RK, Martinez-Martin P, Antonini A, et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. Parkinsonism Relat Disord. 2013;19(7):660–5.
110. Maj M, Veltro F, Pirozzi R, et al. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry. 1992;149(6):795–800.
111. Willner P, Lappas S, Cheeta S, et al. Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. Psychopharmacology (Berl). 1994;115(4):454–62.
112. Kondo T. Dopamine dysregulation syndrome. Hypothetical application of reward system stimulation for the treatment of anhedonia in Parkinson's disease patients. J Neurol. 2008;255 Suppl 4:14–8.
113. Giovannoni G, O'Sullivan JD, Turner K, et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry. 2000;68(4):423–8.
114. Trenkwalder C, Kies B, Rudzinska M, et al. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord. 2011;26(1):90–9.
115. Picillo M, Rocco M, Barone P. Dopamine receptor agonists and depression in Parkinson's disease. Parkinsonism Relat Disord. 2009;15 Suppl 4:S81–4.
116. Pizzagalli DA, Holmes AJ, Dillon DG, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166(6):702–10.
117. Demyttenaere K, De Fruyt J, Stahl SM. The many faces of fatigue in major depressive disorder. Int J Neuropsychopharmacol. 2005;8(1):93–105.
118. Schrijvers D, Hulstijn W, Sabbe BG. Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. J Affect Disord. 2008;109(1–2):1–20.
119. Stein DJ. Depression, anhedonia, and psychomotor symptoms: the role of dopaminergic neurocircuitry. CNS Spectr. 2008;13(7):561–5.

Chapter 14
Anhedonia in Heart Disease

Gwenolé Loas

Abstract Several recent studies have reported that anhedonia could constitute a particular cardiotoxic symptom in subjects with acute coronary syndrome (ACS) or other cardio-vascular diseases. The aim of this overview was to briefly present the recent studies and propose several guidelines taking the limitations of these studies into account. Several hypotheses concerning the relationships between anhedonia and ACS are proposed as well as the relevance of using more restricted and validated definition of hedonic deficits taking into account the distinction between consummatory and anticipatory pleasures.

Keywords Anhedonia • Acute coronary syndrome • Anticipatory pleasure • Consummatory pleasure

Abbreviations

ACM	All-cause mortality
ACS	Acute coronary syndrome
ANP	Atrial natriuretic peptide
BDI-FS	The fast seven-item version of the Beck Depression Inventory
CIDI	The Composite International Interview
HADS-A	Hospital Anxiety and Depression Scale anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale depression subscale
HF	Heart failure

G. Loas (✉)
University Department of Psychiatry, Hôpital Erasme and ULB,
route de Lennik 808, B-1070 Bruxelles, Belgium
e-mail: gwenole.loas@erasme.ulb.ac.be

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_14,

LPS	Lipopolysaccharide
MACE	Cardiovascular mortality, recurrent ACS, unplanned revascularization
MI	Myocardial Infarction
PAD	Peripheral arterial disease
PAS	Physical anhedonia scale
TEPS	Temporal Experiences of Pleasure Scale
SAS	Chapman Social Anhedonia Scale
SHAPS	Snaith and Hamilton Pleasure Scale

14.1 Introduction

In the general cardiovascular literature, there is a recent increased interest in the role of positive affect and notably anhedonia, the lowered ability to experience pleasure, on clinical outcomes. The role of anhedonia has been explored in acute coronary syndrome (ACS) and also in heart disease, peripheral arterial disease and hypotension. Firstly we present the three studies that have explored anhedonia in heart disease, peripheral arterial disease and hypotension. Secondly we present the eight studies that have examined the role of anhedonia in the prognosis of subjects who have ACS.

14.2 Anhedonia in Heart Failure, Hypotension and Peripheral Arterial Disease

Impaired health status of chronic heart failure has been associated with several psychological factors and notably type D personality and one study has tested the potential effect of low positive affect (anhedonia) associated or not with type D personality on health status in a 12-months follow-up study in 276 patients chronic heart failure [1]. After controlling for demographic and clinical confounders, anhedonic non-type D patients reported lower mental health status, more feeling of disability and lower physical health status when compared with patients with non-type D without anhedonia.

Concerning hypotension, researches associating hypotension with depression have produced inconsistent results suggesting to take into account the different symptoms of depression and notably the distinction between negative and positive affects. One study [2] examined the association between hypotension, with depressive symptoms, negative affect and positive affect in a sample of 340 elderly persons aged from 77 to 99 years. Positive and negative affects were rated using the Positive and Negative Affect Scales. Diastolic hypotension was associated with anhedonia and use of antihypertensive medication was independently associated with anhedonia.

Unlike in ACS, the relationship between psychological variables and the symptoms of peripheral arterial disease (PAD) has not been studied. Patients with PAD report intermittent claudication or atypical leg symptoms and one study [3]

has examined the association between these symptoms and anxiety, depressive symptoms and anhedonia in sample of 628 PAD patients. Anhedonia rated by positive affect subscale of the HAD was only significantly associated with pain at rest.

14.3 Anhedonia in ACS

In subjects with ACS, depression has been associated with poor prognosis and notably a high risk of severe cardiac events or mortality. As depression constitutes a heterogeneous psychiatric disorder, several authors have tried to identify more specifically cardiotoxic symptoms. Among potential cardiotoxic symptoms, anhedonia could constitute a major poor prognostic factor, as suggested by six recent studies. Moreover, two studies have reported that when anhedonia is not taken into account separately but included with other symptoms into a specific syndrome, it becomes a non-significant prognostic factor.

Independently of these eight studies, one study found that anhedonia was associated with poor health status and more somatic and cognitive symptoms in patients with coronary artery disease [4].

14.3.1 Presentation of the Eight Studies

In the first study [5], 291 ACS patients completed the Chapman Physical Anhedonia Scale (PAS) and the Hospital Anxiety and Depression Scale depression subscale (HADS-D). Over a 3-year follow-up period, clinical events were classified as severe cardiac events (mortality or Myocardial Infarction, MI) or clinical events (mortality, MI, recurrence of ACS, hospital readmission and onset or deterioration of heart failure (HF)). Anhedonia was the only predictor of severe cardiac events and clinical events after adjusting for demographic and clinical variables. In contrast with depression, categorical anhedonia (PAS > 23) was an independent and significant predictor of severe cardiac events after adjusting for clinical variables. The incidence of death/MI in hedonics versus anhedonics was 11.1 % vs 22.1 %.

In the second study [6], 408 hospitalized ACS patients were followed for 67 weeks. The patients filled out the HADS-D, the fast seven-item version of the Beck Depression Inventory (BDI-FS) and the brief 10-item version of the Maastricht Questionnaire (MQ-10) rating anergia. Three derived depressive symptom scales evaluating fatigue-sadness, anhedonia and depressive cognitions were constructed from these three rating scales. Major adverse cardiac events (MACE: cardiovascular mortality, recurrent ACS, unplanned revascularization) were assessed and the MACE rate at the endpoint was 14.5 %. Using categorical definitions, only the HADS-D and Fatigue-sadness scales were significant predictors of MACE in univariate and multivariate analyses and the anhedonia scale was a significant predictor only in multivariate analysis. Moreover, when both fatigue-sadness and

anhedonia were included in the multivariate models, fatigue-sadness predicted MACE but anhedonia did not.

In the third study by the same team [7] reported in 598 patients with ACS followed during 8 years that all-cause mortality status was significantly associated with the HADS-D score and not with the HADS-A or BDI fast screen scores. The significant effect of the HADS-D score remained significant after adjustment for major clinical/demographic factors.

In the fourth study [8], 453 consecutive ACS patients were followed for 1 year. A structured psychiatric interview assessing depressed mood, anhedonia and major depressive episode was filled out and depressed mood and anhedonia were also assessed using two subscales extracted from the BDI. The mood subscale contains the sadness (item 1) and crying (item 10) items of the BDI, whereas the anhedonia subscale contains the loss of enjoyment (item 4) and loss of interest in others (item 12) items of the BDI. The main outcome measures were all-cause mortality (ACM) and major adverse cardiac events (MACEs: myocardial infarction, hospitalization for unstable angina, or urgent/emergency coronary revascularization). Controlling for demographic and medical covariates, anhedonia was a significant predictor of combined MACE and ACM, but depressed mood was not. Anhedonia remained a significant predictor after controlling for major depression or depressive level. Combined MACE and ACM were present in 29.9 % and 11.7 % of patients with and without anhedonia, respectively.

The fifth study [9] included 568 Myocardial Infarction (MI) patients. During follow-up (2.5 years), 115 MI patients experienced a cardiac event including death. Using the Composite International Interview (CIDI) to assess depressive symptoms, the authors computed sum scores for the presence of cognitive symptoms including lack of interest and somatic symptoms. Univariate as well as multivariate Cox regression analyses found that lack of interest was a significant predictor of cardiac events demonstrating that, after adjusting for potential confounders, interview ratings of anhedonia were associated with a significantly higher risk of cardiac events.

The sixth study [10] found that anhedonia, rated by the positive affect scale of the HAD, was independently associated with increased risk for all-cause mortality during 7 years of follow-up in 1206 patients who survived the first 6 months after percutaneous coronary intervention.

The seventh study [11] included 913 subjects with unstable angina pectoris or MI who were followed for 12 months. Fifty-one patients died (5.6 %) during follow-up and, according to the BDI, only somatic/affective symptoms (including loss of enjoyment (item 4) and loss of libido items (item 21)) and not the cognitive/affective symptoms (including the loss of enjoyment (item 4) and social withdrawal (item 12) items) were significantly related to mortality after adjusting for sociodemographic and clinical variables (Odds ratio = 1.92, 95 % CI = 1.36–2.71, $p < 0.001$).

The eighth study [12] included 226 coronary artery bypass graft patients who filled out the BDI-II and who were followed for a median of 4.9 years. Using confirmatory factorial analyses, the authors found a three-factor solution of the BDI-II. The affective factor contains the loss of pleasure (item 4) and loss of interest (item 12) items, whereas the somatic factor contains the loss of interest in sex item (item 21).

Sixty-five cardiac events (29 %) including deaths (4.4 % deaths or MI) were observed and only the cognitive factor was significantly associated with cardiac events with or without adjustment for covariates (left ventricular function, age, respiratory disease, heart failure, renal disease and diabetes). The affective factor of the BDI-II that contains three items (loss of pleasure (item 4), crying, loss of interest (item 12)) was not associated with cardiac outcome, but a trend towards significance was observed in non-adjusted or adjusted analyses ($p = 0.09$ and 0.08, respectively).

14.3.2 Discussion of the Eight Studies

These studies reported that anhedonia, rated by questionnaires or structured interviews, was an independent predictor of cardiac events in ACS or MI patients. Moreover, this effect remained significant after controlling for demographic and clinical variables. However, in multivariate analyses, when depression [5, 8] or depressed mood [8] was included as predictors, anhedonia remained a significant and independent predictor. When both fatigue-sadness and anhedonia were included in multivariate analysis, only fatigue-sadness was a significant predictor [6]. When anhedonia was rated by one or several anhedonia items (items 4, 12, 21) of the BDI or BDI-II, the results differed according to whether anhedonia was rated alone or together with other BDI items. Firstly, when anhedonia was rated alone it constitutes a poor prognostic factor [8]. Secondly, when anhedonia was rated with other BDI items, variable results were obtained. In the study by Roest et al. [11], using principal component analysis of the BDI, the authors distinguished cognitive/affective and somatic/affective components. Items 4 and 12 loaded on the cognitive/affective component, whereas items 4 and 21 loaded on the somatic/affective component. Only the somatic/affective component was predictive of all-cause mortality in non-adjusted or adjusted analyses. The results concerning anhedonia were uninterpretable, as two-thirds of the anhedonia items of the BDI loaded in each factor. In the study by Tully et al. [12], only the cognitive component of the BDI-II that did not contain any anhedonia item was a significant predictor of cardiac events although the affective component that contains two BDI-II anhedonia items did not reach significance. It is interesting to note that the affective factor of the BDI-II contained three items, two anhedonia items and the crying item. Moreover, several studies have reported that crying is moderately associated with depression severity and that there is no consensus to include this symptom in the diagnostic criteria of depression.

Three main conclusions can therefore be drawn from these studies. Firstly, anhedonia constitutes an independent predictor of cardiac events in ACS or MI patients, with an effect not related to depression. Secondly, the effect of anhedonia is no longer significant when fatigue-sadness is simultaneously taken into account in the analyses. Thirdly, the results concerning the factors extracted from the BDI suggest that the anhedonia items must be taken into account separately instead of in combination with other symptoms.

14.3.3 Guidelines for Better Evaluation of the Role of Anhedonia in ACS: Five Important Points

Firstly, the authors used nonspecific anhedonia scales to explore the relative effects of anhedonia. Nonspecific anhedonia rating scales were built by using either items of structured interviews (CIDI, DSM-IV) or items of questionnaires (BDI, HAD-D). Three of the 21 items of the BDI rate anhedonia [13]: Dissatisfaction (item 4), Social withdrawal (item 12), Loss of libido (item 21). In the study by Davidson et al. [8], only items 4 and 12 of the BDI were used to build an anhedonia scale. In the study by Doyle et al. [6], anhedonia was rated using a 4-item subscale (3 items of the HAD-D with two items rating pleasure and one rating humor, one item of the BDI-FS rating loss of pleasure). The use of these rating scales could lead to poor reproducibility of the results. Moreover, subjects were divided into anhedonic or hedonic groups using ad hoc cutoff scores that have not been rigorously determined. There is a consensus in the psychiatric literature, notably based on meta-analyses of the existing anhedonia scales, in favor of the use of anhedonia scales presenting satisfactory psychometric properties [14, 15]. The most widely used rating scales are the Chapman revised social (SAS) and physical anhedonia (PAS) scales and the Snaith and Hamilton Pleasure Scale (SHAPS). Moreover, well-defined cutoff scores have been proposed for the SAS and the PAS. We therefore suggest that the above limitation should be taken into account to allow replication of studies. It would be useful to conduct meta-analyses to establish a consensus for each relevant psychological variable of the recommended rating scales studied in ACS patients.

Secondly, the dependent variables are relevant severe or non-severe cardiac events at the endpoint, but various definitions for relevant events were used. In the study by Hoen et al. [9], cardiac events including mortality were evaluated but the authors did not distinguish between the various cardiac events. In one study [5], Major Adverse Cardiac Events (MACEs) included cardiovascular mortality, recurrent ACS, and unplanned revascularization but did not include myocardial infarction and, in another study [8], MACE comprised myocardial infarction, hospitalization for unstable angina, or urgent/emergency coronary revascularization but did not include cardiovascular mortality although all-cause mortality was rated independently. The fist study [5] defined severe cardiac events by all-cause mortality and myocardial infarction. The seventh study [11] assessed all-cause mortality and the eighth study [12] evaluated nonfatal cardiac events (MI, unstable angina pectoris, repeat revascularization, heart failure, sustained arrhythmia, stroke or cerebrovascular accident, left ventricular failure) and fatal cardiac events (mortality due to cardiac causes). A consensus should be reached, notably concerning a precise definition of severe cardiac events.

Thirdly, follow-up varied from one study to another (range: 1–4.9 years) but the prevalence of severe clinical events ranged from 4.4 to 15 % in the six studies. These results could suggest that severe clinical events tended to occur during the first year of follow-up.

Fourthly, the nature and number of sociodemographic and clinical covariables entered in the multivariate analyses varied between the studies. Selection criteria were based on either a priori selection (forced choice) or on the significance found in univariate analyses. The number of covariables ranged from 4 to 11. Guidelines must be defined concerning the modalities of covariable selection.

Fifthly, only two studies [5, 8] controlled for depressive level, using depression rating scale scores, when anhedonia was tested as an independent predictor of severe cardiac events. Moreover, the use of separate scales rating depressive level and anhedonia should be recommended to avoid the risk of multicolinearity in multiple regressions.

14.3.4 Concluding Remarks

14.3.4.1 What Is the Status of Anhedonia in ACS?

In the psychiatric literature, anhedonia [16] is conceptualized either as a symptom found notably in depression and schizophrenia or a trait found in specific personalities (e.g. schizoid or pre-depressive personalities). The design of the studies cannot determine whether anhedonia rated after ACS or MI constitutes a premorbid trait. One study [5] used the PAS that evaluates long-term deficit of hedonic capacity, but self-evaluation could be influenced by the subject's present mood state. One hypothesis could be that some subjects present chronic anhedonia that increases the risk of depression following ACS or MI. Only prospective studies in subjects at risk of ACS or MI could test this hypothesis that anhedonia constitutes a premorbid trait.

14.3.4.2 How Can the Relationship Between Anhedonia and Acute Coronary Syndrome Be Explained?

Another hypothesis is that inflammation could be a causal process partly responsible for both the development of depressive symptoms and adverse cardiac outcome. Acute inflammatory response is associated with ACS and the intensity of this acute inflammatory response during ACS is predictive of poor cardiac outcome (see review in 17). Moreover, sickness behavior is characterized notably by anhedonia and is triggered by the release of proinflammatory cytokines. Several studies in animals and humans have demonstrated that introduction of several of these cytokines induced hedonic deficit [17]. However, a recent study [18] in humans reported that inflammation alters reward-related neural responses in humans and that these reward-related neural responses mediate the effects of inflammation on depressed mood. However, a study in mice has assessed whether a chronic stressor of mild intensity that induced anhedonia, when coupled with a bacterial endotoxin (lipopolysaccharide, LPS) increased left ventricular atrial natriuretic peptide (ANP),

a marker for prognosis in cardiac disease [19]. LPS treatment increased atrial and ventricular proinflammatory cytokines (IL-1 beta, TNF-alpha mRNA expression), whereas the stressor had limited effects on these cytokines. In the absence of chronic stressor, circulating ANP was unaffected by LPS intake and the combination of the stressor and LPS administration augmented changes of plasma ANP and ANP mRNA expression in the left atrium. Thus, chronic stressor that induced anhedonia, and LPS treatment synergistically influenced the rise of plasma ANP. Chronic stress combined with inflammatory immune activation could explain the co-occurrence or comorbidity between anhedonia and cardiac disease.

14.3.4.3 An Interesting Perspective: The Use of a More Scientifically Validated Definition of Anhedonia

The usual definition of anhedonia takes into account the distinction between the physical and social components of anhedonia. This distinction is trivial and leads to the construction of well validated rating scales, the Physical and Social anhedonia scales or the Snaith Hamilton Pleasure Scale, but there is no scientific proof to validate this distinction. Taking this limitation of the anhedonia measure into account, several authors have proposed a more circumscribed definition of anhedonia that has been scientifically validated [20]. Recent studies have identified additional important distinctions between various aspects of pleasure, such as consummatory and anticipatory pleasures. Consummatory pleasure refers to satiation and resolution of desire, whereas anticipatory pleasure refers to motivation and goal-directed behavior. A new scale, the Temporal Experiences of Pleasure Scale (TEPS) [20], has recently been developed to evaluate these two trait experiences of pleasure and several studies have reported satisfactory psychometric properties of this scale. By taking this distinction into account, it would be interesting to explore what type of anhedonia may constitute a risk factor for severe cardiac events in ACS patients. For example, one hypothesis could be that consummatory anhedonia that characterizes severe depression could constitute a more severe cardiotoxic symptom than anticipatory anhedonia. It would be useful to separately test the potential predictive power of these two types of anhedonia.

References

1. Pelle AJ, Pedersen SS, Szabó BM, Denollet J. Beyond Type D personality: reduced positive affect (anhedonia) predicts impaired health status in chronic heart failure. Qual Life Res. 2009;18(6):689–98.
2. Jorm AF. Association of hypotension with positive and negative affect and depressive symptoms in the elderly. Br J Psychiatry. 2001;178:553–5.
3. Smolderen KG, Hoeks SE, Pedersen SS, van Domburg RT, de Liefde II, Poldermans D. Lower-leg symptoms in peripheral arterial disease are associated with anxiety, depression, and anhedonia. Vasc Med. 2009;14(4):297–304.

4. Pelle AJ, Pedersen SS, Erdman RAM, Kazemier M, Spiering M, Van Domburg RT, Denollet J. Anhedonia is associated with poor health status and more somatic and cognitive symptoms in patients with coronary artery disease. Qual Life Res. 2011;20(5):643–51.
5. Leroy M, Loas G, Perez-Diaz F. Anhedonia as predictor of clinical events after acute coronary syndromes: a 3-year prospective study. Compr Psychiatry. 2010;51:8–14.
6. Doyle F, Conroy R, McGee H, Delaney M. Depressive symptoms in persons with acute coronary syndrome: specific symptom scales and prognosis. J Psychosom Res. 2010;68:121–30.
7. Doyle F, Conroy R, McGee H. Differential predictive value of depressive versus anxiety symptoms in the prediction of 8-year mortality after acute coronary syndrome. Psychosom Med. 2012;74(7):711–6.
8. Davidson KW, Burg MM, Kronish IM, Shimbo D, Dettenborn L, Mehran R, Vorcheimer D, Clemow L, Schwartz JE, Lespérance F, Rieckmann N. Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. Arch Gen Psychiatry. 2010;67:480–8.
9. Hoen PW, Conradi HJ, Denollet J, Martens E, de Jonge P. Interview-based ratings of somatic and cognitive symptoms of depression and their impact on cardiovascular prognosis. Psychother Psychosom. 2010;79:319–20.
10. Damen NL, Pelle AJ, Boersma E, Serruys PW, van Domburg RT, Pedersen SS. Reduced positive affect (anhedonia) is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: results from the RESEARCH registry. Eur J Prev Cardiol. 2013;20(1):127–34.
11. Roest AM, Thombs BD, Grace SL, Stewart DE, Abbey SE, de Jonge P. Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. J Affect Disord. 2011;131(1–3):158–63.
12. Tully PJ, Winefield HR, Baker RA, Turnbull DA, de Jonge P. Confirmatory factor analysis of the Beck Depression Inventory-II and the association with cardiac morbidity and mortality after coronary revascularization. J Health Psychol. 2011;16(4):584–95.
13. Joiner TE, Brown JS, Metalsky GI. A test of the tripartite model's prediction of anhedonia's specificity to depression: patients with major depression versus patients with schizophrenia. Psychiatry Res. 2003;119:243–50.
14. D'haenen H. Measurement of anhedonia. Eur Psychiatry. 1996;11:335–43.
15. Loas G. Measurement of anhedonia: additional remarks. Eur Psychiatry. 1997;12:266.
16. Loas G, Pierson A. L'anhédonie en psychiatrie: revue. Ann Med Psychol (Paris). 1989;147(7):705–17.
17. Poole L, Dickens C, Steptoe A. The puzzle of depression and acute coronary syndrome: reviewing the role of acute inflammation. J Psychosom Res. 2011;71(2):61–8.
18. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry. 2010;68(8):748–54.
19. Wann BP, Audet MC, Gibb J, Anisman H. Anhedonia and altered cardiac atrial natriuretic peptide following chronic stressor and endotoxin treatment in mice. Psychoneuroendocrinology. 2010;35(2):233–40.
20. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.

Chapter 15
Cerebrovascular Diseases: Post-stroke Depression and Anhedonia

Rocco Salvatore Calabrò, Letteria Spadaro, and Placido Bramanti

Abstract Increasing interest in depression within acute and chronic cerebrovascular pathology is justified for its clinical relevance, since its identification and management is of use in reducing disability, the caregiver's burden and the social-economic impact of cerebrovascular disease. Anhedonia, or markedly diminished interest or pleasure, is a hallmark symptom of major depression, schizophrenia and other neuropsychiatric disorders, including cerebrovascular disorders. Since stroke survivors frequently suffer from depression, research has focused on the incidence, phenomenology, course and risk factors of post-stroke depression (PSD), paying special attention to the biological explanatory models, such as the lesion location and vascular depression hypotheses. Small vessel pathology and microvascular lesions are no longer considered as minor players in the fields of cognitive impairment and mood regulation. Unlike cognition, the relationship between these lesions and mood dysregulation is still a matter of intense debate. However, the chronic accumulation of lacunes in thalamus, basal ganglia and deep white matter has been recently considered as a strong correlate of PSD.

In addition to such biological approaches, the role of psychosocial factors should not be neglected. This chapter is aimed at investigating the complex relationship between depressive mood and cerebrovascular disorders, either acute or chronic, with particular regards to the etiology and prevalence of the disabling symptom anhedonia in PSD.

Keywords Cerebrovascular disorders • Stroke • Leukoaraiosis • Vascular depression • Post stroke depression • Psychosocial factors

R.S. Calabrò (✉) • L. Spadaro • P. Bramanti
IRCCS Centro Neurolesi "Bonino-Pulejo", S.S. 113, Contrada Casazza,
98124 Messina, Italy
e-mail: salbro77@tiscali.it

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2_15,

Abbreviations

NIHSS	National Institute of Health Stroke Scale
Qol	Quality of life
CVD	Cerebrovascular Disease
LA	Leukoaraiosis
WMH	White matter hyperhintesities
LADIS	Leukoaraiosis and Disability in the Elderly Study
MRI	Magnetic resonance imaging
VAD	Vascular Depression
PST	Problem-solving therapy
PSD	Post stroke depression
DSMIVTR	Diagnostic and statistical manual of mental disorders: Fourth Edition Text Revision
ICD-10	International statistical classification of diseases and related health problems 10TH edition
PSDS	Post Stroke Depression Scale
VMPFC	Ventromedial prefrontal cortex

15.1 Introduction Pathomechanisms and Consequences of Stroke: An Overview

Stroke, also known as cerebrovascular accident or "brain attack", is a syndrome caused by a focal disruption in the cerebral blood flow due to occlusion of a blood vessel (i.e. *ischemic stroke*) or rupture of a vessel (i.e. *hemorrhagic stroke*). The interruption in blood flow deprives the brain of nutrients and oxygen, resulting in injury to cells in the affected vascular territory of the brain. When brain cells die, function of the body parts they control is impaired or lost, causing paralysis, speech and sensory problems, memory and reasoning deficits, coma, and possibly death. Stroke is the second leading cause of death in the Western world, ranking after heart disease and before cancer, and causes 10 % of deaths worldwide. Ischemic strokes are more common than hemorrhagic ones (around 80 % vs. 20 %). The incidence of stroke increases exponentially from 30 years of age, and etiology varies by age. Advanced age is one of the most significant stroke risk factors. Indeed, 95 % of strokes occur in people age 45 and older, and two-thirds of strokes occur in those over the age of 65. Nonetheless, stroke can occur at any age including in fetuses.

Cerebral ischemia usually results from thrombi or emboli. Atheromas, particularly if ulcerated, predispose to thrombi, and can occur in any major cerebral artery and are common at areas of turbulent flow, particularly at the carotid bifurcation and at the main trunk of the middle cerebral artery and its branches. Less common causes of thrombosis include vascular inflammation secondary to disorders such as acute or chronic meningitis, vasculitic disorders, and syphilis; dissection of intracranial

arteries or the aorta; hypercoagulability disorders (such as antiphospholipid syndrome, hyperhomocysteinemia); hyperviscosity disorders (such as polycythemia, thrombocytosis, hemoglobinopathies, plasma cell disorders); and rare disorders (i.e. Moya-Moya disease, Binswanger's disease). Emboli may lodge anywhere in the cerebral arterial tree, and they may originate as cardiac thrombi, especially in the following conditions: atrial fibrillation, rheumatic heart disease (usually mitral stenosis), post-MI, vegetations on heart valves in bacterial or marantic endocarditis and prosthetic heart valves. Other sources include clots that form after open-heart surgery and atheromas in neck arteries or in the aortic arch.

Less commonly, ischemic stroke results from vasospasm (i.e., during migraine, after subarachnoid hemorrhage, after use of after use of sympathomimetic drugs such as cocaine or amphetamines) or venous sinus thrombosis (i.e., during intracranial infection, postoperatively, peripartum, secondary to a hypercoagulation disorder).

Lacunars infarcts ($\leq$1.5 cm) result from non-atherothrombotic obstruction of small, perforating arteries that supply deep cortical structures; the usual cause is lipohyalinosis (degeneration of the media of small arteries and replacement by lipids and collagen). Lacunars infarcts tend to occur in elderly patients with diabetes or poorly controlled hypertension.

Intracerebral hemorrhage usually results from rupture of an arteriosclerotic small artery that has been weakened, primarily by chronic arterial hypertension, and is often large, single, and catastrophic. Use of cocaine or, occasionally, other sympathomimetic drugs can cause transient severe hypertension leading to hemorrhage, whereas, less often, intracerebral hemorrhage may result from congenital aneurysm, arteriovenous or other vascular malformation, trauma, mycotic aneurysm, brain infarct (hemorrhagic infarction), primary or metastatic brain tumor, excessive anticoagulation, blood dyscrasia, or a bleeding or vasculitic disorder.

Stroke severity and progression are often assessed using standardized measures such as the National Institute of Health Stroke Scale (NIHSS) [1] that contains 13 items and measures severity of impairment in consciousness, orientation, gaze, motor function, sensation, language, speech and inattention and the modified Rankin scale [2] that measures handicap or death on a scale of 1–6.

During the first days, progression and outcome can be difficult to predict. Older age, impaired consciousness, aphasia, and brain stem signs suggest a poor prognosis. Early improvement and younger age suggest a favorable prognosis. About 50 % of patients with moderate or severe hemiplegia and most with milder deficits have a clear sensorium and eventually can take care of their basic needs and walk adequately. Complete neurologic recovery occurs in about 10 %. Use of the affected limb is usually limited, and most deficits that remain after 12 months are permanent [3]. Subsequent strokes often occur, and each tends to worsen neurologic function. The most difficult aspect of having a stroke is living with the disability caused by this condition, since it is associated with high morbidity rates, meaning that many patients experience both physical and mental disability following the event. In fact, stroke morbidity is the leading cause of decreased independence and

lowered quality of life (QoL) among adults. It should be highlighted that cognitive, psychological, and social function are domains often neglected in stroke outcome assessments. Moreover, sexuality, an integrant and important part of neurological patients' QoL and patient, is often another overlooked issue in patients with stroke.

Thus, these patients should always be investigated and treated for psychological sexual disorders.

15.2 Leukoaraiosis: Asyntomatic or Silent Disease?

Leukoaraiosis (LA) is a term used to describe diffuse abnormalities of the deep white matter. These abnormalities, seen around the horns of lateral ventricle and in the centrum semiovale on a Magnetic Resonance Imaging or Computed Tomography scan, are less defined than the infarctions and may coalesce. The pathogenesis of LA is still not well characterized, although chronic ischemia with consequent arteriolosclerosis probably due to endothelial dysfunction has been suggested. A recent hypothesis suggests that the oxygen trafficking system and neurocellular energy pathways may also be involved. In addition, the role of blood-brain barrier in preventing the progression of LA has been hypothesized, and a potential influence of some candidate genes, i.e. polymorphic variation in the gene encoding angiotensin-converting enzyme and the apoprotein-E, to susceptibility for LA was supposed. Many human diseases, such as hypercholesterolemia, hypertension, diabetes mellitus, cardiovascular diseases, are associated with endothelial dysfunction leading to arterial occlusive disorders. Endothelium-derived nitric oxide (NO) has a number of roles including maintaining basal cerebral blood flow, cerebral vasodilatation, autoregulation and vascular integrity and inhibiting smooth muscle cells proliferation. A lack of endothelium-derived NO would be expected to lead to several features of LA. Over the last years, evidence on prevalence, clinical significance and prognostic value of LA has been dramatically mounting. Nowadays, we know that minimal changes are frequently found in general population and data are sufficient to sustain that the mildest degree of LA can be considered as an almost normal finding in the brain of elderly patients, since it is a part of the normal aging process [4]. In contrast, moderate to severe white matter hyperintesities (WMH) are not so benign and are correlated with motor and gait impairment, depressive symptoms, urinary disturbances and cognitive deficits. The multicenter study LADIS (Leukoaraiosis and Disability in the Elderly Study) has assessed the role of age-related white matter lesions as an independent predictor of the transition to disability in initially non-disabled elderly people showing that LA and lacunar infarcts are independently associated with cognitive decline [5]. Longitudinal studies have demonstrated a predictive role of LA in terms of less favorable prognosis in the general population and in a number of clinical conditions. In fact, the presence of LA is associated at an increased risk of ischemic stroke, dementia, vascular mortality, bleeding in patients on anticoagulation or undergoing cerebral thrombolysis and

carotid artery surgery. The severity of LA at baseline has been considered an independent predictor of the transition from a normal functional status to disability already after 1 year, so that LA can represent a marker of poor prognosis, especially in terms of increased mortality and risk of dementia.

Moreover, in the LADIS study, baseline WMH severity was able to predict depressive symptoms at 2 and 3 year-follow-up, and the progression of WMH was associated with incident depression during the 3 year period of the study [6, 7].

The depressive symptoms also predicted cognitive impairment over a 3 year follow-up period, independent of the effect of WMH. However, an increased prevalence of WMH compared in late life depressed subjects to controls [8–12]. These aspects underline the complex relationship between depressive symptoms and cognitive decline in WMH patient and support the hypothesis that depressive symptoms in patients with WMH are an expression of vascular damage due to frontostriatal disconnection and not a true depression [13]. Janssen et al. [12] report numerous structural magnetic resonance imaging (MRI) studies in which depression is associated with volumetric decreases in the frontal and orbit frontal cortex, striato frontal circuits, periventricular areas, and hippocampus in adult and older subjects.

15.3 Vascular Depression

The "Vascular depression" (VAD) describes a specific cluster of patients with later-onset depression (over 50 years of age), cerebrovascular risk factor, specific neuropsychological deficits, chronic ischemic lesions seen on structural imaging [14, 15]. First Krishnan and McDonald [16] described as 'arteriosclerotic depression' a model of vascular damage to brain circuits related to affective regulation. The vascular depression hypothesis was formulated in 1997 and postulated that cerebrovascular disease can predispose, precipitate or perpetuate, depressive symptoms in older adult [14, 17].

Steffens and Krishnan [18] proposed detailed diagnostic criteria for VAD as subtype of major depression, if A and either B1 or B2 or B3:

A. Major depression occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment.
B1. Clinical manifestations may include history of stroke or transient ischemic attacks, or focal neurologic signs or symptoms (e.g., exaggeration of deep tendon reflexes. extensor plantar response, pseudobulbar palsy, gait disturbance, weakness of an extremity),
B2. Neuroimaging findings may include white or gray matter hyperintensities (Fazekas et al. 1988 criteria >2: or lesion >5 mm in diameter and irregular in shape), confluent white mutter lesions, or cortical or subcortical infarcts.
B3. Cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory, or speed of processing of information.

The diagnosis is supported by the following features:

1. Depression onset after 50 years of age or change in the course of depression after the onset of vascular disease in patients with onset before 50 years of age.
2. Marked loss of Interest or pleasure.
3. Psychomotor retardation.
4. Lack of family history of mood disorders.
5. Marked disability in instrumental or self-maintenance activities of daily living [18]." Patients with VAD have poor outcomes, including persistence of depressive symptoms, unstable remission of depression, and increased risk for dementia [19].

Nevertheless, data concerning the epidemiology of VAD are scant. The Baltimore ECA longitudinal study estimated that incidence of major depression among adults aged older than 65 years was around 1.25 p 100 people, with higher incidence in older women [20]. In this particular sample of population, the cerebrovascular accidents are really common and the age is the aspect most strongly associated with increased prevalence of subcortical ischemic vascular depression [21]. It's important to note that a family history of mental disorder was negatively associated with the diagnosis [21, 22]. The role of vascular risk factors in the etiology of vascular depression is unclear [23]. Miller et al. [24] reported a significant association between a "vascular risk factor score" and le first later – onset depression. In the Cardiovascular Health Study, Steffens et al. [25] under light that hypertension and a history of coronary heart disease was not associated with a history of depression. However, vascular risk factors have an important role in the genesis of WMH [26], which is often involved in the etiopathogenesis of vascular depression [14, 17].

Indeed, severity of WMH is linked to poor response to treatment, relapse rate, and progression to chronic depression [22, 27].

Although the role of vascular risk factor on etiology of both post stroke depression and vascular depression is still not clear [23], CVD might predispose, precipitate, or perpetuate some late-life depressive syndromes [25].

Alexopoulos et al. [14] hypothesized the link of the ischemic damage with striatopallidothalmaocortical pathways with alterations of the serotoninergic and adrenergic circuits in the etiopathogenesis of depressive symptoms in vascular depression. Indeed, the authors proposed two potential mechanisms underlying the role of these WMH in the etiology of VAD: (1) discrete lesions disrupting critical neural circuits could cause depressive symptoms; or (2) a threshold effect with accumulation of lesions could also lead to depressive symptoms. In particular, it has been suggested that the pathophysiological basis of VAD may be a disruption of the striato-frontal circuits implicated in mood regulation, secondary to the ischemic lesions [14, 23]. Newberg et al. [23] also noted that very few studies have suggested the importance of left-sided lesions in vascular depression.

Patients with VAD present with greater disabilities and neuropsychological impairment, including verbal fluency and object naming. Moreover, among behavioral symptoms, apathy, retardation, and lack of insight are more frequent than in the depressed elderly without vascular risk factors, whereas and less agitation and guilt are less prevalent [28]. In fact, patients with vascular depression seems to have

not only a specific symptom profiles but also worse outcomes, poorer response to antidepressant medications, greater disability, and more adverse reactions than age-matched controls [29, 30].

The hypothesis about etiopathogenesis of vascular depression generated potential alternatives for the treatment of VAD. Indeed, drugs used for the prevention of cerebrovascular disease might, for example, reduce the risk for vascular depression. Furthermore, antidepressants that promote ischemic recovery—eg, dopamine or norepinephrine enhancing agents—might be favored in vascular depression and antidepressants that inhibit ischemic recovery—eg, adrenergic blocking agents—are best avoided [28]. Other study focused on the treatment of WMH-related depression. In a sample of 1,077 elderly adults, the severity of WMH was related to the presence of depressive symptom, and a story of late depression onset [31].

In a longitudinal study (during a period of 2 year-follow-up), Taylor et al. [32] showed that a greater progression of WMH volume is associated with poor outcomes in geriatric depression, with a 1 % increase in WMH volume associated with a 7 % increased risk of poor response. Interestingly, another type of treatment compared the efficacy of problem-solving therapy (PST) and supportive therapy (ST) in a group of elderly subjects with geriatric major depression and executive dysfunction and a specific risk for poor response to pharmacotherapy [33]. In this preliminary study, PST was effective in reducing depressive symptoms and disability. The authors explained a substantial part of this change by the subjects' improvement of skills in generating alternatives and in decision-making. If these findings are confirmed, PST may become an important therapeutic alternative for a patient population who may otherwise remain symptomatic and disabled.

There are few data about prognosis of patients with VAD. Levy et al. [34] suggested that there is a relationship between cerebrovascular disease severity and mortality among depressed patients because, deep WMH, and periventricular hyperintensity (PVH) were significantly associated with mortality. Moreover, the correlation between VAD and dementia is another important issue to be taken into consideration. An increase of medical co-morbidity is significantly associated with impaired cognitive performance, whereas a subjective memory complaint correlated with depression [35].

Pseudodementia (i.e. a syndrome seen in older people in which they exhibit symptoms consistent with dementia but the cause is actually Depression) is relatively a common syndrome with a specific cluster of symptoms respect to dementia. Indeed, clinically, people with pseudodementia differ from those with true dementia when their memory is tested; they will often answer that they don't know the answer to a question, and their attention and concentration are often intact, and they may appear upset or distressed. On the contrary, those with true dementia will often give wrong answers, have poor attention and concentration, and appear indifferent or unconcerned.

Depression and vascular disease could be mediated by other factors than traditional vascular risk factors, including the inflammatory processes which may mediate both depression and vascular disease [36]. Santos et al. [37] proposed that the accumulation of small vascular and microvascular lesions constitutes a

common neuropathological platform for both cognitive decline and depressive episodes in old age.

Together, both deficits in neuropsychological function and severity of WMH predict worse outcome [38]. The complex relationship between late-life depression (LLD), vascular risk factors, and cognition is still unclear. Cognitive dysfunction is common in LLD, particularly executive dysfunction, a finding predictive of poor antidepressant response. Over time, progression of hyperintensities and cognitive deficits predicts a poor course of depression and may reflect underlying worsening of vascular disease [39]. The vascular depression hypothesis was proposed as a conceptual framework to better understand late onset of depression in a patient with vascular damage seen at MRI. The link between depression and cerebrovascular diseases seemed to have a clear bidirectional relationship, since vascular disease predisposes to, precipitates or perpetuates depression independently of the psychological mechanism [14, 40].

15.4 Post-stroke Depression

Post-stroke depression (PSD) is defined as 'depression occurring in the context of a clinically stroke event [41, 42]. While the framework of VAD focus on the etiopathophysiologic relationship, this diagnostic category underline the temporally connection between onset of depression and stroke. Indeed, PSD may be included in the category of CVD-related depression, taking into account that depression should arise from specific brain areas and/or from the psychological response to the physical impairment derived from stroke. In the DSM-IV [43], stroke is one of the few conditions listed as "directly" causing depression "due to a general medical condition (i.e. stroke)", a really not specific diagnostic category, that not require any specific diagnostic criteria.

Epidemiology. A detailed description about epidemiology of PSD is really difficult for the difference in study population characteristics, evaluation-time after stroke, inclusion/ exclusion criteria, assessment tools and difficulties in the evaluation of patients with neurological and/or neuropsychological deficit. The prevalence of PSD widely varies from 25 to 79 % [44], with the peak prevalence of major depression being around 3–6 months after the stroke, and a range of prevalence during this time-frame of 9–34 % [41, 45]. In particular, Robinson et al. [46] estimated that the mean frequency of depressive syndromes among stroke patients in acute and rehabilitation hospitals was 19.3 % for major depression and 18.5 % for minor depression, while the mean prevalence of major depression was 14.1 % and minor depression was 9.1 % in a community setting. Similar data were reported in more recent studies [47, 48]. However, a gold shared standard for the assessment of depressive symptoms in stroke is missing. Post-stroke depression is highly prevalent among both men and women; however, it appears that PSD is more common in women when prevalence is compared between the sexes Siren [49]. Moreover, PSD patient prognosis is poor in long term activities of daily living, QoL, cognitive impairment

and increased mortality [50–52]. Santos et al. [37] suggested that vascular burden due to the chronic accumulation of small macrovascular and microvascular lesions may be a crucial determinant of the development and evolution of PSD. In addition, Sibon et al. [53] showed as the prevalence of depression may appear stable during the immediate weeks and months following stroke, but it is likely to be composed of very different symptom profiles.

Etiology. The definition of PSD by DSM-IV TR involves as cause of depression a stroke. The biological mechanism is that the cerebrovascular insult may directly affect aminergic pathways neural and/ or circuits involved in mood regulation [54–56]. Fang and Cheng [57] also included in biological hypothesis four mechanisms: lesion location mechanism, neurotransmitters mechanism, inflammatory cytokines mechanism and gene polymorphism mechanism. As for lesion location, the specific site of a lesion (e.g., basal ganglia or left frontal lobe lesions) seems to play an important role in the etiology of PSD. Indeed, several studies have found left anterior lesion location to be associated with PSD, thus supporting the so called left anterior lesion hypothesis [58–60]. On the contrary, other finding didn't show a clear correlation between the lesion site or side and the development of PSD [51, 61, 62]. Concerning neurotransmitters, decreased serotonin and norepinephrine in the brain were associated with PSD. Increased cytokines [including interleukin (IL) 1b, IL-18, tumor necrosis factor a] after stroke may lead to depression, whereas there was significant association between serotonin transporter gene-linked promoter region short variant genotype and post-stroke major depression. Other authors proposed a psychosocial model, according to which the social and psychological stressors associated with a stroke are considered the primary cause of depression [63, 64]. In addition, in a biopsychosocial perspective, an integrated model may explain the onset and permanence of mood disorder and promote the development of a comprehensive approach to the prevention and treatment of PSD [57, 65]. Risk factors for PSD onset are considered a history of depression, severe disability, previous stroke and female sex, but not the type and site of the vascular lesion [51, 66]. Altieri et al. [62] showed that a higher educational level (P = 0.022, OR 0.084, CI 0.010–0.698) and diabetes (P = 0.007, OR 14.361, CI 2.040–101.108) were the risk factors significantly correlating with PSD in their sample. Interestingly, the DESTRO study showed that depressive symptoms were more severe in patients with earlier onset, with no appreciable difference between those diagnosed between the first and sixth month; they were less severe in cases with later development of depression [51].

Moreover, there is a significantly higher prevalence of PSD among patients with non-fluent aphasia, but not in patients with fluent aphasia. The presence of PSD has been found to have unfavorable impact on the recovery of cognitive function, recovery of ability to perform activities of daily living and on the risk of mortality". To this end, PSD led to 3.4-fold increase in mortality up to 10 years after stroke. Interestingly, There is a bidirectional relationship between stroke and depression; there is a high prevalence of depression in stroke patients and a higher risk of stroke in depressed people (3.36 relative risk), even when other conventional stroke risk factors (hypertension, diabetes, hyperlipidemia, heart disease and tobacco use) are under control (2.67 relative risk) [67].

Clinical features. PSD is characterized by apathy, catastrophic reactions, and hyper-emotionalism and diurnal mood variations while those with endogenous depression had more suicidal thoughts and anhedonia [63]. Differences in the presentation of PSD appear when considering right-sided versus left-sided lesions.

The lasting psychological effects following a brain event in the right hemisphere include significant variance from the person's normal emotional output and relative lack of control. Many of the lesions to the right frontal and parietal lobes leave impairments for recognizing emotions expressed through tone of voice, identification of facial expressions, and difficulty expressing emotion through facial movements, as well as anhedonia (severe lack of interest in people/interests). Cerebral ischemia leads to decrease in acetylcholine release, which may cause many of the post-stroke behavioral changes. Mania and hippomanic reactive responses are more common with right-sided versus left-sided lesions. Patients with right-sided stroke lesions become desocialized. This often is the beginning of strain on social contact and communication. A family history of psychiatric disorders or having had a previous left-sided stroke increases the risk of PSD in right-sided stroke patients. Left-sided lesions in the frontal or basal ganglia areas (putamen and/or caudate nucleus) often result in major depression. An increased catastrophic response is thought to be due to an inability to up-regulate serotonin receptors since serotonin binding is greater on the right. Vascular lesions also may interfere with serotonin transduction throughout the brain. It also is possible to classify depressive symptoms following stroke into direct and indirect cause-and-effect responses. Indicators for reactional depression include aphasia, amnesia and cognitive impairments, anosognosia (denial of disability), denial of depressive signs, aprosodia (poor speech comprehension), catastrophic reaction, neurological apathy syndromes (e.g., frontal lobe syndrome), dementia.

PSD related to lesion location can be characterized by the following:

- Bilateral lesions in the anterior frontal and temporal lobes and caudate nucleus are associated with increased risk of PSD.
- Left basal ganglia lesions at the head of dorsolateral caudate result in apathy and poor initiation.
- Incidence and severity of PSD increase with close proximity to left frontal pole lesions.
- Emotion-related processing impairments are greater with right hemisphere and frontal lobe lesions, since they serve emotional communication.
- Frontal lobe anterior and middle cerebral artery lesions result in apathy.
- Left anterior subcortical lesions show greater incidence of PSD than on the right side.
- When lesions are within 40 % of either frontal pole, the PSD rate is 60 % or greater.

The most frequently used scale for evaluating depression in patients with stroke is the Hamilton Depression Rating Scale (HDRS); in the literature, the General Health Questionnaire (GHQ), Hospital Anxiety and Depression Scale (HAD),

Aphasic Depression Rating Scale (ADRS), or some modified scales such as the Lausanne Emotion in Acute Stroke Study (LEASS).

However, owing to the lack of instruments specifically constructed to study emotional and affective disorders of stroke patients, the nature of PSD remains controversial. With this in mind, Gainotti et al. [68] constructed a new scale, the Post-Stroke Depression Scale (PSDS) which takes into account a series of symptoms and problems commonly observed in depressed stroke patients. From their valuable work the authors found that: (1) a continuum exists between the so-called "major" and "minor" forms of PSD; (2) in both groups of depressed stroke patients the depressive symptomatology seems due to the psychological reaction to the devastating consequences of stroke, since the motivated aspects of depression prevailed in depressed stroke patients, whereas the (biologically determined) unmotivated aspects prevailed in patients with a functional form of major depression; and (3) in stroke patients a DSM III-based diagnosis of major PSD could be in part inflated by symptoms (such as apathy and vegetative disorders) that are typical of major depression in a patient free from brain damage, but that could be due to the brain lesion per se in a stroke patient.

15.5 Anhedonia in Cerebrovascular Disorders

Anhedonia is defined as the inability to experience pleasure from activities usually found enjoyable, including exercise, hobbies, sexual activities, and social interactions particularly when compared to similar experiences that were perceived as pleasurable in the past [69]. By nineteenth century, anhedonia is documented as psychopathological symptoms [70, 71]. Actually, the DSM-IV-TR [43] defines it as diminished interest or pleasure in response to stimuli that were previously perceived as rewarding during a premorbid state. The World Health Organization International Classification of Diseases (ICD) 10 does not use the term anhedonia, but rather 'loss of interest and pleasurable feeling [72]. Anhedonia is one of two required symptoms for a diagnosis of Major Depressive Disorders [43, 72] and a negative symptom in the cluster of schizophrenia [43]. These definitions reflect the assumption that people are motivated to do the things they find pleasurable, and vice versa [73].

In clinical practice and neurobehavioral research, the term anhedonia have to summarize a complex and multi-faced reward-related deficit observed in really numerous neuropsychiatric disorders than that in healthy subjects [74]. However, Ho et al. [75] show that approximately 45 % of the studies that measured anhedonia did not define the concept. The ability to experience pleasure covers not only with desire, reinforcement and subjective pleasure, but also with cognitive aspect as the ability to anticipate and predict reward and/or utility, the memory of reward and/or utility, the association of relative values and cost, the effort required to obtain rewards, the integration of these information, the decision making about this, and the self- motivation to goal-directed behavior [74]. Some authors proposed a

distinction between consummatory and anticipatory anhedonia to better described the lack of a specific aspect of pleasure process. In particular a person feel consummatory pleasure when directly engaged in an enjoyable activity, and anticipatory pleasure, as the experience of pleasure related to future activities. These may explain the different anhedonic behavioral, cognitive and emotional experiences.

Other authors emphasize that clinical symptoms of anhedonia have to be divided into consummatory and motivational anhedonia, focusing the attention on decision-making [73]. Some persons with anhedonia normally felt pleasure, but reported deficits in motivation to participate in pleasurable activities [76]. Thus, Der-Avakian and Markou [74] proposed that only consummatory anhedonia should be classified as anhedonia. Others included in anhedonia experience also the deficits in beliefs about the experience of pleasure, like anticipatory and motivational [75].

How et al. [75] also underline the importance of the intensity of the emotion? When translated verbatim, anhedonia means "without pleasure." However, the authors use anhedonia as the meaning of "inability" and "reduced ability", "diminished or absent ability to experience pleasure". "Inability to experience pleasure suggests that a person with anhedonia does not experience pleasure at all [69, 76–80], while reduced ability to experience pleasure suggests that people with anhedonia can experience some degree of pleasure, but either not as much as usual or possibly not as much as other people [75, 81, 82].

It's important to note that anhedonia experience is usually not an isolate symptom but a specific aspect correlated to multifaceted psychopathological syndromes. To this end, a specific behavioural, cognitive and emotional feature are usually connected with the mayor pathology too. However, the different aspect and gradient of anhedonia are really important to better understand the numerous and different patient's experience and to plan the proper treatment, acting on the different neurobiological involved pathways. Anticipatory pleasure is heavily, though not exclusively, related to dopamine mesolimbic pathway, whereas serotoninergic and opioid systems appear to be more centrally involved in the consummatory pleasure [83–85]. In addition, anticipatory pleasure is linked to motivational processes that promote goal-directed behaviors aimed at achieving desired rewards [84, 86–88].

Gorwood et al. [89] have clearly shown that the severity of anhedonia in depressed patients is correlated with a deficit of activity of the ventral striatum (reflecting decreased function of the nucleus accumbens, probably as a primary event) and an excess of activity of ventromedial region of the prefrontal cortex (VMPFC) (concerning an increased function of the VMPFC and the orbitofrontal cortex, probably as a secondary phenomenon). Interestingly, the basis of hedonic feelings has been more specifically studied through different paradigms, suggesting that euphoric response to dextroamphetamine, cocaine-induced euphoria, monetary reward, and even pleasurable responses to music, pictures, and attractive faces, may be associated with activity within the nucleus accumbens, ventral caudate, and ventral putamen.

To this end, the nucleus accumbens, may indeed have a priority role – according to animal and human studies- in behavioral response to, anticipation of, and/or

monitoring of errors in the pre diction of reward, since it appears to respond to the emotional intensity and self-relatedness of a variety of stimuli, possibly processed along a rostro-caudal gradient. The nucleus accumbens receives projections from midbrain regions (such as the ventral tegmental area), from regions involved in emotion (such as the amygdala, orbitofrontal cortex, and medial prefrontal cortex), from motor regions (such as the dorsal caudate and globus pallidus), and from regions involved in memory (such as the hippocampus), and, moreover, it also indirectly projects to cortical regions, including the thalamus, the cingular and medial prefrontal cortex, the ventral pallidum, the amygdala, and the hypothalamus. Since these regions are mostly implicated in emotion processing, the authors suggested they are a network of tightly anatomically and functionally connected regions. The orbitofrontal cortex is a nexus for sensory integration, the modulation of autonomic reactions, and anticipation in learning, prediction and decision-making for emotional and reward-related behaviors. Because the orbitofrontal cortex may have an important role for representing incentive salience, hedonic impact, and subjective hedonic experience, it could be considered the link between reward and hedonic experience. Harvey et al. [90] found that trait anhedonia severity was negatively correlated with the volume of the anterior caudate and ventral striatum, and was positively correlated with the activity of the VMPFC for the processing of positive information.

Moreover, Keedwell et al. [91] demonstrated that people with anhedonia displayed similar cerebral blood flow patterns as controls in response to aversive stimuli, but differed from controls in response to rewarding stimuli.

Interestingly, it has been supposed that anhedonia may result from the breakdown in the brain's reward system, which also involves the neurotransmitter dopamine [73, 85]. Reward serves to obtain approach to consummatory behaviors, increase the frequency and intensity of the behaviors, maintain the behaviors, prevent their extinction, and induce subjective feelings of pleasure or positive emotional states. Reward is therefore a key concept in assessing anhedonia, and the basis of the majority of animal studies devoted to its neurobiological mechanisms. An interesting case by Miller et al. [24] suggested an association between bilateral lesions of the globus pallidus and a syndrome of anhedonia, loss of drug cravings, and extrapyramidal signs that are consistent with the participation of this brain structure in both reward circuitry and movement.

Therefore, it is plausible that, anhedonia in CVD, when present, may be strictly related to the disruption of specific pathways (mainly dopaminergic) leading to motivation, pleasure, and reward, including those involving nucleus accumbens and the prefrontal cortex.

Unfortunately, there aren't specific assessment tools for patients with CVD, as they often have some physical and neuropsychological deficit that make difficult to understand their emotions or lack of emotions. It's important to note that consummatory and motivational anhedonia involve not only emotional but also cognitive ability that may be affected in CVD. It would be useful to increase the assessment of individual aspects of anhedonia in order to enhance specific pharmacological and rehabilitation strategies.

15.6 Conclusions

Since a recent meta-analysis [92] has confirmed the potential role of depression on post-stroke morbility and mortality, regular screening might help in detecting prevalent depressive symptoms, including anhedonia, in patient suffering from CVD. Further research is needed in order to clarify the nature of PSD and the related pathophysiological processes so to plan proper pharmacotherapy and/or psychotherapy strategies for preventing and treating depression after stroke.

References

1. Lyden P, Lu M, Jackson C, Marler J, et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. Stroke. 1999;30(11):2347–54.
2. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604–7.
3. Dennis MS, Burn JP, Sandercock PA, et al. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. Stroke. 1993;24(6):796–800.
4. Pantoni L. Leukoaraiosis: from an ancient term to an actual marker of poor prognosis. Stroke. 2008;39(5):1401–3.
5. Pantoni L, Poggesi A, Basile AM, et al. Leukoaraiosis predicts hidden global functioning impairment in nondisabled older people: the LADIS (Leukoaraiosis and Disability in the Elderly) Study. J Am Geriatr Soc. 2006;54(7):1095–101.
6. Teodorczuk A, Firbank MJ, Pantoni L, LADIS Group, et al. Relationship between baseline white-matter changes and development of late-life depressive symptoms: 3-year results from the LADIS study. Psychol Med. 2010;40:603–10.
7. Firbank MJ, Teodorczuk A, van der Flier WM, LADIS Group, et al. Relationship between progression of brain white matter changes and late-life depression: 3-year results from the LADIS study. Br J Psychiatry. 2012;201:40–5.
8. Steffens DC, Helms MJ, Krishnan KR, Burke GL. Cerebrovascular disease and depression symptoms in the cardiovascular health study. Stroke. 1999;30(10):2159–66.
9. Kumar A, Bilker W, Lavretsky H, Gottlieb G. Volumetric asymmetries in late-onset mood disorders: an attenuation of frontal asymmetry with depression severity. Psychiatry Res. 2000;100(1):41–7.
10. Firbank MJ, Lloyd AJ, Ferrier N, O'Brien JT. A volumetric study of MRI signal hyperintensities in late-life depression. Am J Geriatr Psychiatry. 2004;12(6):606–12.
11. Hannestad J, Taylor WD, McQuoid DR, et al. White matter lesion volumes and caudate volumes in late-life depression. Int J Geriatr Psychiatry. 2006;21(12):1193–8.
12. Janssen J, Hulshoff Pol HE, de Leeuw FE, et al. Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression. Neurol Neurosurg Psychiatry. 2007;78(6):638–40.
13. Verdelho A, Madureira S, Moleiro C, et al. Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes: the LADIS study. J Neurol Neurosurg Psychiatry. 2013;84:1250–4. doi:10.1136/jnnp-2012-304191.
14. Alexopoulos GS, Meyers BS, Young RC, et al. Clinically defined vascular depression. Am J Psychiatry. 1997;154(4):562–5.
15. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry. 1997;154(4):497–501.

16. Krishnan KR, McDonald WM. Arteriosclerotic depression. Med Hypotheses. 1995;44(2):111–5.
17. Alexopoulos GS. The vascular depression hypothesis: 10 years later. Biol Psychiatry. 2006;60(12):1304–5.
18. Steffens DC, Krishnan KR. Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. Biol Psychiatry. 1998;43(10):705–12.
19. Alexopoulos GS. Frontostriatal and limbic dysfunction in late-life depression. Am J Geriatr Psychiatry. 2002;10(6):687–95.
20. Eaton WW, Kalaydjian A, Scharfstein DO, et al. Prevalence and incidence of depressive disorder: the Baltimore ECA follow-up, 1981–2004. Acta Psychiatr Scand. 2007;116(3):182–8.
21. Krishnan KR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry. 2004;55(4):390–7.
22. Hickie I, Scott E, Mitchell P, et al. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. Biol Psychiatry. 1995;37(3):151–60.
23. Newberg AR, Davydow DS, Lee HB. Cerebrovascular disease basis of depression: post-stroke depression and vascular depression. Int Rev Psychiatry. 2006;18(5):433–41.
24. Miller JM, Vorel SR, Tranguch AJ, et al. Anhedonia after a selective bilateral lesion of the globus pallidus. Am J Psychiatry. 2006;163(5):786–8.
25. Steffens DC, Krishnan KR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. Stroke. 2002;33(6):1636–44.
26. Thomas AJ, Perry R, Barber R, et al. Pathologies and pathological mechanisms for white matter hyperintensities in depression. Ann N Y Acad Sci. 2002;977:333–9.
27. Kramer-Ginsberg E, Greenwald BS, Krishnan KR, et al. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. Am J Psychiatry. 1999;156(3):438–44.
28. Alexopoulos GS. Depression in the elderly. Lancet. 2005;365(9475):1961–70.
29. Kales HC, Maixner DF, Mellow AM. Cerebrovascular disease and late-life depression. Am J Geriatr Psychiatry. 2005;13(2):88–98.
30. Naarding P, Veereschild M, Bremmer M, et al. The symptom profile of vascular depression. Int J Geriatr Psychiatry. 2009;24(9):965–9.
31. De Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and depressive symptoms in elderly adults. Arch Gen Psychiatry. 2000;57(11):1071–6.
32. Taylor WD, Steffens DC, MacFall JR, et al. White matter hyperintensity progression and late-life depression outcomes. Arch Gen Psychiatry. 2003;60(11):1090–6.
33. Alexopoulos GS, Raue P, Areán P. Problem-solving therapy versus supportive therapy in geriatric major depression with executive dysfunction. Am J Geriatr Psychiatry. 2003;11(1):46–52.
34. Levy RM, Steffens DC, McQuoid DR, et al. MRI lesion severity and mortality in geriatric depression. Am J Geriatr Psychiatry. 2003;11(6):678–82.
35. Fischer CE, Jiang D, Schweizer TA. Determining the association of medical co-morbidity with subjective and objective cognitive performance in an inner city memory disorders clinic: a retrospective chart review. BMC Geriatr. 2010;10:89. Available at: http://www.biomedcentral.com/1471-2318/10/89/
36. Baldwin RC. Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. Int J Geriatr Psychiatry. 2005;20(1):1–11.
37. Santos M, Kövari E, Gold G, et al. The neuroanatomical model of post-stroke depression: towards a change of focus? J Neurol Sci. 2009;283(1–2):158–62.
38. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. Arch Gen Psychiatry. 2010;67(3):277–85.
39. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry. 2013;18:963–74. doi:10.1038/mp.2013.20.

40. Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: what is the relationship? J Affect Disord. 2004;79(1–3):81–95.
41. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol Psychiatry. 2002;52(3):253–64.
42. Dieguez S, Staub F, Bruggimann L, et al. Is poststroke depression a vascular depression? J Neurol Sci. 2004;226(1–2):53–8.
43. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: Fourth Edition Text Revision DSM-IV-TR®. Washington, DC: American Psychiatric Association; 2000.
44. Gordon WA, Hibbard MR. Poststroke depression: an examination of the literature. Arch Phys Med Rehabil. 1997;78(6):658–63.
45. Spencer KA, Tompkins CA, Schulz R. Assessment of depression in patients with brain pathology: the case of stroke. Psychol Bull. 1997;122(2):132–52.
46. Robinson RG. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. Biol Psychiatry. 2003;54(3):376–87.
47. De Wit L, Putman K, Baert I, et al. Anxiety and depression in the first six months after stroke. A longitudinal multicentre study. Disabil Rehabil. 2008;30(24):1858–66.
48. Srivastava A, Taly AB, Gupta A, Murali T. Post-stroke depression: prevalence and relationship with disability in chronic stroke survivors. Ann Indian Acad Neurol. 2010;13(2):123–7.
49. Poynter B, Shuman M, Diaz-Granados N, et al. Sex differences in the prevalence of post-stroke depression: a systematic review. Psychosomatics. 2009;50(6):563–9.
50. Pohjasvaara T, Vataja R, Leppävuori A, et al. Depression is an independent predictor of poor long-term functional outcome post-stroke. Eur J Neurol. 2001;8(4):315–9.
51. Paolucci S, Gandolfo C, Provinciali L, et al. The Italian multicenter observational study on post-stroke depression (DESTRO). J Neurol. 2006;253(5):556–62.
52. Robinson RG, Spalletta G. Poststroke depression: a review. Can J Psychiatry. 2010; 55(6):341–9.
53. Sibon I, Lassalle-Lagadec S, Renou P, et al. Evolution of depression symptoms following stroke: a prospective study using computerized ambulatory monitoring. Cerebrovasc Dis. 2012;33(3):280–5.
54. Beblo T, Wallesch CW, Herrmann M. The crucial role of frontostriatal circuits for depressive disorders in the postacute stage after stroke. Neuropsychiatry Neuropsychol Behav Neurol. 1999;12(4):236–46.
55. Starkstein SE, Bryer JB, Berthier ML, et al. Depression after stroke: the importance of cerebral hemisphere asymmetries. J Neuropsychiatry Clin Neurosci. 1991;3(3):276–85.
56. Starkstein SE, Robinson RG. Affective disorders and cerebral vascular disease. Br J Psychiatry. 1989;154:170–82.
57. Fang J, Cheng Q. Etiological mechanisms of post-stroke depression: a review. Neurol Res. 2009;31(9):904–9.
58. Robinson RG, Kubos KL, Starr LB, et al. Mood disorders in stroke patients. Importance of location of lesion. Brain. 1984;107(1):81–93.
59. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. Brain. 1987;110(4):1045–59.
60. Narushima K, Kosier JT, Robinson RG. A reappraisal of post-stroke depression, intra- and inter-hemispheric lesion location using meta-analysis. J Neuropsychiatry Clin Neurosci. 2003;15(4):422–30.
61. Agrell B, Dehlin O. Depression in stroke patients with left and right hemisphere lesions. A study in geriatric rehabilitation in-patients. Aging. 1994;6(1):49–56.
62. Altieri M, Maestrini I, Mercurio A, et al. Depression after minor stroke: prevalence and predictors. Eur J Neurol. 2012;19(3):517–21.
63. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical-clinical correlates of major post-stroke depression. Br J Psychiatry. 1999;175:163–7.

64. House A. Depression associated with stroke. Neuropsychiatry Clin Neurosci. 1996;8(4):453–7.
65. da Rocha e Silva CE, Alves Brasil MA, Matos do Nascimento E, et al. Is poststroke depression a major depression? Cerebrovasc Dis. 2013;35(4):385–91.
66. Farner L, Wagle J, Engedal K, et al. Depressive symptoms in stroke patients: a 13 month follow-up study of patients referred to a rehabilitation unit. J Affect Disord. 2010;127(1–3):211–8.
67. Berg A, Palomäki H, Lehtihalmes M. Poststroke depression: an 18-month follow-up. Stroke. 2003;34(1):138–43.
68. Gainotti G, Azzoni A, Razzano C, et al. The Post-Stroke Depression Rating Scale: a test specifically devised to investigate affective disorders of stroke patients. J Clin Exp Neuropsychol. 1997;19(3):340–56.
69. Calabrò RS, Italiano D, Militi D, et al. Levetiracetam-associated loss of libido and anhedonia. Epilepsy Behav. 2012;24(2):283–4.
70. Haslam J. Observations on madness and melancholy; including practical remarks on those diseases, together with cases, and an account of the morbid appearances on dissection. London: Callow; 1809.
71. Ribot T. La Psychologie des Sentiments. Paris: F. Alcan; 1896.
72. World Health Organization. ICD-10: international statistical classification of diseases and related health problems. 10th ed. Geneva: World Health Organization; 2004.
73. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35(3):537–55.
74. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35(1):68–77.
75. Ho N, Sommers M. Anhedonia: a concept analysis. Arch Psychiatr Nurs. 2013;27(3):121–9.
76. Cohen AS, Najolia GM, Brown LA, Minor KS. The state-trait disjunction of anhedonia in schizophrenia: potential affective, cognitive and social-based mechanisms. Clin Psychol Rev. 2011;31(3):440–8.
77. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. Am J Psychiatry. 2012;169(4):364–73.
78. Komulainen T, Keränen AM, Rasinaho E, et al. Quitting a weight loss program is associated with anhedonia: preliminary findings of the Lifestyle Intervention Treatment Evaluation Study in northern Finland. Int J Circumpolar Health. 2011;70(1):72–8.
79. Cohen AS, Callaway DA, Najolia GM, et al. On "risk" and reward: investigating state anhedonia in psychometrically defined schizotypy and schizophrenia. J Abnorm Psychol. 2012;121(2):407–15.
80. Cohen AS, Couture SM, Blanchard JJ. Neuropsychological functioning and social anhedonia: three-year follow-up data from a longitudinal community high risk study. J Psychiatr Res. 2012;46(7):898–904.
81. Lee JS, Park HJ, Chun JW, et al. Neuroanatomical correlates of trait anhedonia in patients with schizophrenia: a voxel-based morphometric study. Neurosci Lett. 2011;489(2):110–4.
82. Steer RA. Self-reported inability to cry as a symptom of anhedonic depression in outpatients with a major depressive disorder. Psychol Rep. 2011;108(3):874–82.
83. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998;28(3):309–69.
84. Schultz W. Getting formal with dopamine and reward. Neuron. 2002;36(2):241–63.
85. Wise RA. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox Res. 2008;14(2–3):169–83.
86. Carver CS. Affect and the functional bases of behavior: on the dimensional structure of affective experience. Personal Soc Psychol Rev. 2001;5(4):345–56.
87. Dickinson A, Balleine B. Motivational control of instrumental action. Curr Dir Psychol Sci. 1995;4(5):162–7.

88. Gard DE, Kring AM, Gard MG, et al. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93(1–3):253–60.
89. Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci. 2008;10(3):291–9.
90. Harvey PO, Pruessner J, Czechowska Y, et al. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry. 2007;12:703. 767–775.
91. Keedwell PA, Andrew C, Williams SC, et al. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005;58(11):843–53.
92. Bartoli F, Lillia N, Lax A, et al. Depression after stroke and risk of mortality: a systematic review and meta-analysis. Stroke Res Treat. 2013;2013:862978.

Contents to Volume I

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders,* DOI 10.1007/978-94-017-8610-2,

Contributors to Volume I

Roberto Andreatini Universidade Federal do Paraná, Curitiba, PR, Brazil

Kenneth Blum Department of Psychiatry, McKnight Brain Institute, University of Florida, College of Medicine, Gainesville, FL, USA

Charles Bonsack School of Nursing Sciences la Source, University of Applied Sciences of Western Switzerland, Delemont, Switzerland

Eric R. Braverman Department of Psychiatry, McKnight Brain Institute, University of Florida, College of Medicine, Gainesville, FL, USA

Omar Cabrera Behavioral Neuroscience Graduate Program, University of Missouri, St. Louis, MO, USA

Miranda L. Campbell Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Alex S. Cohen Department of Psychology, Louisiana State University, Baton Rouge, LA, USA

Charly Cungi School of Nursing Sciences la Source, University of Applied Sciences of Western Switzerland, Delemont, Switzerland

Alison A. DeLizza Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Jérôme Favrod School of Nursing Sciences la Source, University of Applied Sciences of Western Switzerland, Delemont, Switzerland

Department of Psychiatry, University Hospital Center and University of Lausanne, Prilly, Switzerland

Eliot L. Gardner National Institute on Drug Abuse-IRP, Baltimore, MD, USA

Mark S. Gold Department of Psychiatry, McKnight Brain Institute, University of Florida, College of Medicine, Gainesville, FL, USA

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders,* DOI 10.1007/978-94-017-8610-2,

Stephanie M. Gorka Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Fabian Grabenhorst Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

Zinoviy Gutkovich St. Luke's Roosevelt Hospital, New York, NY, USA

Columbia University College of Physicians and Surgeons, New York, NY, USA

F. Scott Hall Department of Pharmacology, Hyogo College of Medicine, Nishinomiya, Japan

Jessica Hoffman Behavioral Neuroscience Graduate Program, University of Missouri, St. Louis, MO, USA

Jeong Won Jahng Department of Oral and Maxillofacial Surgery, Dental Research Institute, Seoul National University School of Dentistry, Seoul, South Korea

Andrea C. Katz Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Junichi Kitanaka Department of Pharmacology, Hyogo College of Medicine, Nishinomiya, Japan

Nobue Kitanaka Department of Pharmacology, Hyogo College of Medicine, Nishinomiya, Japan

Rebecca K. MacAulay Department of Psychology, Louisiana State University, Baton Rouge, LA, USA

Aida Mallorquí Sant Pere Claver Health Foundation, Mental Health Services, Barcelona, Spain

Cognition and Brain Plasticity Group, ICREA and Department of Basic Psychology (Campus de Bellvitge) [Bellvitge Biomedical Research Institute], IDIBELL, L'Hospitalet de Llobregat, University of Barcelona, Barcelona, Spain

Bruno Jacson Martynhak Universidade Federal do Paraná, Curitiba, PR, Brazil

Jessica E. McGovern Department of Psychology, Louisiana State University, Baton Rouge, LA, USA

Alexandra Nguyen School of Nursing Sciences la Source, University of Applied Sciences of Western Switzerland, Delemont, Switzerland

Marlene Oscar-Berman Departments of Psychiatry, Neurology, and Anatomy and Neurobiology, Boston University School of Medicine, and Boston VA Healthcare System, Boston, MA, USA

Gonçalo Padrao Sant Pere Claver Health Foundation, Mental Health Services, Barcelona, Spain

Cognition and Brain Plasticity Group, ICREA and Department of Basic Psychology (Campus de Bellvitge) [Bellvitge Biomedical Research Institute], IDIBELL, L'Hospitalet de Llobregat, University of Barcelona, Barcelona, Spain

Department of Basic Psychology, Faculty of Psychology, Campus Bellvitge, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

Adrian Preda Irvine School of Medicine, Psychiatry and Human Behavior, University of California, California, CA, USA

Shyhrete Rexhaj School of Nursing Sciences la Source, University of Applied Sciences of Western Switzerland, Delemont, Switzerland

Community Psychiatry Service, Department of Psychiatry, University Hospital Center of Lausanne, Lausanne, Switzerland

Antoni Rodriguez-Fornells Cognition and Brain Plasticity Group, ICREA and Department of Basic Psychology (Campus de Bellvitge) [Bellvitge Biomedical Research Institute], IDIBELL, L'Hospitalet de Llobregat, University of Barcelona, Barcelona, Spain

Department of Basic Psychology, Faculty of Psychology, Campus Bellvitge University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

Catalan Institution for Research and Advanced Studies, ICREA, Barcelona, Spain

Casey Sarapas Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Masayuki Satoh Department of Dementia Prevention and Therapeutics, Graduate School of Medicine, Mie University, Mie, Japan

Stewart A. Shankman Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Thomas Simpatico Human Integrated Services Unit University of Vermont Center for Clinical and Translational Science, College of Medicine, Burlington, VT, USA

Motohiko Takemura Department of Pharmacology, Hyogo College of Medicine, Nishinomiya, Japan

George T. Taylor Behavioral Neuroscience Graduate Program, University of Missouri, St. Louis, MO, USA

Michael T. Treadway Center for Depression, Anxiety and Stress Research, McLean Hospital/Harvard Medical School, Belmont, MA, USA

Department of Psychology, Vanderbilt University, Nashville, TN, USA

George R. Uhl Department of Pharmacology, Hyogo College of Medicine, Nishinomiya, Japan

David H. Zald Department of Psychology, Vanderbilt University, Nashville, TN, USA

Department of Psychiatry, Vanderbilt University, Nashville, TN, USA

Index

M.S. Ritsner (ed.), *Anhedonia: A Comprehensive Handbook Volume II: Neuropsychiatric And Physical Disorders*, DOI 10.1007/978-94-017-8610-2,