Anhedonia in Unipolar Major Depressive Disorder: A Review

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Abstract: Anhedonia, the decreased capacity to experience pleasure, is a defining symptom of unipolar major depressive disorder (MDD). This review summarizes definitions and measurement issues related to the assessment of hedonic capacity in MDD, epidemiological research addressing linkages between anhedonia and MDD, as well as biomedical research investigating the neurobiology of anhedonia in both pre-clinical and clinical contexts. A synthesis of available data is presented that suggests that anhedonia is a core symptom of MDD, the elucidation of which is critical for improved understanding, detection, and treatment of MDD.

Keywords: Major depressive disorder, anhedonia, dopamine, review.

INTRODUCTION

Anhedonia, the decreased capacity to experience pleasure, is a central feature of DSM-IV Unipolar Major Depressive Disorder [MDD, 1]. According to DSM-IV, a diagnosis of MDD is contingent on the presence of five of the following symptoms during a two-week period that are a change from previous levels of functioning: depressed mood, anhedonia, significant weight change, sleep disturbance, psychomotor changes, fatigue, feelings of worthlessness, indecisiveness, and suicidal thoughts. Further, and most critically for the present review, at least one of the symptoms must be either depressed mood *or* anhedonia. In other words, a diagnosis of MDD is possible without depressed mood if anhedonia is present. This diagnostic classification scheme imports particular emphasis to the symptom of anhedonia over and above the other, non-defining seven symptoms of the disorder, and gives equal importance on the symptoms of depressed mood and anhedonia.

The purpose of the present review is to evaluate the diagnostic validity, assessment, and neurobiology of anhedonia in depression. Although there has been a recent increase is interest in of anhedonia research [2, 3], linkages to MDD, optimal standardized assessment procedures, and underlying neurobiology are still not well understood. The present review does not seek to answer definitely these questions, but rather aims to lay out fundamental unanswered questions relevant to the study of anhedonia in MDD and directions for future research to address such questions.

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HISTORICAL THEORIES OF ANHEDONIA AND ITS RELATION TO PSYCHOPATHOLOGY

The use of the term "anhedonia" in clinical psychiatry may be traced to over a century ago when Ribot [4] first defined anhedonia as the "insensibility relating to pleasure alone" to distinguish it from analgesia, the inability to experience pain, and highlighted the role of anhedonia in the diagnosis of melancholia. Systematic investigation of anhedonia in clinical contexts began with the work of Paul Meehl [5-10] who, based on his interactions with patients, conceptualized anhedonia as a central, biologically-based symptom of schizophrenia and hypothesized that anhedonia was the result of an inherited neural defect (i.e., "schizotaxia"). Furthermore, Meehl hypothesized that functioning at the low end of basic hedonic capacity was a risk factor for schizophrenia due to decreased buffering of aversive states by positive reinforcers.

Whereas Meehl highlighted the role of anhedonia in the development of schizophrenia, Klein [11, 12] focused on the relevance of anhedonia to depression. Klein distinguished two types of depression: reactive (i.e., 'neurotic,' 'exogenous,' or 'atypical' depression) and endogenomorphic (i.e., 'classic,' 'endogenous,' or 'melancholic') depression, and proposed that endogenomorphic depression is a central nervous system disorder characterized as anhedonic and more severely depressed.

METHODOLOGICAL CONSIDERATIONS

Researchers assessing pleasure capacity face a variety of methodological and conceptual dilemmas. For example, should pleasure (i.e., self-reported subjective happiness),

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reinforcement value (i.e., change in behavior contingent on feedback), or a neurobiological process (e.g., functioning of brain reward centers) be assessed? Moreover, there is variability associated with pleasurable states; for example, illness blunts hedonic capacity [13] and hunger makes food taste better [14]. Additionally, there is a chronometry to pleasure: it may be anticipated, experienced, or remembered, and the most relevant temporal form of pleasure may vary from context to context [15]. Furthermore, receipt of a putatively pleasurable stimulus may or may not overlap with feelings of relief, decreased displeasure, or a state of frustrative non-reward [16].

In addition to selecting the most relevant construct to measure in studies of pleasure capacity, researchers must select not only the type of pleasurable stimulus to use (e.g., visual, auditory, or gustatory stimuli), but must chose how to assess reactivity: self-report, behavioral, and biological assessments all tap distinct and overlapping components of a psychological response [17]. Further, within each class of responses, a variety of specific measures is available. For example, behavioral reactivity to pleasure may be measured by changes in facial musculature, reaction time, or approach behavior, whereas subjective accounts maybe tapped with a variety of measurement tool, reviewed below.

As these scenarios demonstrate, the pleasure response is likely not a unitary construct, but rather may be decomposed into more specific and elemental components. Further, it would appear that anhedonia shares a number of features with related constructs, including diminution of interest, reactivity of mood, flattening of affect, apathy, anergia, alliesthesia, and analgesia [18]. Clearly, a standardized "toolbox" is needed to allow for a set of consistent methods and measures to allow researchers to systematically address empirical questions related to pleasure capacity.

ANHEDONIA IN UNIPOLAR MAJOR DEPRESSION: DIAGNOSIS AND ASSESSMENT

DSM-IV defines anhedonia in MDD as the "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)" [1]. Similarly, the International Classification of Diseases, *10th Edition* [ICD-10, 19] diagnosis of depression requires two of three essential symptoms (i.e., depressed mood, marked loss of interest or pleasure, and decreased energy and fatigability) as well as two of seven other symptoms. Importantly, both classification systems give equal import to the symptoms of anhedonia and depressed mood and allow for the diagnosis of depression in the absence of symptomatic depressed mood if anhedonia is present.

The Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) is a standard clinician rating scale for assessing depressive severity [20]. Two of 17 HRSD items, (i.e., interest in work and activities, interest in sex) relate to anhedonia. The Beck Depression Inventory (BDI) is a common self-report continuous rating scale of depressive symptoms [21], and three of 21 BDI items (i.e., satisfaction, interest in other people, and interest in sex) relate to anhedonia.

A number of continuous measures of anhedonic function are widely used. Though designed primarily as measures of personality, these scales are routinely used in studies of hedonic functioning in patients with MDD [e.g., 22-24], and thus are included here. The Scales for the Assessment of Physical Anhedonia and Social Anhedonia include a wide range of pleasure items (e.g., "Trying new foods is something I enjoy") [25-27]. The Fawcett-Clark Pleasure Capacity Scale (FCPCS) describes pleasant experiences (e.g., "You lie soaking in a warm bath) [28]. The Pleasure Events Schedule lists pleasant events (e.g., "Being at the beach"), and respondents indicate enjoyability and whether the item occurred in a given period of time [29]. Items from the Snaith-Hamilton Pleasure Scale (SHAPS) begin with the phrase "I would…" (e.g., "I would be able to enjoy my favorite meal") [30]. The Mood and Anxiety Symptom Questionnaire Anhedonic Depression subscale was developed to index feelings of disinterest and lack of energy that are unique features of depression [31, 32]. The Multidimensional Personality Questionnaire Positive Emotionality factor indexes traits reflecting joy, excitement, and vigor (e.g., "Every day I do some things that are fun") [33, 34]. The Positive and Negative Affect Schedule Positive Affect scale indexes the extent to which respondents have experienced a range of adjectives (e.g., 'enthusiastic') during a specified time period [35, 36]. The Behavioral Approach Scale assesses personality traits reflecting Gray's [37] appetitive motivational system (e.g., "I crave excitement and new sensations") [38]. Finally, the Temporal Experience of Pleasure Scale was designed to measure individual trait dispositions in both anticipatory (e.g., "I look forward to a lot of things in my life") and consummatory (e.g., "I love it when people play with my hair") experiences of pleasure [39]. Finally, a relatively new tool assessment tool, the Effort-Expenditure for Rewards Task (EEfRT), was recently developed to assess the capacity to exert effort in the form of motor behavior to attain rewards [40].

ANHEDONIA AND MAJOR DEPRESSION: EPIDEMIOLOGICAL EVIDENCE

The National Institute of Mental Health Epidemiologic Catchment Area (ECA) study compared prevalence rates of MDD symptoms assessed by structured clinical interview for DSM-III-R [41]. Symptomatic anhedonia was based on an affirmative answer to: "In the last month has there been a period of time [when you were] not interested in most things or unable to enjoy the things you used to enjoy [most of the time]" [42]. This study indicated that the lifetime prevalence of dysphoria in a community sample was 29.9%, whereas the comparable figure for loss of interest was only 5.2%. The lifetime prevalence of other symptoms of MDD ranged from 9.1% (psychomotor changes) to 28.2% (thoughts of death). The nearly six-fold difference in base rates between depressed mood and anhedonia suggests that symptomatic anhedonia, as assessed retrospectively by semi-structured interview in a community sample, is relatively rare.

The DSM-IV mood disorders field trial allowed researchers to compare symptom prevalences in individuals with unipolar MDD and dysthymia, a chronic but less severe manifestation of depressive symptoms [43]. Ninety-five percent of those with MDD and 54% of those with dysthymia reported a loss of interest or pleasure, a statistically significant difference. It should be noted, however, that the magnitude of this difference was similar for other symptoms (e.g., difficulty concentrating was endorsed by 90% and 41% of depressed and dysthymic patients, respectively). Thus, although anhedonia is more prevalent in MDD than dysthymia, anhedonia may not discriminate between these two related disorders over and above other symptoms.

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is the largest prevalence study of psychiatric disorders conducted to date [44, 45]. Although new NESARC analyses continue to emerge, available data indicate that 32% of respondents reported depressed mood or anhedonia for a period of 2 weeks at some point in their life [46], and anhedonia, as well as feelings worthless and guilt, were shown to be significantly associated with suicide attempts in this sample [47]. The National Comorbidity Survey (NCS) revealed a current (30-day) prevalence rate of MDD of 4.9% and a lifetime prevalence of 17.1% [48, 49], and the National Comorbidity Survey-Replication (NCS-R) found a 12-month prevalence estimate of mood disorders of 9.5% [50]. However, no analysis to date of NESARC, NCS or NCS-R data has reported prevalence estimates of anhedonia either within the general population or amongst those with MDD.

ANHEDONIA AND MDD SUBTYPES

Anhedonia is the essential feature of the melancholic subtype of DSM-IV MDD, characterized by anhedonia, plus three of six other symptoms (i.e., distinct quality of depressed mood, depression worse in the mornings, early morning awakenings, psychomotor changes, weight loss, and guilt) [1]. Although there is no definitive method of evaluating subtype validity [51], most, but not all, available evidence is supportive of the validity of MDD subtypes [see, e.g., 52, 53 for exceptions]. The majority of such data emanates from psychopharmacologic trials. Patients with melancholic depression demonstrate relatively better response to tricyclic antidepressants, SNRI's, and augmentation strategies, whereas patients with atypical features demonstrate relatively better response to monoamine oxidase inhibitors [e.g., 54-57]. Further, more severely depressed patients and those with melancholic features appear to have relatively worse SSRI response profiles [for reviews, see 58, 59]. Alternatively, endogenous depression appears to predict superior response to a variety of anti-depressant treatments [60-62].

Meta-analytic reviews also indicate general support of depressive subtypes. Nelson and Charney [63] reviewed 33 studies (20 factor analysis, nine cluster analysis, and four discriminant function analysis) evaluating the validity of the melancholic depressive syndrome. Among the 13 factor analytic studies that identified an endogenous factor, loadings of the 'loss of interest' and 'lack of reactivity' symptoms on this factor ranged from 0.35 to 0.77 and 0.26 to 0.76, respectively. However, these factor loadings were not consistently higher than those of other symptoms (e.g., depressed mood (0.17-.079), retardation (0.44-0.71), and early morning awakenings (0.29-0.69)). Among the eight cluster analytic studies identifying an endogenous factor, evidence that 'loss of interest' and 'lack of reactivity' were endogenous symptoms ranged from 'moderate' to 'strong' and from 'slight' to 'strong,' respectively. Comparatively, all eight studies found 'moderate' evidence that difficulty concentrating typified endogenous depression. Finally, none of the discriminant function analytic studies found that 'loss of interest' or 'lack of reactivity' discriminated between depressive subtypes.

Epidemiologic studies have likewise found evidence of a subtype of depression characterized by anhedonia. An analysis of 788 depressed patients from The Collaborative Study of the Psychobiology of Depression [64] found an anhedonic and a vegetative subtype [65]. The conditional probabilities of symptomatic loss of pleasure within each group were 89% and 23%, respectively. These conditional probabilities surpassed those of all other symptoms. In two studies, Maes and colleagues [66, 67] cluster analyzed depressive symptoms and found two depressive subtypes. In both studies, at least 97% of subjects in the 'vital' (i.e., melancholic) group reported anhedonia. Finally, Kendler [68] analyzed symptom profiles from 1902 female twins and concluded that DSM-IV melancholia is a valid subtype with distinct clinical features and high familial lability to depressive illness.

New methods for evaluating the melancholic subtype of MDD are continuously emerging, including studies of gene associations [69], regional blood flow [70], blood oxygen level dependent brain activation [71], and regional brain volumes [72]. These neurobiological approaches will need to be integrated with clinical data to further shape our understanding of the validity of the melancholic depressive subtype.

NEUROBIOLOGICAL EVIDENCE OF ANHEDONIA IN MDD: PSYCHOPHYSIOLOGY AND NEUROIMAGING

Psychophysiology and neuroimaging approaches to assessing anhedonia in MDD allow for the assessment of the integrity of neurobiological architecture supporting pleasure responses. Psychophysiology refers to the branch of science concerned with the physiological bases of psychological processes [73]. Surprisingly, relatively little psychophysiological research has focused on anhedonia in MDD.

A number of groups have investigated affective modulation of the startle eyeblink response (i.e., changes in magnitude of the startle eyeblink reflex due to affective state) in patients with MDD. Allen and colleagues [74] and Dichter and colleagues [75, 76] reported that patients with MDD showed anomalous modulation of the startle eyeblink reflex, but this pattern was in response to a range of affective stimuli (i.e., both unpleasant and pleasant), rather than to

pleasant stimuli per se [see also 77, 78]. It should be noted that most [75-77] but not all [78] of the above studies reported that startle modulation differences were not reflected in subjective ratings of affective stimuli, suggesting that psychophysiology was tapping a unique response to affective stimuli not evident in self-report measures.

In a series of studies by Schwartz and colleagues [79-81] facial electromyography (EMG) responses were recorded from depressed and nondepressed patients during affective imagery. Depressed patients consistently showed an attenuated pattern during happy imagery, a pattern mimicking sadness during neutral imagery, and a slightly accentuated response during sad imagery.

Functional brain imaging is a complimentary technique that allows for *in vivo* visualizing of brain function. Though a range of functional brain imaging techniques is available, fMRI has emerged as the dominant technique because it is non-invasive and has excellent contrast properties. Functional MRI utilizes an endogenous contrast property of the brain, blood oxygenation level dependent (BOLD) contrast, to localize changes in blood oxygenation – an indirect measure of neural activity [82].

Functional neuroimaging studies of responses to pleasant stimuli in MDD have consistently indicated hypoactivation of the brain's reward structures, including dopaminercically-mediated ascending mesolimbic projections areas, including the dorsal and ventral striatum [83-88] as well as a host of other reward structures, including the medial prefrontal cortex [89, 90], the pregenual and subgenual anterior cingulate, and the medial frontal gyrus [91, 92].

For example, Smoski and colleagues [93] presented depressed patients with a gambling task wherein monetary gains were first anticipated and then experienced. The MDD group was characterized by reduced activation of striatal reward regions while processing rewards (but see Knutson and colleagues [94] for a report of intact striatal functioning in MDD). In a followup study, Dichter and colleagues [95] reported that when these same patients were treated with behavioral psychotherapy, improved functioning was observed in these same striatal regions during reward anticipation. The finding of reduced activity in frontostriatal brain regions in response to positive stimuli has been reported by a number of groups and is thus considered a biomarker candidate of anhedonia in MDD [96-102].

An imaging modality that is particularly well-suited to study DA functioning is positron emission tomography (PET). [^{11}C] raclopride PET is capable of assessing dopamine D_2 receptor density and availability, typically expressed as the binding potential of [^{11}C] raclopride. Comparisons between patients with MDD have been equivocal [see 103 for a summary]. For example, Hirvonen *et al.* [103] reported no differences in striatal and thalamic dopamine D_2 receptors between medication-naïve MDD patients and controls, consistent with the pattern of finds in some studies [104-106], but inconsistent with a number of groups who reported altered striatal D_2 receptor binding [107-111]. Though there are multiple possible factors to account for these discrepancies in the [^{11}C] raclopride PET literature, it should be noted that it is not possible to distinguish changes in receptor concentrations from changes in dopamine concentration, and thus it is possible that nonsignificant findings in this area may be due to compensatory changes in receptor expression secondary to alterations in dopamine release, or vice versa.

An area of neglected study within the neuroimaging literature is direct comparisons between MDD and other psychiatric disorders characterized by anhedonia. A notable exception is study by Lawrence *et al.* [112] where euthymic and depressed patients with bipolar disorder and patients with MDD viewed faces with varying emotional intensities. Whereas the bipolar group was characterized by differential responses to nearly all emotion categories, the MDD group was characterized by blunted response to happy but not sad stimuli, suggesting that diminished response to pleasant stimuli may uniquely characterize MDD relative to bipolar disorder. Future three-group studies (i.e., MDD, psychiatric control, control) comparing MDD with other disorders characterized by anhedonia (e.g., bipolar disorder, schizophrenia, and PTSD) are needed to distinguish similarities and differences amongst these conditions with respect to processing pleasant stimuli.

ANIMAL MODELS OF ANHEDONIA

Animal models of anhedonia have focused on the ascending dopaminergic (DA) pathways that mediate reward-seeking behaviors. The potential behavioral functions of these systems, including their role in the control of locomotor activity [113, 114], learning [115-118], and consummatory behaviors [119], have received a great deal of research attention.

An extensive animal literature links DA systems, and the mesolimbic DA system in particular, to reward-oriented behaviors [118, 120-122]. There are four major DA pathways [123]. The tuberoinfundibular tract is involved in neuroendocrine control. The nigrostriatal pathway mediates modulation of extrapyramidal motor function. The mesocortical tract mediates cognition and modulation of behaviors linked with planning, motivation and reward. Most relevant in the present context, the mesolimbic tract projects from the ventral tegmental area to limbic areas, including the nucleus accumbens and the amygdala. This tract mediates response to rewards, emotional processes, and motivated behavior [124]. Dysregulation of this tract is implicated in schizophrenia, affective disorders, and substance abuse [124-126].

Wise and colleagues [127-130] conducted a series of hallmark studies demonstrating that neuroleptics (antipsychotic agents that block DA synaptic transmission) decrease operant responding for rewards but not overall motor capacity [127, 131, 132] They concluded that mesolimbic DA antagonism decreased the capacity of animals to experience normally rewarding stimuli as such. Furthermore, these animals demonstrated spontaneous recovery of operant responding after the neuroleptic wore off [133]. Wise (1982) concluded that decreased activity of the mesolimbic DA system increases the threshold for

responding for rewards and dubbed this effect "the anhedonia hypothesis of neuroleptic action" [129].

The anhedonia hypothesis has been refined in recent years, with a particular emphasis on the temporal properties of hedonic responding that are affected by agents that disrupt mesolimbic DA function. For example, mesolimbic DA blockade does not impact taste reactivity (i.e., the hedonic impact of tastes measures as behaviors in response to the presentation of palatable food) [134, 135]. This important finding indicates that mesolimbic DA blockade selectively impacts "wanting", but not "liking" [136, 137]. More specifically, the mesolimbic DA system appears to mediate *incentive motivation learning,* the learning of an association between a behavior and a reward [117, 137, 138]. Illustratively, mesolimbic DA affects response choices in a manner that favors low-effort outcomes: given the choice between four food pellets blocked by a high barrier or two unblocked food pellets, whereas control animals prefer to climb the barrier for the larger reward, neuroleptically-treated animals chose the no-barrier/two-pellet arm of the maze [139, 140]. In other words, neuroleptics appear shift behavioral choice to favor low-work conditions, even at the cost of receiving decreased reward.

This distinction between so-called "appetitive" and "consummatory" phases of appetitive responses is a critical distinction and suggests that to the extent that anhedonia in MDD is characterized by decreased functional output of mesolimbic DA systems, anhedonia in MDD is likely characterized by decreased anticipatory pleasure, but not necessarily decreased consummatory pleasure, a claim that is corroborated by psychophysiology [76] and neuroimaging [93] data. Though no clinical data addresses whether anhedonia is MDD is characterized by a shift in cost-benefit behavioral output, as reviewed earlier, a new scale, the Effort-Expenditure for Rewards Task, was developed to assess this construct [40], and future studies that assess shifts in cost-benefit gradients to attain rewards in MDD will be necessary to further evaluate the mesolimbic DA model of anhedonia in MDD.

EVIDENCE OF DOPAMINERGIC INVOLVEMENT IN MDD

The previous section characterized the probable nature of anhedonic deficits in MDD based on the effects of DA manipulations in animals. The applicability of such characterizations in human clinical contexts is critically dependent on whether MDD is indeed characterized by altered mesolimbic DA functioning [see, e.g., 141 for reviews, 142]. Studies of DA synthesis, storage, and metabolism have not shown a consistent DA abnormality in individuals with depression [125, 143, 144]. However, there is a growing body of both clinical and preclinical data suggesting that altered functioning of DA systems is involved in the pathogenesis of at least some aspects of depression [145-147]. There is also consistent evidence of decreased plasma DA precursor [148] and cerebral spinal fluid (CSF) DA metabolite (i.e., homovanillic acid) in depressed patients [149-156], and particularly so in MDD patients with marked psychomotor retardation [157-159].

CONCLUSIONS AND FUTURE DIRECTIONS

Anhedonia in MDD is a multi-faceted construct. Decreased pleasure capacity may reflect changes in appetitive or consummatory pleasure capacity. Additionally, anhedonia may be global or specific, may include sensory and motor deficits, and may occur outside the realms of psychopathology or illness. However, despite evidence of such complexities, anhedonia is often conceptualized and assessed as a unitary construct. Furthermore, the lack of behavioral validation of current self-report anhedonia assessment instruments makes existing empirical data difficult to interpret, and thus the relations between anhedonia and MDD are largely unknown.

DSM-IV suggests that anhedonia is a core symptom of MDD, but no study to date has adequately addressed the sensitivity or specificity this symptom for MDD. The results of such research will have important implications for how primary care providers screen for both MDD and other psychiatric conditions. Additionally, hedonic capacity is a personality trait in individuals without frank psychopathology [160], and it is not known if anhedonic individuals are at heightened risk of developing depression [24, 161, 162]. A longitudinal, high-risk study that assesses hedonic capacity and depressive symptomatology over time could evaluate whether individuals with low hedonic capacity are at heightened risk of developing MDD. Furthermore, neuroimaging research will be critical for further understanding potential neurobiological mediators of anhedonia in MDD. A better understanding of anhedonia in MDD will improve assessment of this construct and will elucidate the most effective ways to treat anhedonia in MDD in the future.

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