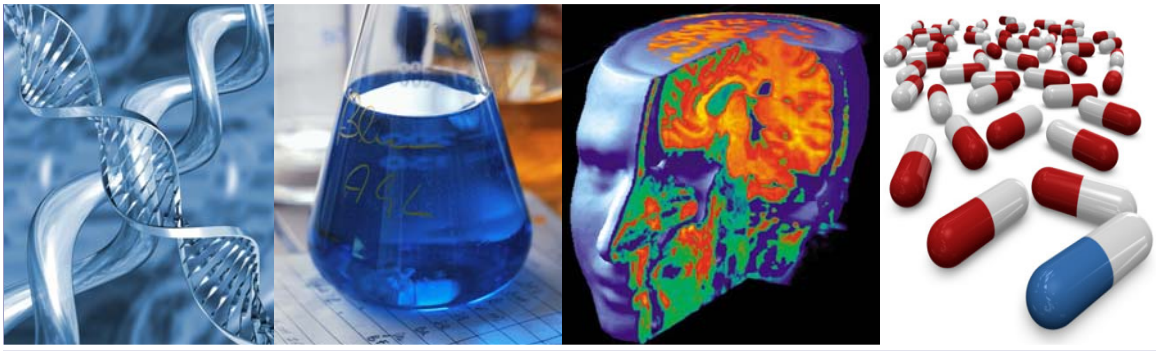
NEXT GENERATION ANTIDEPRESSANTS

MOVING BEYOND MONOAMINES TO DISCOVER NOVEL AND DIFFERENTIATED TREATMENT STRATEGIES FOR MOOD DISORDERS



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CHAPTER 5

Defining Depression Endophenotypes

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Major Depressive Disorder (MDD) is a highly prevalent and recurrent disorder and a leading cause of disease burden across the world [1]. In the United States alone, for example, the lifetime prevalence rate has been estimated to be 16.6%, affecting over 30 million people, with more than 80% of these individuals experiencing recurrent episodes [2,3]. At both the individual and population levels, depression engenders severe impairment in functioning across social, cognitive, and occupational domains [4,5]. Given the pervasive and detrimental effects of depression, it is disconcerting that in the largest prospective treatment study to date (the Sequenced Treatment Alternative to Relieve Depression (STAR*D) study), only about one-third of participants remitted after treatment with a standard, first-line antidepressant (the selective serotonin reuptake inhibitor citalopram), and the probability of remission generally decreased over subsequent treatment levels [6]. Unfortunately, efforts to design more effective treatment strategies for depression are limited by the fact that the etiological pathways underlying this disorder remain complex and elusive.

In recent years, concerns have been raised that the ongoing quest to understand the etiology and pathophysiology of MDD might be hindered in part by difficulties in defining and characterizing psychiatric phenotypes (e.g., [7,8,9]). With respect to MDD, it has been suggested that the current classification criteria encompass a heterogeneous mix of illnesses that share similar final pathways likely reached via multiple pathophysiological processes [7]. One way to address this heterogeneity is to take an ‘endophenotypic’ approach and focus on intermediate phenotypes that are more narrowly defined and quantified than DSM-IV diagnoses [10].

Our goal in this chapter is to summarize literature on the potential utility of applying an endophenotypic approach to depression research, with a focus on one of the most promising depressive endophenotypes—anhedonia, defined as loss of pleasure or lack of reactivity to pleasurable stimuli [11]. We begin with an overview of the endophenotype concept and its central criteria, which include the following [7,10]: 1) biological and clinical plausibility, 2) specificity, 3) state-independence, 4) familial association, 5) cosegregation, and 6) heritability. In depression research, various endophenotypes have been proposed and assessed with respect to these criteria, including impaired reward function (anhedonia), impaired learning and memory, increased stress sensitivity, REM sleep abnormalities, and tryptophan depletion, among others (see [7] for review). Our focus in this chapter will be on anhedonia, as it has received some of the strongest empirical evidence [7,12,13]. To this end, we incorporate epidemiological, behavioral, neuroimaging, and genetic studies to examine the aforementioned endophenotypic criteria for anhedonia. Thereafter, we discuss an objective way to measure anhedonia in a laboratory setting and summarize recent findings using this paradigm. The chapter concludes with a discussion of important directions for future research efforts using an endophenotypic approach.

THE ENDOPHENOTYPE CONCEPT IN RELATION TO PSYCHIATRY

Definition and Value of Endophenotypes

The identification of etiological and pathophysiological processes underlying mental disorders has proven to be an exceptionally difficult mission and these processes remain largely unknown despite vigorous research efforts over several decades. As previously noted, a substantial contributing factor to this difficulty may be the structure of current classification systems, including the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; [11]), in which the diagnosis of mental disorders revolves around symptom clusters and clinical course [7,9]. This descriptive, categorical approach is implemented in an effort to maximize diagnostic reliability, however, it brings the issue of validity into question for various mental disorders, including MDD [14]. As a result of the organizational framework of the DSM-IV, these categories of disorders may encompass a heterogeneous mix of illnesses [7,15]. The heterogeneity of clinical phenotypes is postulated to reflect the involvement of a multitude of genes—none of which is likely necessary or sufficient for triggering a given disorder—as well as complex interactions between genes and environmental factors [10,16,17]. In response to this issue of heterogeneity, one approach is to focus research efforts on 'endophenotypes,' or intermediate phenotypes that are hypothesized to lie within the etiological link between genes and clinical disease [8,10]. Accordingly, the endophenotypic approach enables the identification of "the 'upstream' consequences of genes" as well as "the 'downstream' traits or facets of clinical phenotypes" [p. 637; 10]. One assumption underlying this conceptualization is that endophenotypes involve comparatively fewer genes and enable a more direct measurement of the biological and environmental factors that contribute to a disorder than afforded by the broader perspective of the clinical phenotype [10]. This assumption was recently challenged by Flint and Mufano [18], who contended that some endophenotypes may not be considerably less genetically complex than clinical disease phenotypes, raising potential concerns about the "incremental" validity of the endophenotypic approach with respect to genetic architecture. While this concern is legitimate, it is important to recognize that the conclusions drawn by Flint and Mufano were predominantly based on results restricted to the effects of COMT genotype on endophenotypes, which may limit the generalizability of their conclusion. Moreover, Flint and Mufano acknowledge that an endophenotypic approach may still be beneficial to genetic research and contribute to higher reliability across data by enabling objective quantitative measures to be obtained from the large number of individuals necessary for genetic analyses. Nevertheless, additional research is clearly needed to evaluate the incremental validity of the endophenotypic approach, particularly with respect to etiological pathways underlying mental illnesses. Ultimately, these endeavors could have vast implications for improving the validity of our classification system and the effectiveness of treatment and prevention methods.

Criteria and Validation of Endophenotypes

Putative endophenotypes can be examined using psychological, physiological, neuroimaging, and biochemical methods [7]. In order for a psychological or biological variable to be classified as an endophenotype, it should meet the following criteria [7,10,19,20]:

1) *Clinical and biological plausibility:* Conceptual relationships exist between the endophenotype and the disease of interest.

2) *Specificity:* The endophenotype is linked more strongly to the psychiatric disorder of interest than to other psychiatric disorders.[1]

3) *State-independence:* The endophenotype is stable over time and not dependent on illness status or treatment. In other words, the endophenotype should be apparent in an individual regardless of whether or not s/he is actively experiencing symptoms of the illness.[2]

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[1] Hasler and colleagues [15] recently suggested that the specificity criterion might not be necessary because the biological validity of current definitions of mental disorders remains under question.

[2] In an attempt to take into account developmental factors and symptom provocation methods in phenotypic expression, Hasler and colleagues [15] subsequently modified this criterion to state that it may be age-normed and may require an environmental challenge to be apparent.

4) *Heritability:* A proportion of variance in the endophenotype is attributable to genetic variance.

5) *Familial association:* The endophenotype occurs more frequently in unaffected relatives of ill individuals than in the general population.

6) *Cosegregation:* Within families of ill individuals, the endophenotype occurs more frequently in family members who are affected with the illness than in family members who are unaffected by the illness.

In addition to the aforementioned criteria, it is important to take into account the degree to which a putative endophenotype can be feasibly and reliably measured [15]. Along these lines, in the section "*Current Directions in Objective Laboratory Measurements of Anhedonia*," we will describe our experience utilizing a laboratory-based measure to objectively assess an important component of anhedonia (reward responsiveness).

ANHEDONIA AS A POTENTIAL DEPRESSIVE ENDOPHENOTYPE

The notion that anhedonia may be a trait marker of vulnerability to depression has been under consideration for many years [21,22,23]. Within the past decade in particular, anhedonia has received considerable support as a promising depressive endophenotype [7,12,13]. As summarized in the following sections, empirical evidence supports the endophenotypic criteria of clinical and biological plausibility, familial association, and heritability, mixed or limited findings exist for state-independence and specificity, and few studies have addressed cosegregation. Throughout these sections, the emphasis will be on studies that include laboratory-based tasks in addition to self-report measures, rather than studies focusing exclusively on the latter.

Clinical and Biological Plausibility of Anhedonia as a Depressive Endophenotype

Among the DSM-IV criteria for a major depressive episode, anhedonia is a cardinal symptom with comparable status as depressed mood, given that one of these two features are required for clinical diagnosis [11]. In order to more explicitly understand the role of anhedonia in depression, researchers have examined a variety of domains, including affective and behavioral responses to positive stimuli, perceptual and attentional processing of positive cues, and ability to learn from reinforcement history. Investigations have also been conducted to examine whether anhedonic symptoms have predictive validity with regard to clinical outcome. Moreover, neuroimaging studies have been utilized to explore relationships between abnormal functioning within particular reward-related brain regions and depression. In the ensuing sections, findings stemming from these lines of inquiry will be considered in order to evaluate the clinical and biological plausibility of anhedonia as a depressive endophenotype.

In an early study probing the encoding of positive stimuli, Berenbaum and Oltmanns [24] found that depressed individuals, relative to healthy controls, reported less positive affect and displayed fewer positive facial expressions when presented with positive film clips. Along similar lines, Sloan and colleagues [25] reported that depressed participants rated pleasant picture stimuli less positively, and displayed reduced frequency and intensity of pleasant facial expressions, compared to controls. Importantly, in both studies, findings were selective to positive stimuli and did not extend to negative stimuli. Evidence of reduced facial reactivity, (e.g., [26,27]) and affective responses (e.g., [28,29,30,31]) to positive stimuli has emerged from additional studies, although null findings have also been described (e.g., [32,33]). If present, blunted affective and behavioral reactivity to positive stimuli could arguably influence subsequent retrieval of such stimuli. However, before discussing studies on retrieval, it is worth considering perceptual and attentional processing of positive cues, as these processes could arguably also influence retrieval.

In the realm of perceptual processing, findings are inconsistent regarding whether depressed individuals are impaired in their ability to recognize positive stimuli, such as happy facial expressions. Various researchers report no impairment on face recognition tasks in depression (e.g., [34,35,36]). Meanwhile, others have found that depressed individuals, relative to controls, are less accurate in recognizing happy facial expressions (e.g., [37,38]), and require more time (e.g., [39]) and greater intensity of emotional expression (e.g., [40]) in order to label faces as happy. Of note, recognition impairment was specific to positive facial stimuli only in the latter two studies [39,40]. Discrepancies

across the aforementioned results may be due in part to the heterogeneous nature of depression, or to the possibility that some results may be confounded by response biases, especially if only accuracy and reaction time were measured.

There is also mixed evidence with respect to attentional biases in depression. In several studies using the deployment-of-attention (e.g., [41,42]) or dot-probe [43] paradigms, depressed patients failed to show the positivity bias seen in healthy controls, who directed their attention toward positive stimuli. While these studies lend credence towards a depression-related attentional bias away from positive stimuli, others report null findings (e.g., [44]). Nevertheless, a potentially blunted attentional positivity bias, along with possible impairments in recognizing positive stimuli, and reduced affective and behavioral reactivity to positive stimuli at encoding, may all impede the ability of depressed individuals to retrieve positive cues. Indeed, depressed individuals are more likely to underestimate the occurrence of positive reinforcements received in the past (e.g., [45,46]). It is important to note that this pattern of impairment does not extend to estimations of punishments, as depressed individuals are actually more likely to overestimate the occurrence of punishments received in the past [46]. Furthermore, a biased view of past positive experiences may contribute towards a biased calculation of future outcomes, since individuals with depression also report lower expectations of positive future experiences than control subjects (e.g., [47,48]).

Findings of underestimation of past positive reinforcements received may be related to emerging data in which depressed subjects display a reduced ability to modify behavior as a function of positive reinforcements received, as evident from a monetarily reinforced verbal recognition task [49,50], a gambling task [51], and a probabilistic reward task [13; see below section: *Current Directions in Objective Laboratory Measurements of Anhedonia*]. In sum, the above studies provide evidence that depression is characterized by: reduced affective and behavioral reactivity to positive stimuli; underestimation of the occurrence of past, and the likelihood of future, positive reinforcements; and a reduced ability to use reinforcement history to modify behavior. Evidence of blunted perceptual and attentional processing biases is more tenuous (see also [52]).

Of clinical relevance, anhedonic symptoms and behaviors have been found to have predictive value in determining depression onset, course and outcome, as discussed hereafter. For example, reduced frequency of choosing high-magnitude reward options in a decision-making task predicted depressive symptoms one year later in a pediatric sample [51]. With respect to predicting levels of concurrent depressive symptoms, lower levels of approach-related behavior—but not higher levels of avoidance-related behavior—have been associated with increased severity of depression in currently depressed individuals [53]. Along these lines, lower levels of approach-related behavior [53,54], lower behavioral and heart rate reactivity to amusing films [55], and reduced recall of positive words [56] have been found to predict poorer longitudinal outcome and/or longer time to recovery in depressed individuals. Complementing such studies, Lethbridge & Allen [57] conducted a prospective study in a community sample of individuals with past depression and reported that larger levels of reduced positive affect following a sad mood induction correlated with a greater probability of MDD recurrence a year later; notably, relapse was not predicted by changes in negative affect or dysfunctional thinking, indicating specificity.

Finally, additional support for anhedonia as a potential vulnerability factor for the development of depression comes from the fact that anhedonic symptoms are reported in unaffected individuals with increased genetic risk for depression (see below section: *Familial Association of Anhedonia as a Depressive Endophenotype*), in combination with evidence that anhedonia may be a trait-like characteristic (see below section: *State-independence of Anhedonia as a Depressive Endophenotype*). Collectively, these studies suggest that anhedonic symptoms may have predictive validity with regard to onset and severity of depression, poorer outcome, longer time to recovery, and higher likelihood of relapse.

The biological plausibility of anhedonia as a depressive endophenotype is supported by its association with dysfunctions of the brain reward system in neuroimaging studies [58,59,60]. Important brain areas involved in incentive processing include the dorsal striatum (e.g., caudate, putamen), the ventral striatum (e.g., nucleus accumbens), the anterior cingulate cortex (ACC), and the orbitofrontal cortex (OFC) [59,61,62]. As will be discussed below, neuroimaging studies promise to contribute to a

more explicit understanding of which aspects of reward processing (e.g., hedonic coding, ability to link actions to rewards) are likely dysfunctional in depression, because 1) particular brain regions have been linked to specific facets of incentive processing (e.g., [63,64,65,66,67,68]); and 2) abnormal activation of these neural areas is evident in studies that directly assess reward processing in depression [60,69,70,71,72,73,74].

To begin with, the dorsal striatum (i.e., caudate, putamen) is important for coding reward prediction errors [64,75] and linking actions to rewards [76], and is strongly activated in response to unpredictable rewards [65]. Forbes and colleagues [74] recently reported that depressed adolescents exhibited lower caudate activation than psychiatrically healthy adolescents during monetary reward anticipation and outcome in a card-guessing task. Moreover, among the depressed adolescents, reduced caudate activation was associated with decreased subjective ratings of positive affect in real-world environments. Importantly, findings of lower caudate activation during reward anticipation and consumption in depressed adolescents are in line with similar results emerging from adult depressed samples (e.g., [60]). Specifically, utilizing fMRI and a monetary incentive delay task, we recently found that depressed adults displayed less bilateral caudate and left nucleus accumbens activation than controls during reward feedback and lower left putamen activation to reward-predicting cues [60]. The depressed participants also reported lower affective ratings during reward anticipation and consumption, and showed lower reward-related RT speeding. Accordingly, our results highlight depression-related impairment in functioning of both the dorsal and ventral striatum in response to a reward-processing task. Based on prior findings, we speculate that dysfunction in the dorsal and ventral striatum might index blunted action-reward reinforcement learning [76] and hedonic coding [67,77,78,79], respectively.

Reduced ventral striatal activation (nucleus accumbens) also emerged from a recent study conducted by Steele and colleagues [71], who utilized fMRI and a gambling task to examine post-incentive behavioral adjustments and neural correlates in depression. Following positive feedback, participants with MDD failed to show the activation of ventral striatal regions and reduction in reaction time that was characteristic of controls, and the behavioral findings specifically correlated with anhedonic symptoms [71]. In a subsequent study, these investigators modeled reward prediction errors utilizing fMRI and a Pavlovian reward learning paradigm that involved probabilistic associations between picture stimuli and water delivery to thirsty participants [73]. The authors found that treatment-resistant MDD participants, as compared to controls, had smaller reward-learning signals in the ventral striatum and dorsal ACC. Diminished ACC activation has also been observed in depressed children, relative to controls, during both the reward decision and reward outcome phases of a decision-making task [70]. Given that the ACC, especially its dorsal subdivision, has been implicated in linking outcome representations to actions and integrating reinforcement history to guide action [66], these findings suggest specific reward-related processes that may be impaired in depression.

In addition to the ACC, depressed children in the pediatric sample investigated by Forbes et al. [70] also exhibited lower activation than controls in the caudate and right OFC when receiving low-magnitude rewards. In light of prior findings, OFC dysfunction might index impairments in updating stimulus-reinforcement representations to guide behavior [63,80]. Taken as a whole, results from the aforementioned neuroimaging studies highlight certain aspects of reward processing that are likely to be dysfunctional in depression. For example, dysfunction in dorsal striatal regions, especially caudate hypoactivity, may reflect an impaired ability to learn connections between actions and rewards. Moreover, reduced functioning of the ventral striatal network (e.g., nucleus accumbens) in depression may be related to impaired hedonic coding and, along with dACC dysfunction, may underlie difficulty updating reward predictions. Of note, reduced ventral striatal activation in response to positive cues is largest in depressed individuals reporting elevated anhedonic symptoms [58,81], providing important convergent validity. Finally, OFC dysfunctions may be linked to impaired representation of the reward value of stimuli, as well as difficulty updating associations between stimuli and outcomes. Although the reviewed neuroimaging studies enhance our understanding of reward processing in depression, the aforementioned hypotheses need to be further examined using various paradigms in future studies before these theories can be definitively asserted.

Specificity of Anhedonia as a Depressive Endophenotype

There is limited support for the specificity of anhedonia as a depressive endophenotype because the presence of anhedonia has been demonstrated in other mental illnesses, especially schizophrenia and substance use disorders [82,83]. In a recent examination of anhedonia in patients with depression, psychosis, or substance abuse, all three patient groups demonstrated significantly higher scores on a self-report measure of anhedonia, the Snaith-Hamilton Pleasure scale, relative to controls [84]; however, depressed patients also scored significantly higher than the two other patient groups. With regard to anhedonia in substance abusers, Martin-Soelch and colleagues [85] found that former opiate addicts, as compared to controls, showed reduced activation of neural reward circuits in response to nonmonetary positive reinforcement. Although this neural hypoactivation in former opiate addicts did not extend to monetary positive reinforcement, their subjective ratings of monetary value were significantly lower than controls. Along with characterizing previous drug abusers, anhedonia may play a key role in relapse into drug use, likely due to reduced dopamine (DA) release associated with withdrawal [86]. However, the specific ways in which anhedonia and substance abuse are related, including the directionality between these factors, are complicated by comorbid psychopathology and remain to be fully elucidated.

In addition to its association with substance use disorders, anhedonia has also been closely linked to schizophrenia, and is indeed considered a prominent negative symptom of this disorder [87]. In a longitudinal study of schizophrenia and MDD, Blanchard and colleagues [88] found that both groups had higher scores than controls on a self-report measure of social anhedonia at baseline (inpatient hospitalization). Critically, whereas social anhedonic symptoms significantly declined in recovered depressed patients at a one-year follow-up, these symptoms remained stable in schizophrenia patients, raising the possibility that anhedonic symptoms may be trait-like in schizophrenia and more state-dependent in MDD. In an attempt to clarify the relationships between anhedonia, depression, and schizophrenia, Romney and Candido [89] used factor analysis to examine the loading of anhedonia on three main factors—depression, positive and negative symptoms of schizophrenia. Using self-report measures from schizophrenic and depressed samples, they reported that anhedonia loaded significantly on the depression factor but not the negative symptoms factor, and concluded that anhedonia is predominantly a depressive symptom that should be differentiated from the general affective blunting characteristic of schizophrenia. Conversely, as highlighted by Loas [90], other researchers who conducted related factor analytic studies found anhedonic symptoms in schizophrenia to be independent of depressive symptoms (e.g., [91,92]). In another study relevant to this debate, Joiner and colleagues [93] found that MDD patients, as compared to schizophrenic patients, had significantly higher scores on the Beck Depression Inventory (BDI) anhedonic symptoms scale, while both groups had comparable non-anhedonic depressive symptoms scores and total BDI scores. These authors concluded that a much stronger relationship exists between anhedonic symptoms and depressive versus schizophrenic diagnostic status, lending support for anhedonia as a relatively specific marker for depression.

While the contrasting results of the aforementioned studies remain to be clarified, the use of “objective” laboratory-based measures of anhedonia may help to resolve some of the discrepancies by identifying specific aspects of reward processing that might be differentially affected in various clinical syndromes. In this regard, findings from recent studies by our laboratory [13] and Gold’s group [94] provide initial evidence that different disorders might affect distinct aspects of reward processing. Of note, both studies used the same probabilistic reward task to evaluate how participants modulated their behavior as a function of reinforcement history. We found that unmedicated MDD patients had a reduced response bias toward the more frequently rewarded stimulus in the absence of immediate reward, although they were responsive to single rewards [13]. In contrast, Heerey, Bell-Warren and Gold [94] reported that participants with schizophrenia showed a normative response bias and did not have impaired sensitivity to reward or impaired ability to modulate behavior based on prior rewards received. Of note, these researchers also administered a probabilistic decision-making task to the same participants with schizophrenia and controls, and the schizophrenia group exhibited a reduced ability to evaluate potential outcomes when given competing response options, likely stemming from working memory deficits. Overall, Heerey, Bell-Warren and Gold [94] postulated that the fundamental mechanisms underlying reward-based learning in schizophrenia may actually be unimpaired, but these individuals might lack the ability to integrate such affective cues with other cognitive information to

assess potential outcomes and guide behavior.[3] Accordingly, this initial evidence suggests that reward-related behavior in schizophrenia and MDD might be characterized by distinct dysfunctions.

Although anhedonic symptoms may not be exclusive to depression, some specificity to depression in relation to other mental illnesses, such as anxiety, has been demonstrated. Given the high degree of clinical overlap between depression and anxiety [97], much time and effort has been expended towards parsing out which variables aid in differentiating between these illnesses. As suggested by a tripartite model of symptom clusters proposed by Watson and colleagues [98], although high negative affect characterizes both depression and anxiety, low positive affect is relatively specific to depression. Following from this model, various studies have demonstrated associations between depressive symptoms and reduced generation, recall, and anticipation of positive experiences that are not apparent in relation to anxiety symptoms [47,48,99,100].

For instance, MacLeod et al. [99] found that depressed patients, in contrast to patients with panic disorder or healthy controls, generated fewer positive experiences in response to various time-frame cues for both memory recall and future-thinking in a verbal fluency paradigm. In a subsequent study using a related paradigm, depressive symptoms—but not anxiety symptoms—were associated with a reduction in anticipated future positive experiences [47]. Similarly, Miranda and Mennin [48] reported that a greater propensity to predict that positive events would not happen in the future, and an increased level of certainty about these predictions, was associated with higher depression symptoms, but not anxiety symptoms. Finally, this pattern of results was extended to a pediatric sample of primary school children, in which probability ratings of self-referential future positive events were likewise negatively associated with levels of depression, but not levels of anxiety [100].

There is also evidence of specificity for depression over anxiety with respect to impaired perceptual processing of positively valenced cues and reduced ability to modify behavior as a function of rewards. First, individuals with MDD, as compared to individuals with social anxiety disorder and controls, have been shown to require a higher level of emotional expression in order to identify happy faces [40]. Second, utilizing a probabilistic reward task with a non-clinical sample, Pizzagalli, Jahn, and O'Shea [12] found that a reduced response bias toward a more frequently rewarded stimulus was specifically associated with anhedonic symptoms and not with symptoms of anxiety or general distress. These findings were replicated and extended in later studies using both non-clinical [101] and MDD [13] samples. Finally, in the abovementioned study by Forbes and colleagues [51], a reduced propensity to choose high-probability, high-reward options in a gambling task predicted depressive symptoms, but not anxiety symptoms, one year later. Collectively, the empirical evidence summarized in this section supports the notion that anhedonia symptoms are relatively specific to depression over anxiety.

State-independence of Anhedonia as a Depressive Endophenotype

Relatively few studies in MDD samples have examined whether the symptoms of anhedonia reflect state or trait characteristics. Nevertheless, initial support for the temporal stability of anhedonia has emerged from investigations in which researchers have compared individuals who are actively experiencing clinical symptoms of depression with those who are in a remitted or recovered phase of the illness [43,102,103,104]. In the earliest of these studies, previously depressed patients re-tested during remission continued to demonstrate less frequent endorsement of positive words (non-depressed content adjectives), but not negative words (depressed content adjectives), than control subjects in a self-referent encoding task [102]. As suggested by the authors, these results raise the possibility that reduced positive self-image might represent a vulnerability factor for future depressive episodes. Ramel and colleagues [103] similarly found that remitted depressed participants, but not controls, recalled significantly fewer self-referent positive words following a sad mood induction compared to before the mood induction. The findings in remitted depressed individuals across both of these studies mirror the reduced endorsement and recall of self-referent positive words seen in currently depressed individuals

[3] It is of note that Heerey, Bell-Warren and Gold's [94] findings of unimpaired reward sensitivity in schizophrenia are limited by the fact that patients were medicated during testing and smoking status was not taken into account; the latter is a particularly relevant consideration since there are high rates of smoking in schizophrenia [95], and nicotine has been found to increase response bias in the same task used by Heerey and colleagues [96].

[105]. In another experiment involving a negative mood induction, remitted subjects with a history of MDD were less likely than controls to associate themselves with happiness on an Implicit Association Test (IAT), irrespective of current mood state [104]. Along these lines, Joormann and Gotlib [43] reported that both currently and formerly depressed individuals failed to demonstrate a positive attentional bias towards happy faces that was characteristic of control participants during a dot-probe task. Interestingly, using a similar task combined with a sad mood induction, these researchers also found that unaffected children of depressed mothers failed to demonstrate an attentional bias towards happy faces [106]. Collectively, these findings demonstrate the existence or persistence of anhedonic symptoms (e.g., lower endorsement and recall of self-referential positive traits, and blunted attentional positivity biases) in fully remitted subjects and in other individuals at increased risk for depression. Accordingly, such results indicate that reduced positive self-image and blunted attentional biases toward incentive stimuli might increase vulnerability to depression and be state-independent.

Additional evidence of reduced reactivity to positive cues that continues beyond an active depressive episode comes from psychophysiological studies. For example, in an event-related potential (ERP) study by Nandrino and colleagues [107], first-episode depressed patients exhibited a reduction in P300 amplitude to positive words that was still present after treatment. Since the P300 is thought to index post-identification processes of discriminating and categorizing stimuli [108], these results may reflect state-independent hedonic processing deficits—specifically, impairment in the categorization of positive stimuli. In another electroencephalography (EEG) study, remitted depressed patients demonstrated reduced left-sided anterior resting EEG activity [109], mirroring patterns described in currently depressed patients [110]. Given that left prefrontal cortex activity has been associated with approach-related behaviors and appetitive goals [111,112], the findings of left-sided anterior hypoactivation across depressed and remitted individuals may reflect trait-like anhedonia.

However, it is important to note that not all studies lend credence to the notion of state-independence of anhedonic symptoms. For example, in the aforementioned study by Blanchard and colleagues [88], self-reported social anhedonia scores of depressed patients declined over a one-year follow-up in recovered patients, which suggests state dependence of social anhedonia in depression. A similar conclusion was drawn in a more recent study where individuals with current depression, but not those with remitted depression, reported diminished emotional responsiveness (i.e., lower self-reported ratings of happiness and enthusiasm) to anticipated reward, as compared to never depressed individuals [113]. One factor potentially contributing to both sets of results could be that experimental paradigms may need to include negative mood inductions to prime participants in order to see biased processing in a remitted depressed sample [114]. In a study that used such mood induction methods, results were mixed with respect to state-independence of anhedonic symptoms: both currently and remitted depressed youth recalled a significantly smaller amount of positive words than controls following a sad mood induction, but only currently depressed subjects exhibited a reduced endorsement of positive traits as well [115]. Accordingly, although there is some support for the temporal stability of anhedonia, further studies are necessary to determine whether specific components of anhedonia might persist after remission and be independent of illness status.

Familial Association of Anhedonia as a Depressive Endophenotype

In order to assess whether anhedonia fulfills the criterion of familial association, we turn to studies that have examined anhedonic symptoms in unaffected (e.g., no current or past diagnosis of mental disorder) first-degree relatives of patients with depression as compared to the general population. For example, Le Masurier and colleagues [116] reported that unaffected first-degree relatives of individuals with MDD took significantly longer to make self-referential categorizations of positive personality characteristics than age-matched controls; both groups were faster, however, to categorize positive than negative traits, suggesting a relatively reduced positive bias in the former group. Although a depressed comparison group was not included in this study, depressed patients were slower to identify positive words on a go/no-go task in an earlier study [117], indicating similarities in anhedonia-related information processing between individuals with depression and their unaffected relatives. A reduced positive bias has also been noted in never-disordered daughters of mothers with a history of recurrent MDD as compared to never-disordered daughters of mothers with no history of Axis I psychopathology [106]. In

this study, a dot-probe task with emotional faces was administered to participants after a negative mood induction. The daughters of mothers with a history of depression failed to show the selective attention to positive facial expressions exhibited by the control daughters; rather, unlike controls, they displayed selective attention to negative facial expressions. Of note, the lack of positivity bias seen in the daughters of mothers with a history of depression was also found in both currently and formerly depressed patients by this same group of researchers using a similar dot-probe paradigm [43].

The mother-daughter findings by Joormann and colleagues complement a previous report on another pediatric sample with depressed versus non-depressed mothers [118]. In this earlier study, high-risk children endorsed significantly fewer positive words and recalled a higher proportion of endorsed negative words than low-risk children in a self-referent encoding task, but only following a negative mood induction. However, a notable strength of the more recent study by Joormann and colleagues [106] is that they obtained diagnostic information on the children and thus could rule out the possibility that current or past mental illness in their high-risk sample might have contributed to their results. In this way, assessment of individuals who have never expressed mental illness enables a more unambiguous deduction that observed findings may represent a vulnerability to depression rather than a consequence of psychopathology.

In a further study that took into account history of depression, Farmer and colleagues [119] utilized a sib-pair design and the Temperament and Character Inventory (TCI) to examine the familiality of various personality dimensions including reward dependence—a temperament trait reflecting domains such as social attachment, dependence on the approval of others, and sentimentality [120]. Of note, MDD patients tend to show reduced levels of reward dependence as compared to control individuals [121]. Interestingly, Farmer and colleagues found that never-depressed siblings of depressed probands had higher reward dependence scores than never-depressed siblings of healthy control probands. However, siblings of depressed probands with a history of depression themselves had lower reward dependence scores than either of these groups, indicating the possibility that high reward dependence may act as a protective factor against developing depression.

Finally, in the first fMRI study to compare asymptomatic juvenile offspring of parents with MDD to those of healthy parents, Monk and colleagues [122] found that high-risk offspring showed reduced nucleus accumbens activation when passively viewing happy faces (and increased nucleus accumbens activation when passively viewing fearful faces) relative to low-risk offspring. The neural responsiveness to positive stimuli found in the high-risk offspring parallels findings of reduced activation in the nucleus accumbens in response to happy faces [123] or reward feedback [60] in adults with MDD. Overall, empirical evidence that anhedonia-related emotional processing biases and reduced positivity biases occur more frequently in unaffected relatives of ill individuals than the general population lends support for the familial association of anhedonia as a depressive endophenotype, and suggests it may represent a risk factor for depression.

Heritability of Anhedonia as a Depressive Endophenotype

Relatively few studies have examined the heritability of anhedonia (i.e., whether a proportion of its variance can be attributable to genetic variance), and some have investigated this topic in psychiatrically healthy samples or within the context of disorders other than MDD. In addition, the majority of such research has focused on self-report measures and only one study to date has used an objective behavioral measure of hedonic capacity, along with self-report measures, to investigate potential genetic contributions [124]. In this study, the same probabilistic reward task previously mentioned was administered to a small sample (n = 70; 35 twin pairs) of monozygotic (MZ) and dizygotic (DZ) twin pairs who reported no current or past psychiatric disorder. Model fitting revealed that 46% of the variance in hedonic capacity was accounted for by additive genetic factors, while 54% was accounted for by individual-specific environmental factors [124].

These results extend previous twin studies that have relied solely on self-report measures to assess the heritability of anhedonia. The earliest evidence of genetic influences on hedonic capacity comes from a study in a sample of college undergraduates by Dworkin and Saczynski [125], in which the intraclass correlation coefficients for a scale of hedonic capacity (items selected from the Minnesota Multiphasic Personality Inventory and the California Psychological Inventory) were significantly higher for

MZ twin pairs (.63) than DZ twin pairs (.41). Subsequent twin studies similarly reported intraclass correlation coefficients that were significantly higher for MZ than DZ twin pairs (e.g., [126,127]), lending support for the notion that genetic factors contribute to the phenotypic expression of anhedonia. In one of these studies, at least one member of each twin pair had schizophrenia, and anhedonia levels were rated in a semistructured clinical interview [126]; the other study used an anhedonic subscale of a "schizotypy" Self-Report Questionnaire with a population-based twin registry [127]. Of note, an important limitation of these early studies is that they did not include model fitting on the variance-covariance matrices for MZ and DZ twin pairs to estimate the specific contributions of additive genetic, dominant genetic, common environment, and non-shared environment/measurement error.

In subsequent twin studies where investigators did perform such model fitting, heritability estimates of hedonic capacity range from 22% to 67% [128,129,130,131,132,133,134,135]. This broad range of heritability estimates might be partially accounted for by the fact that various self-report measures might be assessing different facets of hedonic capacity or might have different psychometric characteristics (e.g., validity, reliability). Further research, including the evaluation of anhedonia across monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for depression, and the utilization of objective measures of anhedonia in these samples, is necessary to obtain a more explicit understanding of heritability estimates for anhedonia. Nevertheless, results from twin studies to date suggest that genetic variance accounts for a considerable proportion of the variance in anhedonia. Importantly, given that heritability of MDD is estimated to be between 31% and 42% [136], heritability estimates for anhedonia may be even higher than those for MDD, which underscores a potential advantage of using an endophenotypic approach.

Cosegregation of Anhedonia as a Depressive Endophenotype

There is a notable lack of studies investigating anhedonia across affected and unaffected relatives of depressed individuals. However, in the aforementioned sib-pair study conducted by Farmer and colleagues [119], siblings of depressed individuals who had a history of depression themselves had significantly lower reward dependence scores compared with never-depressed siblings of depressed individuals. Results from this study support the notion that within families of depressed individuals, anhedonia may occur more frequently in family members who are affected with the illness than in family members who are unaffected by the illness. Nevertheless, additional studies are clearly needed to further investigate the cosegregation of anhedonia.

CURRENT DIRECTIONS IN OBJECTIVE LABORATORY MEASUREMENTS OF ANHEDONIA

Given that self-report measures of anhedonic symptoms are inherently subjective and vulnerable to reporting biases, the development of more objective measures of anhedonia is well warranted. As a first step in this direction, our laboratory recently developed a probabilistic reward task to provide an objective measure of reward responsiveness [12]. The task, which was adapted from a prior paradigm described by Tripp and Alsop [137], involves a differential reinforcement schedule to obtain an objective measurement of an individual's ability to adapt behavior as a function of reinforcement history [12]. In this task, participants are briefly presented with one of two stimuli and asked to determine which stimulus appeared on a computer screen. Importantly, the two stimuli are physically very similar and presented very briefly (100 ms), making the differentiation quite difficult. Critically, unbeknownst to the participants, correct identification of one stimulus is followed by reward feedback (e.g., "Correct!! You won 5 cents!") three times more frequently than correct identification of the other stimulus. Under this experimental setting, healthy subjects quickly develop a robust response bias toward the more frequently rewarded stimulus [12,137,138]. Notably, the probabilistic nature of the task prevents participants from being able

to use the outcome of a single trial to deduce which stimulus is more profitable; rather, participants must integrate reinforcement history over time to perform most successfully on the task.

Importantly, based on results from initial studies, the psychometric properties of this task appear promising. For example, in two separate studies, the test-retest reliability for response bias over approximately 38 days was .56-.57 [12,139]. Moreover, as mentioned above, the heritability of reward responsiveness in a twin study using this task was estimated to be approximately 48% [124]. Furthermore, studies utilizing the probabilistic reward task with participants presumed to be impaired in reinforcement learning—such as individuals with affective disorders [7,140]—provide evidence of construct validity. A reduced response bias towards the more frequently rewarded stimulus has been described in unmedicated patients with MDD [13], medicated euthymic patients with bipolar disorder [141], and students with elevated depressive symptoms [12]. In the study with unmedicated MDD patients, trial-by-trial probability analyses indicated that this group had a reduced response bias toward the more frequently rewarded stimulus in the absence of immediate reward, but was responsive to single rewards. Moreover, as noted earlier, this dysfunction was correlated with anhedonic symptoms ($r = .52$, $p < .05$) and not with symptoms of anxiety or general distress.

Importantly, performance on the probabilistic reward task is also associated with activation of reward-related neural regions, in particular the dACC and caudate. Participants who fail to develop a response bias towards the more frequently rewarded stimulus have been found to show significantly lower activation in caudate and dACC regions in response to reward feedback than those who develop such a response bias [139]. Furthermore, activation of dACC regions specifically correlates with this learning ability ($r = .40$, $p < .03$). These findings are in line with previous studies that have demonstrated a link between dACC region activation and the ability to integrate reinforcement history over time (e.g., [66] as well as studies implicating the caudate in learning action-reward contingencies (e.g., [76]).

Finally, given that DA is believed to play a key role in reward-related learning [142], two studies have been conducted to examine whether pharmacological manipulations affecting DA either indirectly [96] or directly [143] would influence development of response bias in the probabilistic reward task. In the first case, healthy nonsmokers were administered a single dose of transdermal nicotine (7-14mg) in a randomized, double-blind, placebo-controlled crossover design; nicotine was found to increase response bias towards the more frequently rewarded stimulus [96]. Further studies will be needed to determine whether the mechanisms underlying these findings are similar to those emerging from animal studies, in which nicotine activates the presynaptic nicotinic receptors on mesocorticolimbic DA neurons to increase appetitive responding [144]. In the second case, healthy participants who received a single 0.5 mg dose of the D2/3 agonist pramipexole two hours prior to completing the probabilistic reward task demonstrated impaired reinforcement learning as compared to those who received placebo [143]. Here again, future studies are necessary to explore whether the mechanisms underlying these findings emulate related animal data [145] and reflect pramipexole-induced activation of DA autoreceptors and corresponding reductions in phasic DA bursts. In spite of the need for studies directly assessing DA signaling in humans, it is important to emphasize that impaired reinforcement learning in the pramipexole group could be simulated by decreased reward-related presynaptic DA signaling in a neural network model of striato-cortical function in subsequent analyses of this dataset [146]. In sum, evidence supports the psychometric properties of the probabilistic reward task, and accordingly, its potential usefulness to objectively measure specific reward-related dysfunctions.

SUMMARY AND FUTURE DIRECTIONS

The overarching goal of this chapter was to review human literature pointing to the potential utility of applying an endophenotypic approach to depression research. In doing so, we specifically focused on anhedonia, which is emerging as one of the most promising endophenotypes of depression (e.g., [7,12,13]). In line with this conceptualization, we discussed empirical evidence suggesting that anhedonia meets the criteria of biological and clinical plausibility, familial association, and heritability; mixed or limited findings exist for state-independence and specificity, and few studies have addressed cosegregation.

The research presented in this chapter supports a strong relationship between anhedonia and depression from both clinical and biological viewpoints. In particular, individuals with depression are

characterized by reduced affective and behavioral reactivity to positive stimuli (highlighting possible encoding dysfunctions) and impaired abilities to use reinforcement history to modify behavior, which might be linked to difficulties in estimating the occurrence of past positive events and predicting future positive events. Although conclusive statements would be premature, it is likely that such behavioral impairments are linked to dysfunctions in reward-related neural regions, including the dorsal and ventral striatum, the ACC and the OFC. Importantly, anhedonic symptoms and behavior have predictive value in determining depression onset, course, time to recovery, and likelihood of relapse. As a corpus, these findings underscore the role of anhedonia in the emergence, maintenance, and exacerbation of depression.

Although anhedonia is not exclusive to depression, it is specific to depression over anxiety, which is an important consideration given the high rates of comorbidity between these disorders [97]. Moreover, there is evidence to suggest that symptoms of anhedonia may be relatively stable over time (e.g., outside of depressive episodes), and are present to a greater degree in the unaffected relatives of depressed individuals than the general population, which lends credence to the notion that anhedonia may be a vulnerability factor in the development of depression. Finally, given that heritability estimates for anhedonia might exceed those for depression, it is plausible that investigations focused on anhedonia may enable us to get closer to pinpointing some of the genes that contribute to an increased risk for depression. Recent findings that specific DA-coding polymorphisms affect activation within the brain reward pathway (e.g., [147,148, 149]) highlight promising targets for future investigations of the genetic underpinnings of anhedonia.

There are many additional avenues for future research that promise to provide a more comprehensive understanding of anhedonia as a depressive endophenotype. First, additional neuroimaging studies are needed to build upon prior findings of associations between various aspects of reward processing (e.g., reward anticipation vs. consumption) and dysfunctions of specific reward-related neural circuitry [58,60]. Second, in light of the well-documented link between stress and depression (e.g., [150]), and initial evidence that anhedonia may serve as a central bridge connecting them [101,151,152,153], further investigations characterizing the relationship and underlying mechanisms between stress and anhedonia are warranted. Third, in order to more fully address the endophenotypic criteria of heritability and cosegregation, there is a critical need for studies that investigate anhedonia across MZ and DZ twin pairs discordant for depression, and across affected and unaffected relatives of depressed individuals. In particular, studies assessing MZ twin pairs discordant for depression may help to clarify whether anhedonia is a vulnerability factor for the development of depression or a consequence of the disorder. Along similar lines, studies focusing on individuals at-risk for depression (e.g., children or siblings of depressed probands) before the onset of a first major depressive episode will be required to elucidate whether anhedonia and related neural dysfunctions are a risk factor for depression or an epiphenomenon of the illness. Fourth, in light of differences in the phenomenology of depression between children and adults [154], as well as gender differences in the epidemiology of depression [155], there is a critical need for research that will examine the developmental trajectory of anhedonia over the lifespan and associated gender differences.

Across all of these lines of inquiry, the use of objective measures of anhedonia (such as the probabilistic reward task described in this chapter), and mathematical modeling of reward prediction errors (e.g., [71,73]), may be beneficial to precisely identify the extent and nature of anhedonic deficits. Finally, in the spirit of moving towards personalized treatment in psychopathology [156], it will be important to determine whether individuals characterized by specific behavioral or neural anhedonic phenotypes might be particularly responsive to cognitive and/or behavioral treatments centered on positive reinforcement (e.g., [157,158]), or pharmacological interventions targeting dopaminergic dysfunctions (e.g. [159]). Ultimately, it is hoped that taking an endophenotypic approach will help us to elucidate the etiological pathways underlying depression, leading to improvements in the validity of our classification system and, more importantly, to increased effectiveness of treatment and prevention methods.

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