Reviews and perspectives

Reward processing in anorexia nervosa

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A B S T R A C T

Individuals with anorexia nervosa (AN) demonstrate a relentless engagement in behaviors aimed to reduce their weight, which leads to severe underweight status, and occasionally death. Neurobiological abnormalities, as a consequence of starvation are controversial: evidence, however, demonstrates abnormalities in the reward system of patients, and recovered individuals. Despite this, a unifying explanation for reward abnormalities observed in AN and their relevance to symptoms of the illness, remains incompletely understood. Theories explaining reward dysfunction have conventionally focused on anhedonia, describing that patients have an impaired ability to experience reward or pleasure. We review taste reward literature and propose that patients’ reduced responses to conventional taste-reward tasks may reflect a fear of weight gain associated with the caloric nature of the tasks, rather than an impaired ability to experience reward. Consistent with this, we propose that patients are capable of ‘liking’ hedonic taste stimuli (e.g., identifying them), however, they do not ‘want’ or feel motivated for the stimuli in the same way that healthy controls report. Recent brain imaging data on more complex reward processing tasks provide insights into fronto-striatal neural circuit dysfunction related to altered reward processing in AN that challenges the relevance of anhedonia in explaining reward dysfunction in AN. In this way, altered activity of the anterior cingulate cortex and striatum could explain patients’ pathological engagement in behaviors they consider rewarding (e.g., self-starvation) that are otherwise aversive or punishing, to those without the eating disorder. Such evidence for altered patterns of brain activity associated with reward processing tasks in patients and recovered individuals may provide important information about mechanisms underlying symptoms of AN, their future investigation, and the development of treatment approaches.

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1. Introduction

Anorexia nervosa (AN) is diagnosed in females in up to 95% of cases (DSM-IV-TR, 2000) with a prevalence of 0.5% (Hudson, Hiripi, Pope, & Kessler, 2007). AN is characterized behaviorally by self-starvation and excessive exercise in up to 80% of patients (Dalle Grave, Calugi, & Marchesini, 2008; Davis, 1997) and has the highest mortality of any psychiatric illness (Sullivan, 1995). There are two types of eating-related behaviors common to AN. Patients with restricting type anorexia primarily lose weight by dieting without binge eating or purging whereas, binge-eating/purging type patients also restrict their food intake to reduce their weight but also periodically engage in binge eating and/or purging as do individuals with bulimia nervosa (Kaye, Fudge, & Paulus, 2009). Although it is well accepted that some patients can experience both syndromes, consistent with shared risk and liability factors (Lilenfeld et al., 1998; Walters & Kendler, 1995), the current review focuses on restricting type AN.

Abnormalities in several neural systems have been identified in patients with AN including: serotonin, dopamine, hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes, appetite-related neuropeptides and other neurochemical systems (Barbato, Fichele, Senatori, Casiello, & Muscettola, 2006; Kaye, 2008; Monteleone et al., 2001; Sodersten, Nergardh, Bergh, Zandian, & Scheurink, 2008). Consistent with these observations, there are many frameworks that have been proposed to explain AN. Examples of these frameworks include: evolutionary explanations that excessive exercise observed in the illness may be ‘displaced food-seeking behavior’ akin to times of food shortage (Sodersten et al., 2008). Disturbances in appetite-related hypothalamic pathways (Kaye, Berrettini, Gwirtsman, & George, 1990; Sodersten et al., 2008) which may contribute to disordered behavior toward food (Sodersten et al., 2008) which tend to be restored following recovery (Sodersten et al., 2008). In addition, serotonin concentrations are hypothesized to inhibit appetite (Simansky et al., 2004) and may lead to anxiety-avoidance behavior toward food (Kaye et al., 2009). Consistent with this, starvation induced reductions in extracellular serotonin concentrations have been proposed to decrease dysphoric symptoms (Kaye et al., 2009). Variations of the anhedonia hypothesis contend that patients engage in disordered behaviors to alleviate a dysphoric and anhedonic mood state (Davis & Woodside, 2002; Kaye, 2008; Kaye et al., 2009) with multiple neurobiological mechanisms (including dopamine (Frank et al., 2005) and serotonin (Kaye et al., 2009)) proposed in these hypotheses.

This review focuses on the framework proposing that behaviors linked to AN (self-starvation and excessive exercise) upregulate the stress hypothalamic-pituitary-adrenal (HPA) axis, the consequence of which is increased dopamine secretion from the ventral striatal terminals of mesolimbic neurons in the brain (Bergh & Sodersten, 1996). The experience of reward associated with these behaviors is proposed to reinforce the illness, plunging patients into a severely emaciated state. Involvement of the HPA axis and dopamine systems have been proposed in the onset of AN (Bergh & Sodersten, 1996). Whether a sensitive HPA axis or dopamine system, or their interaction renders some patients more vulnerable to develop behaviors that ultimately become pathological is not known. The majority of research tends to show that elevated concentrations of cortisol (Boyar et al., 1977; Casper, Chatterton, & Davis, 1979; Gerner & Wilkins, 1983; Gold et al., 1986; Misra et al., 2004; Monteleone et al., 2011) normalize following weight-recovery (Gold et al., 1986; Gwirtsman et al., 1989; Walsh et al., 1981). Nevertheless, supporting a contribution of stress and dopamine systems to the illness the majority of patients with AN show abnormally elevated HPA axis activity (Boyar et al., 1977; Hotta et al., 1986; Licinio, Wong, & Gold, 1996; Monteleone et al., 2001) in addition to which abnormalities in the dopamine system and relevant brain regions linked to reward processing have been revealed (Barbato et al., 2006; Fladung et al., 2010; Frank et al., 2005). The majority of research suggests that dopamine is abnormal in patients with AN as assessed via eye-blink rate (Barbato et al., 2006) as well as evidence for D2 receptor linked genetic polymorphisms (Bergen et al., 2005). In addition, in recovered individuals, abnormalities in the dopamine system have been revealed via reduced D2 and D3 receptor binding in the reward linked ventral striatum (Frank et al., 2005) (Kaye, Frank, & McConaha, 1999). Despite this, research has not yet directly investigated the dopamine system during reward processing tasks in patients with AN, or recovered individuals.

Evidence that dopamine abnormalities are present in the recovered state suggests that changes in reward linked system may be a trait marker for AN. Indeed, changes in reward processing generally have recently been proposed to be a neural biomarker for AN (Cowdry, Park, Harmer, & McCabe, 2011). There are however, few frameworks in which to explain the clinical implications of reward-linked abnormalities that have been revealed in the literature. Recently, the concept of stress induced reward linked to illness behaviors (Bergh & Sodersten, 1996) has been developed to provide an explanation for why patients are able to engage in these behaviors despite them being highly pathological. It has been termed reward contamination theory (Keating, 2010). Reward contamination theory proposes to explain the observation that many patients ultimately experience otherwise rewarding stimuli as punishing, for example food, and vice versa otherwise punishing (or aversive) stimuli as rewarding, for example self-starvation, excessive exercise and emaciated body image (Keating, 2011). Reward contamination theory suggests that while patients’ pathological behaviors are in the first instance rewarding, when relentlessly engaged in, they become reinforced in a manner that becomes pathological (Keating, 2010). Patients, however, may not recognize that they are contaminating aspects of reward with punishment, due to overlapping neurocircuits that process reward and punishment (e.g., dopamine), which may facilitate neural and behavioral reinforcement, thus impairing patients’ ability to regulate their behaviors (Keating, 2010). The anterior cingulate cortex, within a broader fronto-striatal neurocircuit is proposed to represent a key locus for reward-contamination (Keating, 2010).

Since reward contamination theory was first published (Keating, 2010) there have been a number of neuroimaging studies undertaken and published, the results of which, we hypothesize, are consistent with the principles of reward contamination theory. Although the clinical literature base of dopamine-related investigations in patients with AN is relatively few, this system may represent a candidate substrate for dysfunctional reward processing in AN. Theories regarding mechanisms that underlie the expression of AN symptoms, which include reward contamination theory, could have important implications for the development of novel interventions. This review systematically assesses reward processing in AN. We include studies involving food-reward and non-food reward tasks, as well as recent advances involving neuroimaging. We discuss whether theories including anhedonia, a fear of weight gain, or reward contamination (reward conflict) comprehensively account for patients’ responses to reward processing tasks. Future directions for research are considered consistent with elucidating mechanisms underlying symptoms of AN. Understanding such mechanisms may provide insight for the development of novel therapies.

2. Taste-reward processing

Rewards are associated with a subjective feeling of pleasure (Wise, 2004) or hedonism. Anhedonia is the inability to experience pleasure or reward (Wise, Spindler, deWit, & Gerberg,
Anhedonia is an explanatory model for reward-linked abnormalities reported in AN, suggesting that patients have an impaired ability to experience pleasure or reward. Observation (Kaye, 2008) and empirical evidence (Davis & Woodside, 2002) show that some patients with AN experience greater anhedonia (Davis & Woodside, 2002; Kaye, 2008) than other eating disorder patients and healthy controls (HCs). Indeed, patients’ engagement in illness behaviors is proposed to alleviate an anhedonic and dysphoric mood state (Davis & Woodside, 2002; Kaye, 2008). The Physical Anhedonia Scale (PAS) investigates the degree to which AN patients are rewarded by physical sensations (touching, feeling, movement, eating, smell, and sound (Chapman, Chapman, & Raulin, 1976)). In early research on anhedonia in AN, results from more than 180 patients (Davis & Woodside, 2002) revealed that compared to other eating disorders, patients with AN were highly anhedonic which has similarly been demonstrated in research involving eating disorder patients and HCs (Deborde et al., 2006). Although not a diagnostic feature of the illness, consistent with these findings, anhedonia is considered a common comorbidity (Kaye et al., 2009) and a more prevalent characteristic of eating disorder patients with AN (Davis & Woodside, 2002). Extending our understanding of hedonic processing in AN, responses to taste-reward tasks have been investigated.

2.1. Taste-reward tasks: what patients ‘want’ and ‘like’

Taste is one of the most commonly used stimuli to assess hedonics generally, including in AN. Berridge and colleagues (Berridge, 2009; Robinson & Berridge, 1993) have developed a framework for assessing response to taste-reward tasks. According to this framework, reward can be dissociated into ‘liking’ and ‘wanting’ where fulfilling both aspects is necessary for the full experience of reward, and fulfilling only one aspect is akin to ‘partial reward’ (Berridge, 2009). Taste reactivity testing has been relied upon as the measure of ‘liking’ (applicable only to food (Wise, 2004)) and on drug desensitization as identifying the mechanism of ‘wanting’ (Robinson & Berridge, 1993). In the taste reward framework, ‘liking’ is considered a hedonic reaction to the pleasure of a reward and ‘wanting’ on the other hand, is less intrinsic and is not pleasure, even though it is a component of reward (Berridge, 2009). Wanting is considered incentive salience (Berridge, 2009; Robinson & Berridge, 1993) which is attributed to reward, and their predictive cues. The specific cues then become potent triggers for ‘wanting.’ In this way ‘wanting’ is not ‘liking’ because ‘wanting without liking is like a sham or partial reward without sensory pleasure’ (Berridge, 2009). Conversely, ‘liking’ without ‘wanting’ is simply a triggered affective state of pleasure in the absence of an incentive target (Berridge, 2009). Incentive salience attribution makes a specific stimulus or action (behavior), the object of a desire that tags a behavior as the rewarded response, and allows normal behavior to spur the desire for more (Berridge, 2009; Robinson & Berridge, 1993). Where the particular behavior becomes pathological, as is the case for AN, tagging of incentive salience to a behavior (e.g., self-starvation or excessive exercise) may permit a desire for more of the same behaviors to be spurred.

Applying Berridge and colleagues framework, the outcomes of investigations of taste reward in AN reveal differences in patients’ relative to HCs’ ‘wants’ despite evidence that ‘like’ (the capacity to judge/identify an hedonic stimuli) remains intact, and therefore independent of a diagnosis of AN. For example, evidence supports that taste perception (or ‘liking’) may be independent of diagnostic category (Drewnowski, Halmi, Pierce, Gibbs, & Smith, 1987). Sensory estimates of sweetness and fat content (of 20 mixtures of milk, cream and sugar) (Drewnowski et al., 1987), between patients and HCs did not differ. Preference for (or ‘wanting’) sugar relative to fat differed; AN patients (AN restricting subtype, ANR, and AN bulimic subtype, ANB) preferred sweet stimuli but the opposite was the case for high-fat stimuli, whereas HCs demonstrated increased preference for high-fat stimuli. Following weight gain, preference profiles remained unchanged, suggesting that taste responsiveness may also be independent of acute changes in weight (Drewnowski et al., 1987). Similarly, patients with AN have been reported to prefer less (or ‘want’ less) the taste of fattening foods more than HCs, where perceptions and preferences for sweetness did not differ (Simon, Bellisse, Monneuse, Samuel-Lajeunesse, & Drewnowski, 1993). Patients with eating disorders (including AN) have also been reported to prefer (‘want’) high-calorie foods significantly less than low-calorie foods (Stoner, Fedoroff, Andersen, & Rolls, 1996) and compared to HCs, reported lower preference ratings toward pictures of high energy foods, which remained following 8 weeks treatment (although high palatability ratings for low caloric foods was reduced following treatment (Bossert et al., 1991)). Others have not revealed differences between eating disorder groups’ (ANR, ANB, BN) ability to provide intensity (sweetness) ratings of 20 dairy solutions with 5 varying levels of fat and of sucrose, before and after treatment (Stoner et al., 1996; Sunday & Halmi, 1990). Patients with AN did give significantly lower sweetness ratings for sucrose solutions, and for most levels of fat relative to pretreatment testing (Sunday & Halmi, 1990).

Indeed, evidence from these taste-reward studies is compelling: a diagnosis of AN does not change hedonic taste responses (Drewnowski et al., 1987) or the capacity to respond to the ‘likeable’ component of the reward. This pattern of responding to taste-reward stimuli may suggest, consistent with dissociable aspects of reward that patients are able to judge the ‘likability’ of a substance, but unlike healthy controls, it follows that patients do not necessarily ‘want’ it. Findings of reduced preferences or ‘wants’ toward higher fat stimuli are consistent with reports that patients with AN experience aversion to the ingestion of normally palatable foods (Keating, 2010; Wagner et al., 2008) including high fat and sweet foods (Crisp et al., 2006; Kaye, 2008). Although the stimuli involved in taste reward tasks (sucrose) is often highly caloric (relatively), and patients have been reported to prefer or ‘want’ sweet as opposed to fattening stimuli (Drewnowski et al., 1987), stimuli-responses may be contingent upon the relative calorice-content of stimuli being compared in a given context.

A primary neural deficit in taste has also been investigated in AN (Wagner et al., 2008). Comparing the neural response to sucrose and water and correlating these with subjective pleasantness ratings (‘wanting’ because the appraisals were based on a Likert scale), results from recovered individuals revealed significantly lower neural activation of the insula which is linked to taste processing and sensory integration, including the primary cortical taste region, striatum (dorsal striatum and middle caudate) to both sucrose and water, relative to HCs (Wagner et al., 2008). Reduced activation was also seen in regions related to executive control; the anterior cingulate cortex (ACC) and areas of the putamen including the dorsal and ventral subdivisions, the ventral subdivision within proximity of the anhedonic-linked nucleus accumbens. Both recovered individuals and HCs responses to hedonic (sucrose) and neutral (water) stimuli were not distinguished at a neural level. Nevertheless, recovered individuals showed reduced brain activation to the stimuli, which may indicate reduced sensitivity to taste stimuli generally, not necessarily specific to reward processing.

A reduced sensitivity to rewarding stimuli would be notionally consistent with the anhedonic hypothesis (Davis & Woodside, 2002; Kaye, 2008) however, further research using greater variation in the concentration/nature of the hedonic stimuli such as high-caloric sugar and fat, and including individuals when unwell, are required to confirm this. Subjective pleasantness ratings (‘wanting’) linked to the sucrose condition correlated with activity in the insula, putamen (right and left ventral and dorsal subdivisions
– consistent with the role these regions play in reward processing) and ACC (Wagner et al., 2008), in HCs. The absence of a relationship between subjective ratings and brain activity in recovered individuals may reflect that the recovered individuals experienced reduced subjective pleasantness ratings or ‘wanted’ it less.

In general, similar ‘like’ responses suggest that AN and HCs alike can identify a hedonic stimuli, however, differences in ‘wants’ suggests that patients do not enjoy hedonic stimuli in the same way HCs do. This ‘partial reward’ may be explained by anhedonia if indeed there is an abnormality in the way in which a substance judged ‘likeable’ is translated into a pleasurable sensory experience (perhaps via the insula), leading the individual to not ‘want’ it, or want it less. Patients’ reduced preferences (‘wanting’) of otherwise rewarding stimuli, requires further analysis. An aversion toward palatable and high fat or sweet foods (Keating, 2010; Wagner et al., 2008) is logically consistent with a fear of weight gain. Specifically, we propose that reduced preferences/wants of otherwise rewarding taste stimuli reflects more complex, illness specific, cognitive processing linked to the caloric nature of the stimuli, rather than anhedonia, or potential taste related disturbances.

There are several interpretations of the outcomes of taste-related investigations in AN, including that differences between patients and HCs responses to such tasks reflect a disturbance in appetite (Kaye et al., 2009) and a disturbance in reward processing, linked to dysfunctional attribution of salience toward taste stimuli (Cowdrey et al., 2011). Logically consistent with evidence that patients dislike high fat foods (Drewnowski, Pierce, & Halmi, 1988; Fernstrom, Weitzin, Neuberger, Srinivasagam, & Kaye, 1994) and find reward-linked stimuli including sucrose to be less preferable than do HCs (Sunday & Halmi, 1990), appetite-related disturbances have been proposed (Kaye et al., 2009). Although findings support a relationship between the illness and alterations in appetite-related neuropeptides including illness linked elevated neuroptide Y (Kaye et al., 1990) and leptin levels (Eckert et al., 1998), these disturbances tend to be restored following long-term weight restoration (Eckert et al., 1998; Kaye et al., 1990; Sodersten et al., 2008). Nevertheless, patients’ food preferences (avoidance of high fat foods), reportedly remain following recovery (Kaye et al., 2009).

2.2. Is a ‘Fear’ of weight gain (linked to caloric stimuli) driving patients’ altered responses to simple taste-reward tasks?

It remains incompletely understood what drives altered ‘wants’ expressed by patients, relative to HCs, on taste-reward tasks. We propose, consistent with empirical evidence (from Eiber, Berlin, de Brettes, Foulon, & Guerli, 2002) that altered ‘wants’ may be more comprehensively explained by a ‘fear of weight gain’. That is, a fear of weight gain associated with the caloric nature of the taste-stimuli may drive altered ‘wants’ (reduced preferences) toward otherwise ‘likable’ (e.g., sucrose) stimuli. This proposal has been illustrated by a reward processing sucrose experiment demonstrating that AN patients experienced less reward when sweet solutions were swallowed, relative to when they were spat out (Eiber et al., 2002). This finding was suggested to reflect an excessive fear of gaining weight rather than a diminished ability to experience pleasure, because less reward was experienced when the sucrose had to be swallowed (Eiber et al., 2002), perhaps reflecting aversion to the caloric intake. In this way, calories associated with the rewarding substance may influence the degree to which patients ‘want’ or feel incentivized/motivated by the stimulus. It may then be expected that recovered individuals’ responses to taste-reward stimuli may reflect HCs, with similar responses to ‘liking’ but also restored ‘wanting’ of taste reward, assuming a fear of weight gain has attenuated in the recovered state.

The scope of conventional taste-reward investigations has tended to include sucrose and diary stimuli. Whether reduced ‘wanting’ in patients relative to HCs would be observed if the hedonic task were relevant to illness-specific rewards e.g., non-conventional rewards such as a choice between water (neutral stimulus) or a hypothetical diarrhetic (potentially a positive stimulus for a patient) has not yet been investigated (Keating, 2010). Patients’ responses to such conditions may be expected to fulfill both aspects of reward (‘liking’ and ‘wanting’). Investigating responses to such stimuli may reveal that patients both ‘like’ and ‘want’ the diarrhetic thus, challenging partial reward and anhedonia as an explanation for reward linked abnormalities in AN.

3. Complex taste-reward tasks: reward is not always what it seems

More recently, research has extended our understanding of reward processing to more complex cognitive tasks, including responses to reward and aversive/conflicted conditions. For example, investigators used disorder-relevant stimuli, chocolate and moldy strawberries, during fMRI to study 15 recovered individuals relative to 16 healthy controls matched for age and body mass index. The rewarding condition was the sight and flavor of chocolate and their combination, and the aversive condition comprised the sight of moldy strawberries and an unpleasant taste (Cowdrey et al., 2011). During imaging of these conditions, researchers simultaneously recorded participants’ subjective ratings of “pleasantness,” “intensity,” and “wanting” (Cowdrey et al., 2011). Results revealed an absence of group differences in subjective ratings. Although this would appear to go against previously reviewed studies in food hedonics, the previous investigations involved patients. In recovered individuals, response to pleasant chocolate taste was associated with increased neural response in the ventral striatum, and response to the sight of chocolate was associated with activation in the occipital cortex (Cowdrey et al., 2011). Recovered individuals’ response to the taste of aversive moldy strawberries was associated with increased activation in the putamen and insula, and sight of aversive strawberries resulted in increased activation of the ACC, caudate and dorsolateral prefrontal cortex (DLPFC), relative to HCs. Different activity in reward linked regions (e.g., putamen and caudate) may be considered unexpected in the context that HCs did not show the same pattern of reward linked activity during processing of the aversive condition (e.g., moldy strawberries).

Although not the intention of the study, the reward-linked neural activity (e.g., caudate and putamen) shown in response to both the taste and sight of moldy strawberries, are consistent with reward contamination theory given it could otherwise be expected that reward processing regions (caudate and putamen) would not be recruited for processing of the aversive stimuli, as was the case for the HCs. These results were suggested to show that individuals recovered from AN have increased neural responses to both rewarding and aversive food stimuli compared to HCs, which was suggested to reflect increased salience attribution to food stimuli in recovered individuals (Cowdrey, Harmer, Park, & McCabe, in press). We propose that a specific fronto-striatal neurocircuit comprising the ACC and striatum contributes to recovered individuals’ altered reward processing, in particular where recovered individuals exhibit reward linked activation of brain regions such as the striatum in response to stimuli that are otherwise considered aversive to HCs. These brain regions are also implicated in other neuroimaging investigations in patients during other complex reward processing tasks, which will be reviewed.

4. Beyond taste-reward processing

To more comprehensively understand reward processing in AN, we have considered the scope of patients’ abnormal experiences of reward beyond food hedonic-stimuli. In the context of reward
linked to AN, researchers have investigated reward-processing specific to stimuli that translate to symptoms of the illness. For example, patients find emaciated body images and self-starvation to be inherently reinforcing and rewarding, consistent with clinical features of the illness. Recent neuroimaging studies with AN have shown that processing of disorder-specific stimuli such as, pictures of women at different weights, processed in a self-referent manner (Fladung et al., 2010) and processing of a complex reward-aversion task (Cowdrey et al., 2011) during neuroimaging supports engagement of reward linked regions during the presentation of otherwise non-rewarding (even aversive (Cowdrey et al., 2011)) stimuli for both patients and recovered individuals. Processing of disorder non-specific stimuli such as, processing reward and loss on a gambling task (Wagner et al., 2007) (reviewed previously (Keating, 2010)) in recovered individuals has also been investigated. These investigations support an endogenous neurocircuit that contributes to abnormal reward processing and relevant symptom domains in patients and recovered individuals.

In a recent investigation by Fladung et al. (2010), activity of the ventral striatum was compared between patients and HCs in response to viewing self-referent (Fladung et al., 2010) stimuli depicting features of underweight, normal weight, and overweight variants of a canonical female body. Data from this research (Fladung et al., 2010) revealed that patients in contrast to HCs, made more positive appraisals of underweight relative to normal weight women. HCs reported more positive appraisals of normal weight women than underweight women. Despite opposing preferences, appraisals from both patients and HCs correlated with activity in the ventral striatum (Keating, 2011). Although not the original intention, these outcomes reveal important differences between the preferences of patients with AN and HCs regarding self-relevant weight appraisals. Opposing preferences correlated with activity in the same reward linked brain region.

We propose that these outcomes indirectly illustrate a conflicted or contaminated pattern of reward-processing given that it would otherwise be expected that an underweight picture may induce feelings of aversion (Keating, 2011) which is supported by evidence (from Fladung et al., 2010) that HCs gave more positive ratings of normal weight compared with underweight women. These outcomes suggest that the ventral striatum is potentially relevant in reinforcing patients’ faulty self-perceptions. In one interpretation, these findings may also be explained by reward contam-ination theory on the basis that opposing preferences were shown by patients for underweight images, and HCs to normal weight images, despite correlating with activity in the same brain region (ventral striatum).

The outcomes of Fladung et al. (2010) may also be interpreted as reflecting that the ventral striatum and the release of dopamine are easily conditioned (consistent with Willuhn et al., 2009). Indeed the findings (from Fladung et al., 2010) likely reflect a conditioning effect. Any process of behavioral reinforcement is essentially an example of conditioning. AN has been proposed to represent an illness characterized by behaviors that have become reinforced in a manner that has become pathological (Keating, 2010). That is, the development of reward-linked behaviors in the first place requires conditioning and reinforcement processes to occur. Nevertheless, it is challenging to account for how normal conditioning processes could explain the relatively small number of dieting individuals that go on to develop the illness, nor explain experimentally, the differences observed in neural engagement between AN and HC participants to stimuli that for one group is rewarding, and for the other, aversive (Fladung et al., 2010).

The results of the investigation by Fladung et al. (2010) have also been explained by starvation dependence (Zink & Weinberger, 2010). That is, because starvation is linked to reward (Bergh & Sodersten, 1996; Keating, 2010), accordingly, patients may engage in starvation to relieve an anhedonic disposition, and thus develop a dependency on this mechanism. Starvation dependency was described based on the finding (Fladung et al., 2010) that the reward-linked ventral striatum was activated and preference was shown for processing of underweight images, which is inherently linked to self-starvation. This interpretation could be explained by anhedonia, such that starvation is associated with reward hence the patient develops a dependency on starvation to alleviate their anhedonia. It is also plausible that, on face value, the images of thin women are more rewarding for patients with AN, and thus, these images activate the reward system compared to HCs. Regardless, it is not clear how this inappropriate (Zink & Weinberger, 2010) and conflicted (Keating, 2010) desire for starving oneself initially develops and in this context, it remains unknown what enables the disproportionately small number of individuals who diet, to develop full-blown symptoms of AN. The inappropriate desire has been proposed to be ultimately processed by the dopamine ventral-striatal reward system (Keating, 2010; Zink & Weinberger, 2010).

Indeed, it would seem that reward dysfunction in AN is specific to key symptoms of the illness (e.g., body image and food related stimuli) rather than other forms of reward. For example, social reward has been investigated in recovered individuals compared to HCs, where participants were asked to view happy and fearful emotional faces (Cowdrey et al., in press). All participants accurately identified the emotion and gender of stimuli presented. There were however, no group differences (in whole brain or region of interest analyses) to the contrasts of fear versus happy faces, and vice versa, including in the amygdala or fusiform gyrus (Cowdrey et al., in press), regions linked to emotion and face processing respectively. The absence of any group differences in processing emotional faces in recovered individuals and HCs reported (Cowdrey et al., in press), suggests therefore, that differences between patients, recovered individuals and HCs linked to body image (Fladung et al., 2010) and food-stimuli (Cowdrey et al., 2011), may be disorder specific.

5. Dopamine and reward processing

Neuroimaging investigations have consistently demonstrated differences in patients and recovered individuals compared to HCs in areas of the striatum and more executive regions (e.g., ACC) during reward processing. The precise neurochemistry, however, providing a substrate for the differences reported in fMRI investigations, remains unclear. Dopamine has been the most widely studied reward candidate in AN. Increased D2 and D3 receptor binding in the striatum has been revealed in recovered individuals relative to HCs during a positron emission tomography (PET) study (Frank et al., 2005) in addition to which, dopaminergic activity (as assessed via eye blink rate, a measure of dopamine function [Karson, 1983]) has been shown to be abnormally elevated in patients relative to HCs (Barbato et al., 2006). Other investigations have shown reduced concentrations of dopamine metabolites (homovanillic acid) in the CSF of recovered individuals relative to HCs (Kaye et al., 1999) in addition to a large study revealing polymorphisms of the D2 receptor in patients with AN relative to controls (Bergen et al., 2005). Taken together these findings provide compelling evidence that the dopamine system contributes to AN. The clinical significance of these findings however, requires further investigation.

Although dopamine has not been investigated in AN patients (or healthy controls) during reward processing, Berridge and colleagues’ work has investigated the role of dopamine in reward tasks in animal models, and clearly demonstrates in animals that dopamine is not involved in hedonic evaluation of taste (‘liking’) but rather, linked more to ‘wanting’ (Berridge, Venier, & Robinson, 1989). Specifically, Berridge et al. (1989) made the observation that damage of the ascending dopamine innervations of the forebrain...
has no effect on hedonic ("like") taste evaluation in experimental animals. Further, extensive analysis of neural engagement in ‘reward’, including hedonic taste responses, has put dopamine into perspective (Smith, Berridge, & Aldridge, 2011) in the context that dopamine induction has been shown to enhance only the motivation component (which is consistent with altering ‘wanting’) but did not alter the hedonic (e.g., ‘liking’) impact or learned prediction signals (Smith et al., 2011). Whether dopamine can similarly be revealed as a system functionally involved in ‘wanting’ as opposed to ‘liking’ components of taste reward (consistent with (Smith et al., 2011)) in AN, or indeed more broadly whether hedonic evaluation of reward (e.g., receipt of the reward) or merely ‘wanting’ the reward, or both, are associated with dopamine function, requires further research in patients with AN and recovered individuals.

6. Summary of reward processing in AN

In light of the literature reviewed, taste-reward tasks reveal abnormalities in the way in which patients with AN experience simple stimuli (Drewnowski et al., 1987; Simon et al., 1993; Stoner et al., 1996). Although ‘liking’ or appropriately identifying/judging a taste-reward remains intact, patients experience reduced preferences (‘wants’) to the stimuli, relative to HCs (Drewnowski et al., 1987; Simon et al., 1993; Stoner et al., 1996). Whereas anhedonia has been proposed as an explanation for reduced preferences seen in patients with AN, others have proposed that these outcomes may be driven by a fear of weight gain associated with the caloric stimuli involved in the tasks (Eiber et al., 2002), which is supported by evidence that reduced ‘preferences’ (‘wanting’) were reported by patients with AN when stimuli were swallowed relative to spat out (Eiber et al., 2002).

More complex taste-processing tasks performed during neuroimaging, including those involving a conventional reward condition, e.g., chocolate, and an aversive-reward condition, e.g., moldy strawberries (Cowdrey et al., 2011), and less conventional reward tasks, e.g., pictures of emaciated body images self-referently appraised (Fladung et al., 2010) have demonstrated differences between recovered individuals and HCs (Cowdrey et al., 2011) and patients and HCs (Fladung et al., 2010). In essence, results of these investigations reveal a pattern of responding by those with AN, and those recovered from the illness that is opposite to HCs. For example, greater activation of reward linked brain regions, i.e., ventral striatum to pictures of overweight women in AN, and conversely, greater activation of the ventral striatum to pictures of normal weight women in HCs (Fladung et al., 2010). In the study by Cowdrey et al. (2011), increased activation was shown in the ventral striatum toward pleasant taste (chocolate) and increased activation in the putamen and insula toward the aversive taste of moldy strawberries in recovered individuals compared to HCs. Different activity in reward linked regions (e.g., putamen and caudate) to the aversive condition may be considered unexpected in the context that HCs did not show the same pattern of reward linked activity during processing of the aversive stimuli; it may be that recovered AN as well as demonstrating abnormalities with reward also have difficulty attributing salience to food items. This later point is argued by Cowdrey et al. (2011). The finding that a difference exists between those recovered from the illness and HCs, supports that reward processing may provide a biomarker for the illness (Cowdrey et al., 2011).

These investigations also show that patients are able to fully experience reward in the context of disorder relevant pleasures such as, emaciated body image, both at a neural and perceptual level given preference was shown for underweight images which correlated with ventral striatal activity (Fladung et al., 2010). These observations go against an explanation of anhedonia for reward processing in AN. We propose that these outcomes of complex symptom specific processing tasks including self-referent body image processing, may be explained by reward contamination theory. Reward contamination explains that patients may ultimately experience otherwise rewarding stimuli (food) as aversive or punishing, and vice versa, aversive stimuli as rewarding (Keating, 2010) including self-perceived emaciated body image (Fladung et al., 2010) or reward linked activity of the striatum linked to moldy strawberries (Cowdrey et al., in press). Reward contamination theory explains that patients inappropriately experience reward linked to certain stimuli. In this way, it may explain important clinical observations regarding body image misperceptions and self starvation (Keating, 2011).

7. Limitations of reward contamination theory

There have not been any studies specifically designed to investigate reward contamination theory, despite clear evidence for altered reward processing, which is consistent with reward contamination as an explanation. Although the outcomes of reward processing investigations can be explained by reward contamination, it is also not yet clear from the evidence whether reward contamination begins as a result of an aversion to food, or increasing social/cognitive goals of thinness. Whether a heritable component of the dopamine system (consistent with findings that there are polymorphic abnormalities linked to the D2 receptor) renders some individuals vulnerable to processing reward associated with particular everyday behaviors such as feeding and exercising and cognitive processes associated with these behaviors, in a manner consistent with inappropriate desire linked to these behaviors, also remains unclear.

The precise mechanisms underlying abnormal processing of reward remain incompletely understood, however, brain regions engaged in AN patients and recovered individuals during the studies reviewed consistently include; the ACC, insula and striatum. Although the full complement of neurochemical, endocrine and anatomical mechanisms (including volumetrics and cytoarchitectons) potentially supporting altered reward processing is somewhat off, the underlying mechanisms contributing to, and reinforcing neural activity linked to the inappropriate desire toward certain stimuli (including self-starvation) have been hypothesized to relate to the stress and reward systems (Keating, 2010; Zink & Weinberger, 2010).

7.1. A neurocircuit for reward processing in AN

Consistent with the literature reviewed previously, we present brief evidence for a neurocircuit for reward processing in AN. Of the five neuroimaging investigations that have explicitly addressed reward processing in AN three involve acute patients and two involve recovered individuals. Stimuli used in these studies included food/taste stimuli (Brooks et al., 2011; Cowdrey et al., in press; Wagner et al., 2008), processing pictures of body images in a self-referent way (Fladung et al., 2010) and processing rewards (and losses) on a simple gambling task (Wagner et al., 2007). Although several other investigations have thoroughly researched the neural substrates of body image processing in patients compared to HCs, the outcomes of these studies have not been linked to reward processing in AN per se, they have been interpreted in the context of for example, altered interoceptive awareness (Friederich et al., 2010).

In taste-processing investigations, recovered individuals have been shown to have reduced neural activation of the insula, ventral and dorsal striatum (regions of interest in the study) to taste stimuli generally (both sucrose and water) compared to HCs (Wagner et al., 2008). Results of this investigation were suggested to reflect altered
taste processing in AN linked to differences in activity of an insular-striatal circuit (Wagner et al., 2008). Although the outcomes of this investigation did not reveal differences specific to reward and neutral stimuli, the outcomes of a more recent investigation, again in recovered individuals, revealed distinctions between recovered individuals and HCs' processing of reward, the sight and taste of chocolate, and aversive conditions, sight and taste of moldy strawberries (Cowdrey et al., 2011). Results revealed involvement of the reward linked striatum and frontal regions during processing of complex taste reward and taste-aversion (Cowdrey et al., 2011). Recovered individuals' response to pleasant chocolate taste was associated with increased neural response in the ventral striatum, and response to the sight of chocolate was associated with activation in the occipital cortex (Cowdrey et al., 2011). Recovered individuals' response to the taste of aversive moldy strawberries was associated with activation in the putamen and insula, in addition to which the sight of moldy strawberries activated the ACC and caudate (Cowdrey et al., 2011). Greater activity of the ACC and reward linked caudate during fMRI in recovered individuals, in response to the sight of a moldy strawberry, the aversive condition as reported (Cowdrey et al., 2011), further supports that a neurocircuit encompassing the ACC through to striatum may contribute to reward contamination in AN (Keating, 2010).

The ACC has been proposed as a key locus in the reward contamination process, within a broader neurocircuit including the striatum (Keating, 2010, 2011). The ACC is involved in diverse functions: decision making, conflict processing (Pochon, Riis, Sanfey, Nystrom, & Cohen, 2008), reward anticipation (Beck et al., 2006) and punishment processing (Wrase et al., 2007) in addition to being implicated in using reinforcement information to control behavior (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006) (discussed in Keating, 2010). The ACC has been established as consistently dysfunctional in a number of imaging studies in patients with AN (Kojima et al., 2005; McCormick et al., 2008; Naruo et al., 2001; Takano et al., 2001) including in patients following weight gain (Kojima et al., 2005). It is plausible that this functionally heterogeneous region, may contribute to patients' inability to engage in decision-making strategies that optimize behavioral choices (Keating, 2010), linked to processing of reward-relevant behavior and/or stimuli. Consistent with a role for the frontal regions involved in processing reward linked stimuli, more recently, Brooks et al. (2011) investigated the neural response of AN and BN patients to food stimuli, revealing that compared to HCs, AN had relative deactivation in the parietal lobe and cingulate (dorsal posterior) but greater activation in the caudate, superior temporal gyrus, right insula and supplementary motor area (Brooks et al., 2011). In response to food versus non-food images, women with AN showed greater activation in the right dorsolateral prefrontal cortex (DLPFC), cerebellum and right precuneus. Again, outcomes supporting a neurocircuit comprising the insula and fronto-striatal regions involved in processing reward–relevant stimuli in patients with AN. It was suggested that women with AN activate top-down cognitive control in response to food images (Brooks et al., 2011). Although further research including more diverse cognitive processing tasks linked to reward are required to confirm a pivotal role for the ACC in reward processing in this illness, evidence from recovered individuals (Cowdrey et al., in press; Wagner et al., 2007) suggests that the regions implicated, including the ACC and potentially the DLPFC as shown in patients (Brooks et al., 2011) may be vulnerability markers for the development of symptoms in AN. A role for the ACC, insula and striatum may also be relevant for body image disturbances in AN. In addition to taste-reward processing, body dissatisfaction has also been linked to processing by the ACC (Friederich et al., 2010). For example, patients and HCs have been imaged while comparing themselves with pictures of idealized female bodies (Friederich et al., 2010). Reward processing was not the original intention of this study (unlike other body image (Fladung et al., 2010) processing investigations involving activity of the striatum). Relative to the HCs, patients revealed greater anxiety to the self-other body shape comparison, and were less satisfied with their current body shape. Relative to HCs, patients' self-other body shape comparison was associated with less activation of the rostral ACC, and greater activity of the right insula and premotor cortex. Insula hyperactivation along with ACC hypoactivation was considered potentially critical for altered interoceptive awareness to body self-comparison and/or for altered implicit motivation to thin-idealized body images in AN (Friederich et al., 2010). These findings are also consistent with outcomes in healthy individuals, where participants were encouraged to compare their own body shape to the one in the stimuli presented (and compare their own home in terms of the control condition) to the stimuli presented. Anxiety during exposure to slim bodies correlated with established measures of shape and weight concern and brain activation in several regions including the ACC (bilateral dorsal subdivision) and PFC (left inferior lateral region) bilateral basal ganglia, left amygdala, (Friederich et al., 2007). Indeed, it has been proposed that brain networks associated with anxiety induced by self-comparison to slim images may be involved in the genesis of body dissatisfaction and hence with vulnerability to eating disorders (Friederich et al., 2010). This evidence further supports that processing of stimuli by the ACC (and other frontal regions) may ultimately contribute to abnormal experiences of body shape in patients with AN.

Regarding a neurocircuit for reward processing in AN, the ACC has been established as consistently dysfunctional in a number of imaging studies in AN (Kojima et al., 2005; Naruo et al., 2001; Takano et al., 2001) and in weight-recovered individuals (Kojima et al., 2005) including being revealed as dysfunctional during processing of body image stimuli (Friederich et al., 2010). Similarly engagement of subdivisions of the striatum have been demonstrated to differentiate patients from HCs during reward processing (Fladung et al., 2010) as well as recovered individuals from HCs (Cowdrey et al., in press; Frank et al., 2005; Wagner et al., 2007). Engagement of the insula during food/taste processing has also been demonstrated to differentiate patients and HCs (Brooks et al., 2011) and differentiated recovered individuals and HCs during the aversive condition (moldy strawberries) of a reward processing task (Cowdrey et al., 2011), although insula engagement has also been found to be independent of stimuli valence (Wagner et al., 2008). Reduced insula engagement has been found to differentiate patients from HCs during body image (versus interior home design images) processing (Friederich et al., 2010), although this was not the case when patients were asked to process images of varying weights of a canonical female body in a self-referent manner (Fladung et al., 2010). Taken together, these investigations support that the ACC, striatum and insula are relatively consistently found to be dysfunctional during reward processing in AN, and recovered individuals, and may be involved in processing information relevant to symptoms of the illness including self-starvation and body image dissatisfaction.

8. Conclusions and future directions

The outcomes of our assessment of reward processing literature in AN (and recovered individuals) in the context of competing theories for reward processing in AN, demonstrates that anhedonia is limited in its capacity to explain patients' experience of simple taste-reward tasks. The results of these conventional taste-reward tasks, when interpreted in the context of modern theories for reward processing (e.g., liking and wanting) reflect that patients and HCs similarly rate the hedonic properties of
taste-reward, however patients’ reduced preference for the same stimuli (reduced ‘wanting’) may be associated with the caloric nature of the stimuli, and thus be driven more by patients’ fear of weight gain, than an impaired ability to experience reward (anhedonia). The results of more complex reward processing tasks, tapping symptoms of the illness (self-starvation and ema- tiated body image) may plausibly be accounted for by reward contamination theory because stimuli that are otherwise aversive to HC’s, such as emaciated body image, are considered rewarding and activate relevant reward linked brain regions in patients, and aversive conditions, such as, contaminated stimuli (moldy strawberries) also activate relevant reward linked brain regions in recovered individuals. Brain imaging during food hedonic tasks, with measures of anhedonia and fear of weight gain reporting, may enable the contribution of each dimension to patients’ responses to reward linked tasks, to be further understood. Further investigation of reward contamination theory as a framework for understanding body image misperceptions and self-starvation in AN are also required (Keating, 2010, 2011). An understanding of the mechanisms underlying symptoms of AN may provide the opportunity for development of future treatments for the illness.

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