Neural correlates of impaired decision-making in Anorexia Nervosa.

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Introduction

Eating disorders (EDs) are defined as 'a definite disturbance of eating habits or weight-control behaviour, which results in a clinically significant impairment of physical health or psychosocial functioning and is not secondary to any general medical disorder or to any other psychiatric condition' (Fairburn & Harrison, 2003). In the diagnostic and statistical manual of mental disorders fifth edition (DSM-5) anorexia nervosa (AN) is characterized by restricted eating, extremely low body weight, distorted body image and an intense fear of gaining weight or becoming fat (American Psychiatric Association, 1994). The prevalence is around 0.6% (Treasure et al., 2010). The age of onset is usually during early adolescence and tends to affect mainly women (Treasure et al., 2010). AN is associated with one of the highest risks of all psychiatric illnesses for premature death (Hoek, 2006). Two types of AN are categorized in the DSM-5, the binge/purging type (AN-bp) where individuals regularly engage in binge-eating followed by purging behaviour (e.g. self-induced vomiting or the abuse of laxatives, diuretics or clysters) and the restricting type (AN-r) where individuals do not engage in binge-eating of purging behaviour (American Psychiatric Association, 1994). Genetic heritability accounts for approximately 50-80% of the risk of developing AN (Bulik et al., 2006) and the genetic risk factors are associated with specific personality traits in AN (Kaye et al., 2013a). Specifically, these traits include perfectionism, behavioural rigidity, harm avoidance and high sensitivity to punishment (Kaye et al., 2013a). Individuals with AN also tend to have other puzzling stereotypic symptoms, like a lack of insight about being ill and emaciated, and they often have a resisting or refusing attitude towards treatment (Kaye et al., 2013a). Many individuals with EDs also suffer from comorbid disorders such as depression and anxiety disorders (Treasure et al., 2010). In addition, evidence-based treatments are inconsistent across EDs (Treasure et al., 2010).

At its most basic level, adequate decision-making involves selecting one option that will result in the most beneficial long-term outcome over a number of alternatives (Buelow & Shur, 2009; Davis et al., 2007). Poor decision-making holds that an individual chooses an option that is disadvantageous in the long run, often driven by either an oversensitivity to immediate reward, or oversensitivity for punishment (Buelow & Shur, 2009). It has been implicated that individuals with AN do not seem to guide their decision-making by future consequences, but rather base their decision-making on serving some immediate goal (Danner et al., in press; Merwin et al., 2011). This tendency is most prominent in their eating habits

(Treasure et al., 2010; Kaye et al., 2013b). Since AN is characterized by an extreme fear of gaining weight, individuals with AN resist food (or purge after a binge) to immediately relieve this anxious state (Kaye et al., 2013b) (i.e. 'if I don't eat (or purge after I eat), I don't gain weight'), at the expense of long-term physical and mental health (Merwin et al., 2011). It appears, however, that poor decision-making in individuals with AN is not restricted to their eating behaviour (Brogan et al., 2010, Cavedini et al., 2004).

One economic decision-making task that assesses the participant's ability to base decisions on either short-term or long-term goals is the Iowa Gambling Task (IGT) (Bechara & Damasio, 2005; Damasio, 1994). The IGT simulates real-life economic decision-making because it incorporates factors such as immediate gain versus ultimate long-term gain, punishment and uncertainty of outcome (Davis et al., 2007). In everyday life, people often make economic decisions with long-term and short-term consequences in mind (e.g. betting an amount of money on a race-horse versus investing that same amount of money in a retirement-plan). The design of the IGT is based on the theory that adaptive decision-making not only requires unimpaired rationale, but also accurate emotional processing (Bechara & Damasio, 2005). This theory is known as the Somatic Marker Hypothesis (SMH) (Damasio, 1994). Specifically, the SMH proposes that emotion-related bodily signals (somatic markers) that the individual need not be consciously aware of, such as changes in heart rate, gut motility and hormone secretion, aid in the cognitive process of decision-making (Reimann & Bechara, 2010).

It has been shown that ill AN patients show impairments on this task in economic decision-making (Brogan et al., 2010; Cavedini et al., 2004, 2006; Chan et al., 2014). Some, but not all, of these results in ill AN patients have been replicated in recovered AN individuals (Danner et al., 2012) and decision-making abilities during the acute phase of the illness have been identified as a predicting factor for recovery (Cavedini et al., 2006). This might suggests that poor decision-making is a possible vulnerability to the development of AN as opposed to being an effect of malnutrition (Danner et al., 2012). According to the SMH, emotional processes in decision-making are guided by the responses to previous choices that resulted in either reward or punishment. These need to be used to adapt cognitive strategy for a better choice next time (Damasio, 1994; Reimann & Bechara, 2010). Impairment on the IGT indicates that individuals with AN do not seem to learn adequately from the emotional feedback through their bodily response to reward and feedback, in order to adapt strategy to

serve a long-term goal (Danner et al., in press). Cognitive strategy processes in decision-making entail making accurate estimations of risks and benefits, being able to learn risk/benefit ratio's and retrieve them from memory, and compare them to the alternatives (Chan et al., 2014). In addition, it entails accurate set-shifting and cognitive flexibility to feedback (Chan et al., 2014). So, according to the SMH, adequate somatic signaling and emotional processing of uncertain reward and punishment is necessary to guide the cognitive process of economic decision-making (Reimann & Bechara, 2010).

In addition to AN (Chan et al., 2014), poor decision-making as measured with the IGT is also a symptom of comorbid disorders such as depression (Cella et al., 2010) and anxiety disorders (Mueller et al., 2010; Starcke et al., 2010). A better comprehension of potential differences or similarities across AN and comorbid disorders that both show impairments in decision-making is crucial from a clinical perspective: a better understanding on which processes are impaired exactly might be useful in adapting treatment to improve decision-making abilities in individuals with AN. If individuals with AN are better able to choose advantageous long-term outcomes for themselves, this might improve long-term recovery.

In order to better understand the different processes underlying impaired decision-making in AN as measured with the IGT, this review will attempt to disentangle the concept of decision-making according to the SMH into emotional and cognitive processes separately. First, the theoretical framework of real-life economic decision-making with the IGT will be further discussed. Second, two sets of neurobiological systems that are implicated in decision-making will be presented, underlying the emotional and cognitive aspects of decision-making. Neurobiological alterations that have been found in these systems will then be linked to emotional and cognitive impairments seen in AN. Next, it will be investigated how these impairments might contribute to the deficits in decision-making seen in AN. Finally, this review will conclude with suggestions for future research directions in the field of assessing decision-making in AN.

1. Theoretical framework of decision-making using the IGT

The SMH is a theory that provides a system-level neurobiological and cognitive framework for decision-making (Damasio, 1994). The theory holds that homeostasis, emotion and feeling need to be incorporated in the decision-making process in order to adequately evaluate the effects of different options in the long-term and short-term (Li et al., 2009). An *emotion* is

defined as ‘a collection of changes in body and brain states triggered by a dedicated brain system that responds to specific contents of one’s perceptions, actual or recalled, relative to a particular object or event’ (Damasio, 1994). Emotion-related bodily signals (i.e. somatic signals) may be considered a biological form of anticipation to stimuli that are relevant to the organism in order to survive, such as an opportunity to feed or engage in social interaction (e.g. to promote group-formation and social support) (Reimann & Bechara, 2010). In the first studies (Damasio, 1994; Bechara et al., 1996), a correlation was found between adequate performance on the IGT and the development of somatic marker signals, as measured by skin conductance responses (SCRs) in healthy participants. In the course of the task, healthy individuals gradually shift their strategy to more advantageous decision-making (Bechara et al., 1996). Consistent with the SMH, healthy individuals eventually demonstrate measurable bodily responses (the somatic markers) prior to taking a risky choice during the course of the task. This indicates that they have ‘learned’ from previous choices which choices are risky, since they are not explicitly informed about this prior to testing (Damasio, 1994, Bechara et al., 1996). Interestingly, these somatic marker signals were absent in patients with vmPFC lesions that performed poorly on the IGT (Damasio, 1994; Bechara et al., 1996). Consequently, the vmPFC was considered a crucial neural basis for the processing of somatic signals in order to make advantageous decisions (Damasio, 1994). Since then, the IGT has been used extensively to assess decision-making impairments in several neurological and psychiatric conditions (Cella et al., 2010; Starcke et al., 2010), including AN (Brogan et al., 2010; Cavedini et al., 2004;2006; Chan et al., 2014).

In the IGT, the participant is presented with four decks of cards with monetary gains or losses and is asked to choose cards from these decks (100 choices in total) with the goal to win as much money as possible (Bechara et al., 1996). Decks A and B are disadvantageous in the long run: cards in these decks have greater immediate gains, but also greater losses, resulting in an overall nett loss over 100 trials. Decks C and D on the other hand, are advantageous in the long run: cards in these decks have smaller immediate gains, but also smaller losses, resulting in an overall nett gain over 100 trials (Bechara et al., 1996). Prior to testing, the participants are informed that some decks are more advantageous than other decks, but not which decks these are. They need to find out themselves which deck is safer and more advantageous in the long-term. In the IGT, performance is traditionally indexed by the net number of cards chosen from advantageous decks over 100 trials (Chan et al., 2014). So, the IGT does not measure subtle impairments in the multiple processes underlying complex

decision making separately (Chan et al., 2014). As stated before, these processes include emotional processes (e.g. sensitivity to reward and punishment and generating somatic signals), and cognitive processes (e.g. estimate risk/benefit ratio's, retrieve them from memory and compare them to alternatives). The nett scores on the IGT represent decision-making as a unidimensional construct and possibly oversimplifies the complex process (Chan et al., 2014). Performance on the IGT might therefore require a more nuanced assessment of decision-making including emotional and cognitive aspects separately (Dunn et al., 2006).

In sum, it has been indicated that individuals with AN show impairments in decision-making in eating behaviour and economic decision-making as measured with the IGT (Brogan et al., 2010; Cavedini et al., 2004;2006; Chan et al., 2014). This task is based on a neurobiological theory that holds that advantageous decision-making relies on adequate emotional and cognitive processing incorporating uncertainty of outcome and reward and punishment (Damasio 1994; Bechara et al., 1996). What is of particular interest, is that the neurobiological structures underlying the incentive value of food and money largely overlap, as well as the structures implicated in the cognitive control over food intake and monetary gain (Kaye et al., 2011). Therefore, it is important to investigate how disturbances in these emotion- and cognition-related structures might contribute to pathological eating behaviour and disadvantageous decision-making.

2. Neurobiology of decision-making

From a neurobiological perspective, decision-making relies on integrating at least two basic sets of neural systems corresponding to emotional and cognitive processing. The first is important for translating visceral responses into subjective emotions that need to be incorporated in the decision-making processs (Reimann & Bechara, 2010, Treasure et al., 2010). This set includes structures such as the hypothalamus, amygdala, striatum, and cortical structures that receive afferent input from the internal milieu (visceral information) such as the insula, vmPFC and cingulate cortex (Reimann & Bechara, 2010; Treasure et al., 2010). The second set of neural systems is important for working memory, rationale and attention, and includes structures such as the hypothalamus, dorsolateral prefrontal cortex (dlPFC) and frontoparietal networks (Friederich & Herzog, 2011; Treasure et al., 2010). This system is also implicated in self-regulation, the ability of behavioural inhibition (i.e. impulsivity), cognitive flexibility and overall top-down control that contextualizes food/eating behaviour

and economic decision-making within long-term goals (Reimann & Bechara; 2010; Treasure et al., 2010; Friederich & Herzog, 2011).

Complicating the research on the etiology of AN is the starvation process itself during the illness. Many of the neurobiological findings in AN can be understood as a result of starvation. Since the brain uses about 20% of caloric intake and is particularly dependent on glucose, it is highly vulnerable to the consequences of malnutrition (Treasure et al, 2010). Starvation literally shrinks the brain, and malnutrition during adolescence, a period of major brain reorganization, can negatively affect the course of the illness and result in a enduring ED (Treasure et al., 2010). Specifically, long-standing malnutrition during adolescence has been associated with hormonal and neuropeptide dysfunction that may produce 'biological scars' that maintain certain functional impairments in adulthood (Herpertz-Dahlmann et al., 2011). In addition, starvation has been associated with altered brain metabolism in frontal (Kaye et al., 2011), cingulate (McCormick et al., 2008) and parietal regions (Delvenne et al., 1997).

Therefore, it is important to consider the influence of state- and trait dependent impairments when assessing neuropsychological functioning (i.e. decision-making). Clearly, studies during the ill phase of AN may be confounded by the effects of malnutrition. For this reason, this review will clearly differentiate between individuals with AN (acute phase of the illness) and individuals recovered from AN (with a normal weight and diet).

3. Neurobiological alterations and decision-making impairments in AN

Alterations that underlie gustatory, emotionality and reward processes may have an influence on decision-making beyond 'eat' or 'don't eat' in AN, because these structures are also involved in multiple behaviours that require adequate emotional processing of other rewarding stimuli, like monetary gain (Kaye et al., 2011; Cools et al., 2008a, 2008b; Wagner et al., 2007). In the same way, alterations in the frontoparietal circuit that is involved in cognitive control over food intake might be implemented in the cognitive control over monetary decision-making (Friederich & Herzog, 2011). In addition, limbic and cortical brain circuits that are involved in emotionality and reward-processing or cognitive control are of particular interest for AN, because these circuits show persistent altered function after recovery and suggest a vulnerability for the development of the illness (Rastam et al, 2001, Uher et al., 2003).

Gustation, emotionality and reward-neurocircuitry.

The neurocircuitry of gustation, emotionality and reward in humans is complex (Frank & Kaye, 2012). Chemoreceptors on the tongue detect sweetness in food. This signal is conveyed through the brainstem and thalamus to the primary gustatory cortex, which is densely interconnected with and adjacent to the anterior insula (AI). The AI is an integral part of a ventral limbic circuit including the amygdala, ACC and vmPFC that has projections to the ventral striatum (Frank & Kaye, 2012; Kaye et al., 2011). In addition, the ventral striatum also receives input from the hypothalamus. The hypothalamus relays energy storage information from secreted hormones in the body to the VS (Avena & Bocarsly, 2012). The ventral striatum receives information regarding the taste and the nutritional value of food (Avena & Bocarsly, 2012) and is implicated in reward and motivation (O'Doherty et al., 2004). Neuroimaging studies in humans suggest a distinct role for the dorsal striatum in cognitive control and evaluation of reward value of stimuli, especially stimulus and response associations (O'Doherty et al., 2004). Through this neurofunctional chain, higher cortical areas might modulate hedonic and motivational aspects of taste with cognitive strategies (Kaye et al., 2011).

Neuroimaging studies indicate altered functioning of the insula (Frank & Kaye, 2012; Wagner et al., 2008) and ventral and dorsal striatal regions in AN (Frank et al., 2005). The insular cortex has been associated with interoceptive awareness of homeostatic state in the body, and affective and motivational responses to these interoceptive sensations (Frank & Kaye, 2012; Paulus & Stein, 2006). Interoception therefore, provides the link between current somatic state and affective and cognitive modulation of the somatic state (Paulus & Stein, 2006). Alterations in insular functioning could impede accurate processing of homeostatic state, which in turn might interfere with the motivation to change eating behaviour (Kaye et al., 2011). In addition to altered interoceptive processing in the insular cortex, inaccurate reward-processing of food might also contribute to the disturbed eating patterns (Frank & Kaye, 2012; Kaye et al., 2011). The amygdala, striatum and vmPFC are associated with the stimulus-reward value of both food and money, and are implicated in future reward-prediction and may play a role in integrating the reward-prediction to guide decisions regarding eating and economics (Kaye et al., 2011). So, disturbed eating patterns could be associated with altered gustatory and homeostatic state processing mediated by the insula, or could be associated with inaccurate processing of the reward-value of food mediated by the

dopaminergic reward system (i.e. the striatum, nucleus accumbens (NAc) and vmPFC). Since money is also a stimulus of reward and processed by largely the same neurobiological structures, it is of interest to examine this possibility further regarding the impairments found on the IGT in AN.

a. Dopamine

In animals and humans, ingestion of palatable foods is associated with dopamine (DA) release in the striatum and the NAc, a structure implicated in the motivation to eat and a terminal field of ventral striatal projections (Bassareo & DiChiara, 1999; Kaye et al., 2013b). Genetic, pharmacologic and physiological data have indicated that AN individuals have abnormal DA function in striatal regions, which may alter reward-related processing of eating (Kaye et al., 2011; 2013b). Paradoxically, studies have indicated that DA release in the striatum is associated with dysphoric and anxious mood in AN individuals, in contrast to euphoric mood in healthy individuals (Bailer et al., 2012). Specifically, DA release in the ventral striatum through experimental ingestion of amphetamine is associated with euphoria in healthy individuals (Bailer et al., 2012). In contrast, in recovered AN individuals, this DA release in the ventral striatum is associated with increased anxiety (Bailer et al., 2012). Also, DA receptor binding in the ventral striatum in healthy individuals contributes to adequate motivational responses to reward stimuli (Frank et al., 2005). PET studies have shown that recovered AN individuals have increased DA receptor binding in the ventral striatum compared to healthy controls (Frank et al., 2005). However, since AN individuals experience anxiety rather than euphoria during DA release, this increased DA receptor binding might underlie a neurobiological mechanism for enhancing the anxiolytic response to food (Kaye et al., 2013b). Indeed, indices of greater anxiety were associated with DA receptor binding in the ventral striatum (i.e. the caudate and putamen) (Bailer et al., 2012). In addition, recovered AN individuals, in particular AN-r individuals, have decreased homovannilic acid, a DA metabolite, in cerebrospinal fluid in comparison to control women, indicating that DA disturbances persist after AN individuals have gained a normal weight and diet (Kaye et al., 1999; Kaye et al., 2006). If DA release in the striatum after food intake is associated with anxiety instead of euphoria in AN individuals, this might explain their pursuit of starvation. For them, restricting food intake, and thereby decreasing DA release in the ventral striatum, might be the means to relieve anxious and dysphoric mood (Kaye et al., 2013b).

As stated earlier, decision-making requires the integration of two sets of neural systems, of which one is important in processing emotional stimuli and includes the ventral striatum (Reimann & Bechara, 2010). Decision-making might be influenced though the processing of anxiety-related somatic signals related to altered DA function in the VS (Bailer et al., 2012; Kaye et al., 2013a). In healthy but high anxious individuals, risk and uncertainty may be particularly aversive since anxious individuals experience heightened arousal mediated by the amygdala towards risky choices (Hartley & Phelps, 2012). This heightened arousal is associated with a neuropsychological bias towards negative and aversive possible outcomes (i.e. punishment) (Hartley & Phelps, 2012). When making economic decisions with uncertain outcome, this bias towards possible punishment might impair IGT performance. Even though the amount of punishment (i.e. monetary loss) varies between decks A and B, and C and D, the possibility of punishment is present in all four decks. If AN individuals are preoccupied with the possible punishment, this bias might interfere with adequate benefit/risk assessment during the IGT. If food has a 'rewarding aspect' for AN individuals in that it heightens anxious and dysphoric mood, this might cause a imbalance of striatal processes away from healthy automatic reward-responses mediated by the ventral striatum, and towards a more cognitively mediated approach mediated by the dorsal striatum (Kaye et al., 2011).

Harm avoidance has been positively correlated with DA receptor binding in the dorsal striatum (Frank et al., 2005), suggesting a trait influence on reward-processing. In contrast, decreased DA receptor binding has been associated with substance abuse and bulimia nervosa (Yilmaz et al., 2012). So, it appears that decreased DA receptor binding underlies a sensitivity for rewarding stimuli (like food or drugs), while increased DA receptor binding in AN might be associated with a particular insensitivity to rewarding stimuli (Frank et al., 2005). Increased DA receptor binding might then also help explain why individuals with AN seem to be anhedonic in general, ignoring and refusing themselves other pleasures in life (Frank et al., 2005). The dorsal striatum has been implicated in especially stimulus-response associations (O'Doherty et al., 2004), and in AN the food stimulus is associated with an anxiety response (Kaye et al., 2013b). Impaired healthy automatic reward-processing in AN might underlie a 'dominance' of more cognitively mediated reward-processing through the dorsal striatum (Kaye et al., 2011). Also, typical anorexic traits such as harm avoidance have an influence on reward-processing through the dorsal striatum (Frank et al., 2005).

In AN, the cognitive strategy for not getting fat is to not eat. If altered reward processing in striatal regions is associated with a 'dominance' of cognitive strategy, this might interfere with the generation of somatic signals in the body processed by automatic reward-processes mediated by the ventral striatum and vmPFC (Damasio, 1994; Bechara et al., 1996; Kaye et al., 2011). According to the SMH, somatic signals are crucial in guiding adaptive decision-making, and if AN individuals adapt a pathological cognitive strategy and overrule their bodily response towards hunger, then this imbalance may have an effect on the bodily responses generated by the reward of monetary gain as well. A tendency towards using cognitive strategy in the IGT does not mean that it will result in advantageous long-term outcomes, because the SMH holds that emotional processing needs to be unimpaired (Bechara et al., 1996). The disturbances found in emotionality and reward-related structures might underlie anxiety and high sensitivity to punishment, and might therefore help explain why individuals with AN perform poorly on the IGT (Brogan et al., 2010; Cavedini et al., 2004;2006; Chan et al., 2014).

b. Serotonin

In addition to DA disturbances, a second neurobiological component might contribute to disturbed eating patterns and anxiety in AN. Neuroimaging data has indicated serotonin (5-HT) receptor and transporter alterations in AN (Bailer & Kaye, 2011). This neurotransmitter is of particular interest for the research in AN, since the metabolite for synthesis of 5-HT is tryptophan, and this protein must be obtained through the diet (Bailer & Kaye, 2011). Alterations in 5-HT systems have been associated with feeding behaviour (i.e. satiety processing), but also mood and cognitive control (i.e. anxiety and behavioural inhibition) (Bailer & Kaye, 2011). Again, some alterations in the 5-HT systems have been shown to be persistent in recovered AN individuals (Bailer & Kaye, 2011). What is particularly relevant for this review is that reduced levels of 5-HT have been associated with enhanced punishment prediction learning, but not reward prediction, in healthy individuals (Cools et al., 2008b). This suggests a specific role of 5-HT in an 'aversive motivational system' (Daw et al., 2002) as opposed to DA in a reward motivational system (Cools et al., 2008a, 2008b; Kaye et al., 2011). If 5-HT is implicated in punishment prediction learning, then investigating the role of 5-HT in AN individuals that shown impairments on decision-making involving feedback learning from punishment is important.

Studies have shown reduced endogenous levels of 5-HT in ill AN patients (Kaye et al., 2013b). However, since AN is characterized by a restrictive diet, it is possible that decreased 5-HT levels is secondary to the decreased ingestion of tryptophan, suggesting that decreased 5-HT levels are a state-dependent neurobiological alteration in AN (Bailer & Kaye, 2011). However, experimental depletion of tryptophan was associated with decreased anxiety and decreased dysphoric mood in both ill and recovered AN individuals, but did not have anxiolytic effects for healthy controls (Kaye et al., 2003). This might indicate that ill AN patients again restrict their food intake to relieve anxiety (Kaye et al., 2003). Premorbidly, reported high levels of anxiety may thus be associated with a hyperactive 5-HT system posing as a vulnerability for the development of AN (Bailer & Kaye, 2011).

Paradoxically however, experimental depletion of 5-HT has also been associated with greater amygdala responses to fearful faces in individuals with high sensitivity to threat (Cools et al., 2005). In addition, depletion of 5-HT enhances behavioural brain responsiveness to aversive signals, with an increase in sensitivity to punishment in particular (Cools et al., 2008a). Also, depletion of 5-HT is thought to modulate the effect that punishment has on emotion and learning (Cools et al., 2008a, 2008b). Specifically, decreased 5-HT can impair cognitive performance by enhancing the impact of punishment (Cools et al., 2008a). Additional evidence from studies in recovered AN individuals show increased cerebrospinal fluid levels of the major brain metabolite of 5-HT, indicating higher endogenous levels of 5-HT in recovered individuals (Kaye et al., 2013b). Neuroimaging studies indicate a hyperresponsive fear network in AN in response to visual food cues, including the ACC and amygdala (Frank & Kaye, 2012; Zhu et al., 2012). It is known that 5-HT modulates the responsiveness of the amygdala and connected medial frontal regions to fear-triggering stimuli (Cools et al., 2005; 2008a). A hyperresponsive fear network in AN might result from the lack of available 5-HT that is needed to downregulate the neurobiological fear response generated by, among other structures, the amygdala.

These two lines of evidence seem to contradict each other. Decreased 5-HT levels have been associated with both reduced anxiety in healthy individuals and AN individuals, and a hyperresponsive fear network in AN individuals (Cools et al., 2005, 2008a). These findings underscore the dynamic and complex role of 5-HT in anxiety, fear and dysphoric mood (Cools et al., 2005, 2008a, 2008b; Kaye et al., 2013b). In the study of affective disorders, the effect of 5-HT on multiple aspects of emotion regulation, mood and cognition is unclear, and

understanding of the working of the neurotransmitter is difficult (Cools et al., 2008a). For instance, the pharmacological treatment for anxiety disorders is often benzodiazepines, a drug that reduces endogenous 5-HT levels and anxiety. In contrast, dysphoric mood is most often treated with selective serotonin reuptake inhibitors (SSRIs) that increase endogenous 5-HT levels and relieve dysphoric mood. The paradox is that anxiety is often comorbid with dysphoric mood in many psychiatric disorders (Cools et al., 2008a), including AN (Kaye et al., 2013a; Treasure et al., 2010; Fairburn & Harrison, 2003).

However, despite the heterogeneity in findings, studies in AN suggest that high reported levels of anxiety predate the onset of AN (Bailer & Kaye, 2011). In addition, trait high anxiety persists after recovery (Wagner et al., 2007) and is associated with elevated 5-HT metabolite levels in the cerebrospinal fluid (Kaye et al., 2013b). Thus, a normal diet and normal food intake in AN individuals may be associated with exaggerated 5-HT secretion and anxiety (Bailer & Kaye, 2011). Restricting food intake then, results in a brief respite from anxious mood by decreasing tryptophan intake and reducing 5-HT levels (Bailer & Kaye, 2011). Anxiety itself may influence economic decision-making (Hartley & Phelps 2012). To high anxious individuals, unpredictable stimuli are more aversive than predictable stimuli, compared to normal individuals (Hartley & Phelps, 2012). Risk and uncertainty during the IGT may be particularly aversive to anxious individuals, resulting in an enhancement of aversive processing (Hartley & Phelps, 2012). In other words, trait anxiety might mediate a form of inaccurately processing aversive feedback (i.e. punishment) that impairs AN individuals in the ability to correctly compare beneficial and risky options after feedback. Essentially, this might mean that trait anxiety interferes with a good performance on the IGT even when the individual is recovered from AN, because trait anxiety withholds an individual from trying a possible better option, because it *could* be worse (Merwin et al., 2011).

Cognition and frontoparietal neurocircuitry

Characteristic for the illness, AN individuals show rigid and stereotypical behaviours concerning eating and weight, in accordance with preoccupations regarding body image (Treasure et al., 2010). Cognitive inflexibility is considered a key characteristic of individuals with AN (Kaye et al., 2013a). Also, AN individuals often have other particular traits including anxiety and harm avoidance, and perfectionism (Fairburn & Harrison, 2003; Kaye et al., 2013a) that tend to occur in childhood already, and may be considered as a vulnerability to

develop AN in adolescence. In addition, these traits often persist after treatment and recovery (Wagner et al., 2006).

Traditional theory with respect to the cognitive aspect of motivated decision-making is that impaired decision-making is either the result of cognitive inflexibility or response inhibition deficits (Zakzanis et al., 2010) or both (Fagundo et al., 2012). AN patient studies have indeed shown impairments in set-shifting (Danner et al., 2012), cognitive flexibility (Danner et al., 2012; Fagundo et al., 2012), and response inhibition (Fagundo et al., 2012) but also in other cognitive domains, like processing speed (Zakzanis et al., 2010) and specific aspects of memory (Chan et al., 2014; Nikendei et al., 2011) in AN. Some impairments in cognitive function improve with weight restoration, including working memory and attention (Kidd & Steinglass, 2012) and indicate an effect of starvation rather than a characteristic of the illness (Kidd & Steinglass, 2012). However, cognitive inflexibility may be a manifestation of exaggerated cognitive control seen in AN that predates the onset of AN and persists after recovery (Friederich & Herzog, 2011).

In a large study sample including both ill and recovered AN individuals and healthy controls, only ill AN patients performed poorly on a cognitive flexibility task (Tchanturia et al., 2011). Recovered AN did not perform different from healthy controls, indicating that poor cognitive flexibility is associated with ill AN state only (Tchanturia et al., 2011). However, later work using the same sample but a different task revealed that recovered AN individuals still performed better than ill AN patients, but showed more perseveration errors compared to healthy controls (Tchanturia et al., 2012). Key difference between the two tasks was ambiguity: in the first task, explicit instruction was given, in the second task, no explicit instruction was given. So, it appears that recovered AN individuals are able to adaptively change strategy after explicit feedback, but remain rigid in strategy when no explicit feedback is given. The variety of errors made by ill AN patients during the ambiguous task are argued to be a reflection of malnutrition and impaired attention, while the specific perseverance errors made by recovered AN individuals might be interpreted as a specific trait for AN (Tchanturia et al., 2012). Additional evidence for impaired cognitive flexibility as a trait marker comes from findings of impaired set-shifting in healthy sisters of AN individuals (Holliday et al., 2005) and the finding that suboptimal set-shifting performance was associated with childhood rigidity (Tchanturia et al., 2004).

Neuroimaging studies have indicated that impaired cognitive behavioural flexibility in individuals with AN is associated with dysfunctional striatocortical circuits (Friederich & Herzog, 2011). As stated before, the ventral striatocortical circuits is involved in motivational and reward-related processes, and has been shown to be altered in AN individuals in response to wins and losses (Frank et al., 2005). Also, the lateral prefrontal cortex, ACC and vmPFC have been found to be associated with set-shiting and inhibitory control in general (Friederich & Herzog, 2011). Subcortical structures such as the striatum facilitate behavioural response shifting mediated by the frontoparietal cortices (Monchi et al, 2006). The more cognitive demanding the task, the greater the top-down control of the frontoparietal network (Miller & Cohen, 2001). In a study that required AN individuals to inhibit a prepotent impulse in favor of an alternative, less automatic behaviour, ill AN patients show preserved activity in the right ventral frontoparietal network that was not observed in healthy individuals (Friederich & Herzog, 2011). Similar findings indicating a dominant frontoparietal network implicated in cognitive control have been reported in a study in recovered AN individuals using a reward-paradigm (Wagner et al., 2007).

Decision-making in the IGT requires the ability to learn in hindsight from previous (non)adaptive card choices, incorporate this feedback and adapting strategy accordingly. If AN individuals tend to be rigid and cognitively inflexible in adapting prepotent behaviours, then impairments in decision-making measured by the IGT should be evident. Furthermore, if impaired set shifting is associated with childhood rigidity (Tchanturia et al., 2004) and impairments persists after recovery from AN (Danner et al., 2012; Friederich & Herzog, 2011) this implies that cognitive inflexibility is a trait-not-state marker of AN that might have an effect on various aspects of long-term decision-making extending beyond taking economic risk in the IGT.

However, a recent study has indicated that the influence of rigidity on economic decision-making as measured with the IGT remains unclear (Danner et al., 2012). The study found that problems in set-shifting in recovered individuals with AN did not correlate with impaired decision-making on the IGT (Danner et al., 2012). This indicates that cognitive inflexibility is not directly associated with poor decision-making (Danner et al., 2012). Personality traits associated with exaggerated cognitive control such as perfectionism and harm avoidance appear to be heritable, occur in unaffected familiy members and are independent of weight and nutritional status (Bulik et al., 2007) which strongly support the argument that these traits

are vulnerabilities for the development of AN, not residual 'scarring' from the starvation process. Some of these traits have been associated with impaired economic decision-making (Davis et al., 2007) suggesting that specific personality traits, rather than impaired executive function, might interfere with adaptive decision-making. In addition, this trait rigifity might impede effective treatment, since cognitive-behavioural therapy encourages individuals with AN to drastically change their cognitions and behaviour.

4. Limitations and future directions

Several limitations regarding the interpretation of the research in this review should be noted.

First, the research discussed in this review hardly differentiates between the different subtypes of AN. Eating pathology in both AN-r and AN-bp is characterized by extremely restricted eating, but individuals with AN-bp alternate between periods of restricted eating and binge-eating and purging (Fairburn & Harrison, 2003; Treasure et al., 2010). Purely restrictive eating and binge-eating have been associated with very different neurobiological alterations in the brain (Kaye et al., 2013b). For instance, binge-eating has been implemented as a form of substance abuse (Yilmaz et al., 2012). In terms of symptom presentation and diagnosis, binge-eating and substance abuse disorders show striking similarities. Both psychiatric groups show a loss of control over the substance of abuse (either drugs or food), a preoccupation with the substance, secrecy and shame regarding the use of the substance and, most importantly, depending on the substance to relieve anxious and/or dysphoric mood (Yilmaz et al., 2012). Binge-eating is often comorbid with substance abuse, while restrictive eating is not (Kaye et al., 2013b). In contrast, AN-r individuals appear more compulsive than AN-bp individuals (Kaye et al., 2013b). Future research should differentiate between different subtypes of AN when conducting research, in order to better understand different pathological eating patterns and etiology (Chan et al., 2014).

Second, drawing inferences about pathological behaviour from DA and 5-HT research is speculative by definition. No neurotransmitter works in isolation in the brain, and neurotransmitters often exert their effect on multiple pathways, structures and other neurotransmitters (Kaye, 2008). In addition, neurotransmitters are involved in a several domains of neuropsychological functioning, such as mood-regulation (Kaye et al., 2013a) and executive control (Cools et al., 2008a). Existing literature suggests that psychiatric disorders

are complex, consisting of multiple neurobiological, environmental and genetic factors, each of small effect (Kaye, 2008).

Third, there is a striking lack of studies of AN psychopathology conducted in adolescents. Neuropsychological and neurobiological findings in adolescents is inevitably confounded by the massive brain reorganization effects during this phase in life, and should be interpreted cautiously. For instance, it has been found that IGT performance was impaired in adolescence in healthy individuals (Smith et al., 2012), suggesting that brain reorganization rather than psychopathology explains impairments on the IGT during adolescence. Still, future research should aim to conduct more research in adolescents, since the onset of AN is primarily during adolescence (Treasure et al., 2010).

Fourth, longitudinal studies should be set up to assess neuropsychological functioning before the age of onset of AN, since only premorbid data can shed light on the debate whether a finding in ill and/or recovered individual with AN is a vulnerability or an effect of starvation (Treasure et al., 2010). Cross-sectional studies can not adequately capture information on which individuals may develop comordid diseases later in life (Yilmaz et al., 2012). Also, individuals classified as healthy during assessment may also suffer from psychiatric symptoms after they participate in the study, possibly confounding the research with existent vulnerabilities during assessment (Yilmaz et al., 2012). More epidemiology studies with a longitudinal nature are needed to predict possible vulnerabilities for development of AN more accurately (Yilmaz et al., 2012).

Fifth, all the neuropsychological processes underlying adaptive decision-making are not uniquely measured by the IGT (Chan et al., 2014). The IGT is one measure of economic decision-making that focuses on accurate emotional processing of somatic signals in response to reward and punishment (Damasio, 1994; Bechara et al., 1996). Studies assessing decision-making with the IGT in recovered AN individuals do not have consistent results; some report impaired decision-making in recovered individuals with AN (e.g. Danner et al., 2012), while others report recovered AN individuals to perform even better than healthy controls (e.g. Lindner et al., 2012). Other neuropsychological tests however, may also inform about short- and long-term decision-making. For instance, it has been shown that individuals with AN-r are better able to delay monetary reward (Steinglass et al., 2012), suggesting an enhanced ability to choose advantageously in the long-run. However, individuals with AN do not seem to take long-term health consequences in mind when they restrict their eating (Danner et al.,

in press). Future research should take these counterintuitive findings into account, and critically evaluate the validity of each neuropsychological test.

Finally, comorbidity is a major confounding factor in the research on AN. Because of the high comorbidity of anxiety, mood and obsessive-compulsive disorders in AN (Treasure et al., 2010), excluding individuals with these comorbid disorders in AN experimental research would result in too little power and generalizability of the findings. Indeed, one of the core characteristics of AN is an extreme fear of gaining weight or getting fat (American Psychiatric Association, 1994). Moreover, some have hypothesized that AN is a form of a phobic-like fear of food (Wildes et al., 2013), suggesting anxiety and fear is inevitably coupled with a disturbed eating pattern. Future research will need to address one of the biggest challenges in developing better strategies in treating AN together with comorbid disorders (Yilmaz et al., 2012).

5. Summary and conclusions

Individuals suffering from AN are characterized primarily by an extreme fear of gaining weight and getting fat (American Psychiatric Association, 1994). They exhibit a disturbed eating pattern, whereby they resist food (or purge after a binge) to immediately relieve the anxious feelings of possible weight-gain (Kaye et al., 2013b) (i.e. 'if I don't eat (or purge after I eat), I don't gain weight'), but at the expense of long-term physical and mental health (Merwin et al., 2011). Therefore, it has been implicated that individuals with AN do not seem to guide their decision-making by future consequences, but rather base their decision-making on serving some immediate goal (Danner et al., in press; Merwin et al., 2011). It has been shown that individuals with AN also tend to choose immediate gain at the expense of long-term gain in a economic decision-making task (Brogan et al., 2010, Cavedini et al., 2006). This might suggest a behavioural tendency towards short-term goals at the expense of long-term goals that results in disturbed eating patterns as well as impaired decision-making.

The economic decision-making task discussed in the current review distinguishes itself from others in that it is based on a theory that holds that adequate emotional processing is necessary in the cognitive process of decision-making (Damasio, 1994; Bechara et al., 1996). Specifically, it proposes that an individual generates bodily responses to reward and punishment, and that the individual needs to 'learn' from this bodily feedback which choices are advantageous (Bechara et al., 1996). Since the neurobiological structures underlying this

type of decision-making overlap with the neurobiological correlates of eating behaviour, reward and cognitive control, it is interesting to investigate neurobiological alterations in these structures that might contribute to disturbed eating patterns and impaired decision-making (Kaye et al., 2011). In the current review neurobiological alterations have been discussed regarding reward processing, sensitivity to punishment and cognitive control that might underlie disturbed eating patterns as well as impaired decision-making in AN.

It remains unclear whether the behavioural tendency for short-term versus long-term goals in eating behaviour is fully applicable to economic decision-making. The IGT does not measure subtle impairments, only a nett score of short-term versus long-term advantageous decisions (Chan et al., 2014). Other studies have indicated that individuals with AN are indeed very well capable of choosing long-term reward over short-term reward (Steinglass et al., 2012). However, the IGT is designed to incorporate emotional processing specifically, in addition to short-term versus long-term decision-making (Bechara et al., 1996). Thus, it might be that AN is characterized by a short-term goal tendency guided by inadequate emotional processing that results in impairments on the IGT. This might explain why individuals with AN do not always perform poorly on decision-making tasks that do not incorporate emotional processing. In addition, it has been shown that most deficits in executive function are caused by malnutrition, and are not part of AN psychopathology (Kidd & Steinglass, 2010). This suggests that the cognitive inflexibility is inherent to AN personality traits, not pathology. This further supports inadequate emotional processing as the major impairment resulting in disturbed eating patterns and decision-making as assessed with the IGT. Moreover, even though decision-making findings in ill AN individuals are fairly consistent (Brogan et al., 2010; Cavedini et al., 2006), few studies have assessed decision-making as measured with the IGT in recovered AN individuals directly (Danner et al., 2012; Tchanturia et al., 2007; Lindner et al., 2012) and these studies have showed inconsistent results. Therefore, conclusions about a possible vulnerability versus an effect of malnutrition can not be drawn yet.

References

Avena, N. M., & Bocarsly, M. E. (2012). Dysregulation of brain reward systems in eating disorders: Neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology, 63*(1), 87-96.

Bailer, U. F., Narendran, R., Frankle, W. G., Himes, M. L., Duvvuri, V., Mathis, C. A., et al. (2012). Amphetamine induced dopamine release increases anxiety in individuals recovered from anorexia nervosa. *International Journal of Eating Disorders, 45*(2), 263-271.

Bailer, U. F. & Kaye, W.H. (2011) Serotonin: Imaging Findings in Eating Disorders, *Current Topics in Behavioural Neurosciences 6* (1), 59-80

Bassareo, V., & Di Chiara, G. (1999). Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. *Neuroscience, 89*(3), 637-641.

Bechara, A., & Damasio, A. R. (2005). The somatic marker hypothesis: A neural theory of economic decision. *Games and Economic Behavior, 52*(2), 336-372.

Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cerebral Cortex, 6*(2), 215-225.

Brogan, A., Hevey, D., & Pignatti, R. (2010). Anorexia, bulimia, and obesity: Shared decision making deficits on the iowa gambling task (IGT). *Journal of the International Neuropsychological Society, 16*(4), 711-715.

Buelow, M. T., & Suhr, J. A. (2009). Construct validity of the iowa gambling task. *Neuropsychology Review, 19*(1), 102-114.

Bulik, C. M., Hebebrand, J., Keski-Rahkonen, A., Klump, K. L., Reichborn-Kjennerud, T., Mazzeo, S. E., et al. (2007). Genetic epidemiology, endophenotypes, and eating disorder classification. *International Journal of Eating Disorders, 40*(7 SUPPL.), S52-S60.

Bulik, C. M., Sullivan, P. F., Tozzi, F., Furberg, H., Lichtenstein, P., & Pedersen, N. L. (2006). Prevalence, heritability, and prospective risk factors for anorexia nervosa. *Archives of General Psychiatry, 63*(3), 305-312.

Cavedini, P., Bassi, T., Ubbiali, A., Casolari, A., Giordani, S., Zorzi, C., et al. (2004). Neuropsychological investigation of decision-making in anorexia nervosa. *Psychiatry Research, 127*(3), 259-266.

Cavedini, P., Zorzi, C., Bassi, T., Gorini, A., Baraldi, C., Ubbiali, A., et al. (2006). Decision-making functioning as a predictor of treatment outcome in anorexia nervosa. *Psychiatry Research, 145*(2-3), 179-187.

Cella, M., Dymond, S., & Cooper, A. (2010). Impaired flexible decision-making in major depressive disorder. *Journal of Affective Disorders, 124*(1-2), 207-210.

Chan, T. W. S., Ahn, W. -., Bates, J. E., Busemeyer, J. R., Guillaume, S., Redgrave, G. W., et al. (2014). Differential impairments underlying decision making in anorexia nervosa and bulimia nervosa: A cognitive modeling analysis. *International Journal of Eating Disorders, 47*(2), 157-167.

Cools, R., Calder, A. J., Lawrence, A. D., Clark, L., Bullmore, E., & Robbins, T. W. (2005). Individual differences in threat sensitivity predict serotonergic modulation of amygdala response to fearful faces. *Psychopharmacology, 180*(4), 670-679.

Cools, R., Roberts, A. C., & Robbins, T. W. (2008a). Serotoninergic regulation of emotional and behavioural control processes. *Trends in Cognitive Sciences, 12*(1), 31-40.

Cools, R., Robinson, O. J., & Sahakian, B. (2008b). Acute tryptophan depletion in healthy volunteers enhances punishment prediction but does not affect reward prediction. *Neuropsychopharmacology, 33*(9), 2291-2299.

Damasio, A. R. (1994). Descartes' error and the future of human life. *Scientific American, 271*(4), 144.

Danner, U. N., Sanders, N., Smeets, P. A. M., Van Meer, F., Adan, R. A. H., Hoek, H. W., et al. (2012). Neuropsychological weaknesses in anorexia nervosa: Set-shifting, central coherence, and decision making in currently ill and recovered women. *International Journal of Eating Disorders, 45*(5), 685-694.

Danner, U.N., Sternheim, L. Bijsterbosch, J.M., Dingemanse, A.E. & Van Elburg, A.A. (2014) Influence of negative affect on decision making in women with restrictive and binge-purge type anorexia nervosa, *in press.*

Davis, C., Patte, K., Tweed, S., & Curtis, C. (2007). Personality traits associated with decision-making deficits. *Personality and Individual Differences, 42*(2), 279-290.

Daw, N. D., Kakade, S., & Dayan, P. (2002). Opponent interactions between serotonin and dopamine. *Neural Networks, 15*(4-6), 603-616.

Delvenne, V., Goldman, S., Biver, F., De Maertalaer, V., Wikler, D., Damhaut, P., et al. (1997). Brain hypometabolism of glucose in low-weight depressed patients and in anorectic patients: A consequence of starvation? *Journal of Affective Disorders, 44*(1), 69-77.

Dunn, B. D., Dalgleish, T., & Lawrence, A. D. (2006). The somatic marker hypothesis: A critical evaluation. *Neuroscience and Biobehavioral Reviews, 30*(2), 239-271.

Fagundo, A. B., de la Torre, R., Jiménez-Murcia, S., Agüera, Z., Granero, R., Tárrega, S., et al. (2012). Executive functions profile in extreme eating/weight conditions: From anorexia nervosa to obesity. *Plos One, 7*(8)

Fairburn, C. G., & Harrison, P. J. (2003). Eating disorders. *The Lancet, 361*(9355), 407-416. doi:http://dx.doi.org/10.1016/S0140-6736(03)12378-1

Frank, G. K., Bailer, U. F., Henry, S. E., Drevets, W., Meltzer, C. C., Price, J. C., et al. (2005). Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [11C]raclopride. *Biological Psychiatry, 58*(11), 908-912.

Frank, G. K. W., & Kaye, W. H. (2012). Current status of functional imaging in eating disorders. *International Journal of Eating Disorders, 45*(6), 723-736.

Friederich, H. C., & Herzog, W. (2011). Cognitive-behavioral flexibility in anorexia nervosa. *Current Topics in Behavioral Neurosciences, 6*, 111-123.

Hartley, C. A., & Phelps, E. A. (2012). Anxiety and decision-making. *Biological Psychiatry, 72*(2), 113-118. doi:http://dx.doi.org/10.1016/j.biopsych.2011.12.027

Herpertz-Dahlmann, B., Seitz, J., & Konrad, K. (2011). Aetiology of anorexia nervosa: From a "psychosomatic family model" to a neuropsychiatric disorder? *European Archives of Psychiatry and Clinical Neuroscience, 261*(SUPPL. 2), S177-S181.

Hoek, H. W. (2006). Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. *Current Opinion in Psychiatry, 19*(4), 389-394.

Holliday, J., Tchanturia, K., Landau, S., Collier, D., & Treasure, J. (2005). Is impaired set-shifting an endophenotype of anorexia nervosa? *American Journal of Psychiatry, 162*(12), 2269-2275.

Kaye, W.H., Wagner, A., Fugde, J.L. & Paulus, M. (2011) Neurocircuitry of Eating Disorders, *Current Topics in Behavioural Neurosciences* 6 (1), 37-57

Kaye, W. H., Bailer, U. F., Frank, G. K., & Wagner, A. (2006). *Persistent alterations of serotonin and dopamine activity after recovery from anorexia and bulimia nervosa*

Kaye, W. H., Frank, G. K. W., & McConaha, C. (1999). Altered dopamine activity after recovery from restricting-type anorexia nervosa. *Neuropsychopharmacology, 21*(4), 503-506.

Kaye, W. H., Wierenga, C. E., Bailer, U. F., Simmons, A. N., & Bischoff-Grethe, A. (2013a). Nothing tastes as good as skinny feels: The neurobiology of anorexia nervosa. *Trends in Neurosciences, 36*(2), 110-120.

Kaye, W. (2008). Neurobiology of anorexia and bulimia nervosa. *Physiology & Behavior, 94*(1), 121-135. doi:http://dx.doi.org.proxy.library.uu.nl/10.1016/j.physbeh.2007.11.037

Kaye, W. H., Wierenga, C. E., Bailer, U. F., Simmons, A. N., Wagner, A., & Bischoff-Grethe, A. (2013b). Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? *Biological Psychiatry, 73*(9), 836-842. doi:http://dx.doi.org/10.1016/j.biopsych.2013.01.002

Kidd, A., & Steinglass, J. (2012). What can cognitive neuroscience teach us about anorexia nervosa? *Current Psychiatry Reports, 14*(4), 415-420.

Li, X., Lu, Z. -., D'Argembeau, A., Ng, M., & Bechara, A. (2010). The iowa gambling task in fMRI images. *Human Brain Mapping, 31*(3), 410-423.

Lindner, S. E., Fichter, M. M., & Quadflieg, N. (2012). Decision-making and planning in full recovery of anorexia nervosa. *International Journal of Eating Disorders, 45*(7), 866-875.

McCormick, L. M., Keel, P. K., Brumm, M. C., Bowers, W., Swayze, V., Andersen, A., et al. (2008). Implications of starvation-induced change in right dorsal anterior cingulate volume in anorexia nervosa. *International Journal of Eating Disorders, 41*(7), 602-610.

Merwin, R. M., Timko, C. A., Moskovich, A. A., Ingle, K. K., Bulik, C. M., & Zucker, N. L. (2011). Psychological inflexibility and symptom expression in anorexia nervosa. *Eating Disorders, 19*(1), 62-82.

Miller, E. K., & Cohen, J. D. (2001). *An integrative theory of prefrontal cortex function*

Monchi, O., Petrides, M., Strafella, A. P., Worsley, K. J., & Doyon, J. (2006). Functional role of the basal ganglia in the planning and execution of actions. *Annals of Neurology, 59*(2), 257-264.

Mueller, E. M., Nguyen, J., Ray, W. J., & Borkovec, T. D. (2010). Future-oriented decision-making in generalized anxiety disorder is evident across different versions of the iowa gambling task. *Journal of Behavior Therapy and Experimental Psychiatry, 41*(2), 165-171.

Nikendei, C., Funiok, C., Pfüller, U., Zastrow, A., Aschenbrenner, S., Weisbrod, M., et al. (2011). Memory performance in acute and weight-restored anorexia nervosa patients. *Psychological Medicine, 41*(4), 829-838.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science, 304*(5669), 452-454.

Råstam, M., Bjure, J., Vestergren, E., Uvebrant, P., Carina Gillberg, I., Wentz, E., et al. (2001). Regional cerebral blood flow in weight-restored anorexia nervosa: A preliminary study. *Developmental Medicine and Child Neurology, 43*(4), 239-242.

Reimann, M., & Bechara, A. (2010). The somatic marker framework as a neurological theory of decision-making: Review, conceptual comparisons, and future neuroeconomics research. *Journal of Economic Psychology, 31*(5), 767-776.

Smith, D. G., Xiao, L., & Bechara, A. (2012). Decision making in children and adolescents: Impaired iowa gambling task performance in early adolescence. *Developmental Psychology, 48*(4), 1180-1187.

Starcke, K., Tuschen-Caffier, B., Markowitsch, H. J., & Brand, M. (2010). Dissociation of decisions in ambiguous and risky situations in obsessive-compulsive disorder. *Psychiatry Research, 175*(1-2), 114-120.

Steinglass, J. E., Figner, B., Berkowitz, S., Simpson, H. B., Weber, E. U., & Walsh, B. T. (2012). Increased capacity to delay reward in anorexia nervosa. *Journal of the International Neuropsychological Society, 18*(4), 773-780.

Tchanturia, K., Davies, H., Roberts, M., Harrison, A., Nakazato, M., Schmidt, U., et al. (2012). Poor cognitive flexibility in eating disorders: Examining the evidence using the wisconsin card sorting task. *Plos One, 7*(1)

Tchanturia, K., Harrison, A., Davies, H., Roberts, M., Oldershaw, A., Nakazato, M., et al. (2011). Cognitive flexibility and clinical severity in eating disorders. *Plos One, 6*(6)

Tchanturia, K., Liao, P. -., Uher, R., Lawrence, N., Treasure, J., & Campbell, I. C. (2007). An investigation of decision making in anorexia nervosa using the iowa gambling task and skin conductance measurements. *Journal of the International Neuropsychological Society, 13*(4), 635-641.

Tchanturia, K., Morris, R. G., Anderluh, M. B., Collier, D. A., Nikolaou, V., & Treasure, J. (2004). Set shifting in anorexia nervosa: An examination before and after weight gain, in full recovery and relationship to childhood and adult OCPD traits. *Journal of Psychiatric Research, 38*(5), 545-552.

Treasure, J., Claudino, A. M., & Zucker, N. (2010). Eating disorders. *The Lancet, 375*(9714), 583-593.

Uher, R., Brammer, M. J., Murphy, T., Campbell, I. C., Ng, V. W., Williams, S. C. R., et al. (2003). Recovery and chronicity in anorexia nervosa: Brain activity associated with differential outcomes. *Biological Psychiatry, 54*(9), 934-942.

Wagner, A., Aizenstein, H., Mazurkewicz, L., Fudge, J., Frank, G. K., Putnam, K., et al. (2008). Altered insula response to taste stimuli in individuals recovered from restricting-type anorexia nervosa. *Neuropsychopharmacology, 33*(3), 513-523.

Wagner, A., Aizenstein, H., Venkatraman, V. K., Fudge, J., May, J. C., Mazurkewicz, L., et al. (2007). Altered reward processing in women recovered from anorexia nervosa. *American Journal of Psychiatry, 164*(12), 1842-1849.

Wagner, A., Barbarich-Marsteller, N. C., Frank, G. K., Bailer, U. F., Wonderlich, S. A., Crosby, R. D., et al. (2006). Personality traits after recovery from eating disorders: Do subtypes differ? *International Journal of Eating Disorders, 39*(4), 276-284.

Wildes, J. E., Forbush, K. T., & Markon, K. E. (2013). Characteristics and stability of empirically derived anorexia nervosa subtypes: Towards the identification of homogeneous low-weight eating disorder phenotypes. *Journal of Abnormal Psychology, 122*(4), 1031-1041.

Yilmaz, Z., Kaplan, A. S., & Zawertailo, L. A. (2012). Bulimia nervosa and alcohol use disorder: Evidence for shared etiology and neurobiology. *Current Psychiatry Reviews, 8*(1), 69-81.

Zakzanis, K. K., Campbell, Z., & Polsinelli, A. (2010). Quantitative evidence for distinct cognitive impairment in anorexia nervosa and bulimia nervosa. *Journal of Neuropsychology, 4*(1), 89-106.

Zhu, Y., Hu, X., Wang, J., Chen, J., Guo, Q., Li, C., et al. (2012). Processing of food, body and emotional stimuli in anorexia nervosa: A systematic review and meta-analysis of functional magnetic resonance imaging studies. *European Eating Disorders Review, 20*(6), 439-450.