

UC San Diego

UC San Diego Previously Published Works

Title

Temperament-based Treatment for Anorexia Nervosa

Permalink

<https://escholarship.org/uc/item/5nd1b57h>

Journal

European Eating Disorders Review, 23(1)

ISSN

1072-4133

Authors

Kaye, Walter H
Wierenga, Christina E
Knatz, Stephanie
et al.

Publication Date

2015

DOI

10.1002/erv.2330

Peer reviewed

REVIEW

Temperament-based Treatment for Anorexia Nervosa

Walter H. Kaye^{1*}, Christina E. Wierenga¹, Stephanie Knatz¹, June Liang¹, Kerri Boutelle^{1,2}, Laura Hill³ & Ivan Eisler⁴

¹Department of Psychiatry, University of California San Diego, San Diego, CA, USA

²Department of Pediatrics, University of California San Diego, La Jolla, CA, USA

³Department of Psychiatry, Ohio State University, Columbus, OH, USA

⁴Institute of Psychology, Kings College London, London, UK

Abstract

Anorexia nervosa (AN) tends to be a chronic and deadly disorder with no proven treatments that reverse core symptoms in adults. New insight into neurobiological mechanisms that contribute to symptoms may support development of more effective interventions. We describe the development of a temperament-based treatment for AN on the basis of empirically supported models. It uses a systemized approach and takes into consideration an understanding of how neurobiological mechanisms are expressed through behaviour and personality and contribute to specific AN symptomatology. This model integrates the development of AN-focused constructive coping strategies with carer-focused strategies to manage temperament traits that contribute to AN symptomatology. This intervention is consistent with the recent Novel Interventions for Mental Disorders initiative mandating that treatment trials follow an experimental medicine approach by identifying underlying mechanisms that are directly targeted by the intervention to influence symptoms. Copyright © 2014 John Wiley & Sons, Ltd and Eating Disorders Association.

Received 6 August 2014; Revised 19 September 2014; Accepted 2 October 2014

Keywords

anorexia nervosa; treatment

*Correspondence

Walter H. Kaye, MD, Professor of Psychiatry, Director, UCSD Eating Disorder Research and Treatment Program, Department of Psychiatry, University of California San Diego, Chancellor Park, 4510 Executive Dr, Suite 315, San Diego, CA 92121, USA. Cell: 858 205 7293; Office: 858 534-3951; Fax: 858 534 6727. <http://eatingdisorders.ucsd.edu>

Email: wkaye@ucsd.edu; whkaye@gmail.com

Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/erv.2330

Introduction

Anorexia nervosa (AN) typically affects adolescent girls at onset and is characterized by restricted eating, emaciation and distorted body image. Approximately 50% of individuals with AN develop a chronic, relapsing course that characterizes severe and enduring AN (SE-AN; defined as having a mean illness duration of 5 or more years) (Hay, Touyz, & Sud, 2012; Keel, Mitchell, Miller, Davis, & Crow, 1999; Klein & Walsh, 2003; Touyz et al., 2013). To date, there is no proven psychological treatment or United States Food and Drug Administration approved medication for adults with SE-AN that reverses symptoms (Bulik, Berkman, Brownley, Sedway, & Lohr, 2007; Jimerson, Wolfe, Brotman, & Metzger, 1996; NICE, 2004; Rigaud, Pennacchio, Bizeul, Reveillard, & Vergès, 2011; Watson & Bulik, 2012). Consequently, adults with SE-AN have substantial and costly medical morbidity (McKenzie & Joyce, 1992) and the highest mortality rate of any psychiatric disorder (Papadopoulos, Ekblom, Brandt, & Ekselius, 2009). Moreover, adults with SE-AN have high rates of disability and tend to be a significant burden to carers (CA) and healthcare funders (Striegel-Moore et al., 2008; Touyz et al., 2013; Treasure et al., 2001). This underscores the critical need, both clinically and as a public health initiative, to improve treatment of SE-AN

given the lack of substantial progress the field has made in developing interventions that effectively achieve weight restoration and remission of symptoms (Hay et al., 2012; Touyz et al., 2013).

The emergence of neurobiological models of eating disorders (ED) supported by neuroscience data suggest that in order to develop effective treatments for AN, a paradigm shift is necessary and 'treatment of ED cannot remain "brainless"' (Schmidt & Campbell, 2013). The lack of a mechanistic understanding of AN has thwarted efforts to develop evidence-based interventions. Recent scientific advances reveal a neurobiologically based AN temperament characterized by anxiety, reward insensitivity, altered interoceptive awareness and cognitive inflexibility and rigidity (Anderluh, Tchanturia, Rabe-Hesketh, & Treasure, 2003; Cassin & von Ranson, 2005; Fassino, Piero, Gramaglia, & Abbate-Daga, 2004; Harrison, O'Brien, Lopez, & Treasure, 2010; Kaye et al., 2004; Lilienfeld, 2011; Lilienfeld, Wonderlich, Riso, Crosby, & Mitchell, 2006; Wagner et al., 2006). These temperament and personality traits, which are related to neural circuit function, are important in the development and maintenance of the disorder (Kaye & Bailer, 2011; Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013). In addition to predating the disease, these traits often persist to a mild to modest degree after recovery (Anderluh et al., 2003; Cassin & von Ranson, 2005; Kaye et al., 2004; Lilienfeld, 2011;

Wagner et al., 2006). This personality and behaviour profile may provide a framework to guide the development of interventions designed to address symptoms specific to AN. We expect that treatments that target these neurobiological mechanisms will be more effective at reducing clinical symptoms than existing treatments.

This paper presents a novel behavioural treatment approach composed of intervention strategies targeting these neurobiologically defined core symptoms underlying AN. This treatment approach is consistent with a recent NIMH initiative (RFA-MH-15-300 Exploratory Clinical Trials of Novel Interventions for Mental Disorders) that mandates that future treatment trials follow an experimental medicine approach in which treatments must identify a target or mediator that the intervention affects to influence symptoms. We describe the development of a temperament-based treatment for AN (TBT-AN) on the basis of empirically supported models explaining underlying neurobiological mechanisms that cause AN pathology and symptomatology. To do so, we first describe temperament constructs targeted by TBT-AN to affect clinical outcome by taking the following into consideration: (i) the underlying neurobiological mechanisms; (ii) an understanding of how these mechanisms are expressed through behaviour and personality; and (iii) their contribution to specific AN symptomatology. We then discuss the overarching treatment approach that integrates the development of AN-focused constructive coping strategies with CA support and CA-focused temperament management strategies. We propose a framework for delivering treatment, offer examples of targeted treatment strategies that adhere to the proposed treatment framework and present preliminary data on this treatment approach in the Supporting Information.

Neurobiological traits and temperament constructs targeted by temperament-based treatment for anorexia nervosa

Anxiety

Individuals with AN have exaggerated anxiety related to food and eating (Steinglass, Walsh, & Stern, 2006), elevated intolerance of uncertainty (IU) (Frank, Roblek, et al., 2012) and exaggerated harm avoidance (HA), a multifaceted temperament trait that contains elements of anxiety, inhibition and inflexibility (Cassin & von Ranson, 2005; Klump et al., 2004; Lilienfeld, 2011; Wagner et al., 2006). Individuals with AN have increased frequency of comorbid anxiety disorders with lifetime prevalence rates of up to 50% (Raney et al., 2008).

Neurobiological mechanisms

As discussed in recent reviews (Kaye et al., 2013), recent research (Bailer, Frank, et al., 2012; Bailer et al., 2005; Frank et al., 2005) implicates anxiety in AN with altered function of executive dorsal caudate (DC) and limbic regions, including altered dopamine (DA) and serotonin (5-HT) function. A study (Bailer, Narendran, et al., 2012) using positron emission tomography [¹¹C]raclopride binding with amphetamine to assess endogenous DA production found that DA release in the DC was associated with increased anxiety in recovered AN, in contrast to the normative experience of euphoria in response to limbic DA release

(Brauer & de Wit, 1996; Gabbay, 2003). That is, DA release associated with usually pleasurable events (such as eating) may be experienced as anxiogenic in AN. Animal studies (Eagle et al., 2011; Simon et al., 2011) confirm that risk avoidance and inhibition correlate with DA function in the DC and related regions, providing evidence that such neural processes contribute to anxiety and avoidant behaviours in AN. Because endogenous DA release occurs both in response to the delivery of a stimulus, and also in anticipation of upcoming stimuli, these processes may contribute to aversive anticipatory states. Imaging data support the contention that individuals with AN have an exaggerated anticipatory response to interoceptive cues for food and pain that is anxious and aversive. In addition, there is diminished insula and striatal response to receipt of food (Cowdrey, Park, Harmer, & McCabe, 2011; Frank, Reynolds, et al., 2012; Oberndorfer, Simmons, et al., 2013; Strigo et al., 2013; Vocks, Herpertz, Rosenberger, Senf, & Gizewski, 2011; Wagner et al., 2008). This suggests significant sensitivity to anticipation that likely contributes to their ability to restrict food.

Behavioural expression

Exaggerated levels of anticipatory anxiety, characterized by excessive concern and worry over upcoming events, may underlie the commonly noted behavioural tendencies of individuals with AN to be excessively inhibited and risk avoidant. Avoidance behaviours may be a method for reducing anxious feelings. Consistent with these findings, individuals with AN also exhibit high levels of IU (Frank, Roblek, et al., 2012). This trait has been heavily implicated in the aetiology and maintenance of anxiety disorders (Anderson et al., 2012; Gentes & Ruscio, 2011). Individuals who score high in IU demonstrate excessive worry prior to engaging in a task, leading to difficulty in decision-making, slower reaction times and avoidance behaviours in response to ambiguous tasks (Ladouceur, Gosselin, & Dugas, 2000; Ladouceur, Talbot, & Dugas, 1997). Such behaviours (e.g. anticipatory anxiety, difficulty in decision-making and avoidance) have been commonly noted in AN related to eating, implicating IU as an important factor in eating pathology characterizing AN.

Contribution to anorexia nervosa symptomatology

If individuals with AN experience endogenous DA release as anxiogenic, rather than hedonic, it may explain avoidance of food and eating. That is because food refusal may be an effective means of diminishing such anxious feelings. Consistent with these findings, individuals with AN have been shown to experience elevated levels of anxiety before engaging in a meal. Furthermore, they report a degradation in mood and physical state following food consumption (Kaye, Strober, & Klump, 2003; Steinglass et al., 2010). Thus, restriction is likely an inhibitory response resulting from aversive anticipatory states, which is pursued in an effort to avoid the expected negative consequences of eating (Steinglass et al., 2010). Imaging data showing an exaggerated anticipatory response to food cues that is anxious and aversive in AN further support the notion that anticipatory anxiety contributes to restrictive eating (Cowdrey et al., 2011; Frank, Reynolds, et al., 2012; Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013; Oberndorfer, Frank, et al., 2013; Oberndorfer, Simmons, et al., 2013). Moreover, elevated anxiety and HA not only maintain

ED symptoms but may also predict poor outcome (Bloss et al., 2011; Bulik, Sullivan, Fear, & Pickering, 2000; Crane, Roberts, & Treasure, 2007; Kaye et al., 2004; Klump et al., 2004; Lock, Agras, Bryson, & Kraemer, 2005), suggesting that a treatment designed to reduce or manage HA/anxiety may improve outcome. In fact, a recent food exposure and response prevention open trial and randomized control trial showed reduction in anxiety was associated with increased caloric intake in a post-treatment laboratory meal. Treatment did not increase caloric intake in the open trial (Steinglass et al., 2012), but it did in the randomized control trial (Steinglass et al., 2014), indicating the potential relevance of pre-meal anxiety as a treatment target.

Reward insensitivity

Neurobiological mechanisms

Adults with AN have high punishment sensitivity and low reward reactivity during both the ill and recovered states (Harrison et al., 2010). Our imaging data suggest that altered reward sensitivity (Bischoff-Grethe et al., 2013; Wagner et al., 2007; Wierenga et al., In Press) and increased behavioural inhibition in AN (Oberndorfer, Simmons, et al., 2013; Wierenga et al., 2014) are related to underactive limbic (reward) circuitry and overactive executive (inhibition) neural circuitry (Dietz, 1998). For example, adults recovered from AN (Wagner et al., 2007) exhibit a failure to differentiate feedback valence in ventral striatal regions and an exaggerated response to both reward and punishment in dorsal executive regions in a simple monetary choice feedback task (Delgado, Nystrom, Fissel, Noll, & Fiez, 2000) relative to healthy peers. Ill adolescents with AN also exhibited an exaggerated response to losses compared with wins in posterior executive and sensorimotor striatal regions (Bischoff-Grethe et al., 2013).

Behavioural expression

Behavioural studies show that underweight ill adults with AN have an enhanced ability to delay reward compared with healthy peers (Steinglass et al., 2012). Adults with AN may be unable to appreciate rewarding stimuli (Bischoff-Grethe et al., 2013; Wierenga et al., Under Review) because they are preoccupied with consequences. Conversely, individuals with AN have been shown to be hypersensitized to criticism, tending to perceive their actions as incorrect or flawed. The disproportional bias towards failure/punishment contributes to a tendency towards avoidance *versus* approach behaviour. Thus, an altered balance between reward and inhibition appears to be a hallmark of AN.

Contribution to anorexia nervosa symptomatology

Clinically, this insensitivity to reward and increased sensitivity to punishment is likely to interfere with motivation or ability to learn from experience. That is, ill individuals with AN have difficulty appropriately proportioning reward and punishment. The overvaluation of potential negative consequences in comparison with potential reward likely contributes to the lack of motivation for recovery, a unique feature of this disease. Perseverative concerns over the consequences of recovery, including weight gain, appear to overshadow even the most salient reasons to recover (e.g. return to school or ability to participate in physical activity). The neurobiologically driven reward–punishment imbalance

likely explains the relentless pursuit of emaciation at the expense of other life activities, where consequences of recovery such as weight gain and other associated effects appear to be more salient than natural reinforcers such as the return to normal life activities. With respect to food restriction, the ability to delay reward and overvaluation of consequences may help to maintain persistent food restriction (Steinglass et al., 2012).

Interoceptive awareness

Neurobiological mechanisms

Altered sensitivity for one's internal bodily signals ('interoceptive awareness') might be a precipitating and reinforcing factor in AN (Fassino et al., 2004; Lilenfeld et al., 2006). The anterior insula is involved in integrating interoceptive information (e.g. internal physical sensations including taste, pain and hunger) with motivational and emotional processes, supporting feeling states and giving rise to conscious visceral perception of homeostatic states (Craig, 2004, 2009). Altered insula activity found in adults with AN (Oberndorfer, Frank, et al., 2013; Wagner et al., 2008) supports the notion that they might suffer from a fundamentally and physiologically altered sense of self and that brain circuits may misperceive signals regarding hunger and satiety (Pollatos et al., 2008).

Behavioural expression

Adults with AN endorse poor interoceptive awareness on self-report measures and behaviorally demonstrate impaired ability to detect their own heartbeats (Pollatos et al., 2008). In addition to difficulty in perceiving physical states, individuals with AN have also demonstrated deficits recognizing and regulating emotional experiences (Harrison et al., 2010). Accordingly, alexithymia (i.e. difficulty identifying emotions) is a commonly noted feature of individuals with AN. Individuals with AN also demonstrate difficulty tolerating and regulating emotional experiences, suggesting that in addition to recognition difficulties, interoceptive deficits may also arise from reduced ability to tolerate negative internal states (Merwin et al., 2013).

Contribution to anorexia nervosa symptomatology

Disturbed interoceptive awareness of satiety or hunger, or even a primary alteration of gustatory processes, could play a role in assessing body states and responding to hunger cues. Indeed, many of the symptoms of AN (Nunn, Frampton, Gordon, & Lask, 2008), such as distorted body image, lack of recognition of the symptoms of malnutrition (e.g. a failure to appropriately respond to hunger) and diminished motivation to change, could be related to disturbed interoceptive awareness. Such disturbances could also be tied to the preponderance of alexithymia in AN (Sexton, Sunday, Hurt, & Halmi, 1998; Strigo et al., 2013).

Summary

These three temperament traits are interrelated. Together, they contribute to appetite dysregulation and pathological eating in AN, suggesting treatments that target these constructs may see improved clinical effects. Arguably, the most critical issue in treating individuals with AN is addressing food refusal and pursuit of emaciation. In this paper, we will describe the initial

development of a new treatment approach designed to reduce dietary restriction by targeting anticipatory anxiety, reward insensitivity and interoceptive awareness to change mealtime behaviour in AN.

Temperament-based treatment for anorexia nervosa

Behavioural strategies

The primary goal of this treatment is not to attempt to change temperament, which is a relatively fixed set of traits. Rather, we seek to teach AN and their CA to recognize temperament patterns and develop strategies for the following goals: (i) to build external structures that promote pro-recovery behaviours and (ii) to learn coping skills to manage their temperament. Thus, we take a two-pronged approach to modify temperamentally driven behaviour via the following: (i) constructive coping strategies directed at adults with AN and (ii) management strategies directed at their CA.

Focus on development of constructive coping strategies for individuals with anorexia nervosa

Studies indicate that biological and personality factors that contribute to the development of AN persist after recovery (Anderluh et al., 2003; Cassin & von Ranson, 2005; Kaye et al., 2004; Lilenfeld, 2011; Wagner et al., 2006). This may suggest that individuals with AN recover, in part, by developing constructive, rather than destructive, ways to use their temperament. Because there is a very limited literature, clinical observation provides important clues that need to be empirically tested. For example, recovered adults with AN have told us that they tend to eat the same food and amounts at the same time every day because they have difficulty with food choices (which increases anxiety) and gauging hunger and satiety. Thus, adults with AN may learn to manage temperament successfully by reducing choice (uncertainty) and using their tendency to stick to rules and structure in a way that will ensure sufficient daily caloric intake. The TBT-AN approach acknowledges difficulty with tolerating uncertainty and novelty and a tendency towards rigidity by formulating a treatment plan that takes into account the effect of these traits on behaviour. By doing so, adults with AN work *with* their temperament instead of *against* it, to maximize the probability of compliance and allow for symptoms to be targeted successfully.

Engage the support of carers

Treatments for adolescent AN are more promising than for adults, and evidence suggests that family involvement is critical to treatment success in adolescent AN. Considerable data show that family-based therapy (FBT), which focuses primarily on weight restoration by empowering the family to take control of refeeding the child, is the most effective approach in treating adolescents with AN (Lock & le Grange, 2005). Implementing standard FBT in adults is difficult because parental authority is diminished. However, there is growing evidence that CA involvement in the treatment of SE-AN may be critical and should be a target of treatment (Bulik, Baucom, Kirby, & Pisetsky, 2011; Treasure et al., 2008), although there are no data to date examining whether improving AN/CA interpersonal factors improves patient outcomes (Goddard et al., 2013). In a study evaluating

adult patients' perceptions of factors contributing to recovery, 'supportive relationships' was the most frequently cited catalyst for recovery (Tozzi, Sullivan, Fear, McKenzie, & Bulik, 2003). A new couples approach to treat AN (uniting couples in the treatment of AN), on the basis of cognitive-behavioural couple therapy, also shows promise to improve communication and reduce marital distress, but data showing clinical outcomes are needed (Bulik, Baucom, & Kirby, 2012; Bulik et al., 2011).

Few interventions for adults have leveraged the support of CA to become directly involved in managing the specific behavioural disturbances and appetite dysregulation of SE-AN, despite the fact that dietary restriction is likely the most challenging and pervasive symptom of the disorder. Our treatment approach addresses this critical need by developing a treatment designed to teach CA the skills needed to target and manage temperament underlying core SE-AN pathology to help their loved ones eat. For example, this treatment is intended to help CA to understand that the biological traits of AN, such as being oversensitive to errors, punishment, change and uncertainty, contribute to overwhelming anxiety. Many CA need to develop empathy and strategies to work in constructive ways to improve mealtime behaviour. Distressed, critical or hostile relationships elevate the risk for illness persistence and relapse in many psychiatric disorders (Hooley & Hiller, 2001), and recovered patients with AN identify a supportive relationship as a key driving force in recovery (Bulik et al., 2012; Maxwell et al., 2011; Tozzi et al., 2003).

This novel treatment will enlist CA support to implement a structure of strategies and expectations to manage AN temperament. Modifications are particularly focused on reducing dietary restriction and developing skills to shape behaviour around meals. The first goal is to adapt an adolescent FBT intervention by making it more developmentally appropriate for adults with AN who have a CA involved. We maintain the FBT emphasis on weight restoration through family meals but recognize that not all strategies that work in adolescents are likely to work in adults because adults have more autonomy and are likely to be ambivalent about change or complying with the CA. An example of an age-appropriate modified approach is to involve the patient and CA in a collaborative process to devise a behavioural contract. This serves as a motivation system that outlines the following: (i) specific guidelines for recovery and associated target behaviours (e.g. number of meals required and meal times); (ii) contingencies for target behaviours (e.g. negative consequence for food restriction and positive consequence for completing meal); and (iii) assignment of CA to a specific role in recovery by outlining how they can support and enforce target behaviours (e.g. CA responsible for preparing meals and presenting supplement drink if meal is not eaten).

The second goal is to provide CA with the means to manage AN temperament and interact with AN in a way that reinforces recovery-oriented behaviours, reduces stress and conflict and improves function. This is accomplished through neurobiology psychoeducation, skills training and practice (Table S1). CA and patients often lack insight into the aetiology of AN symptoms. For example, CA may interpret symptoms as manipulative, which negatively impacts their relationship with the individual with AN. CA can learn strategies to deliver a realistic perspective and avoid frustration or burnout. Didactic sessions and experiential exercises

are used to illustrate the powerful neurobiological underpinnings of AN symptoms that make engaging in recovery-oriented behaviours difficult. These strategies are designed to provide a common language to discuss the disorder, increase empathy, neutralize patient and CA reactions by depersonalizing symptoms and decreasing blame and reduce negative emotionality (guilt, shame and resentment) to facilitate collaboration and CA support. This educational foundation positions CA to be receptive to adapting their approach and learning new skills to be effective in supporting the patient and managing symptoms. For example, CA are taught to moderate expressed emotion, such as critical responses, which may lead to increased animosity and reduced motivation in the patient (Sepulveda, Lopez, Todd, Whitake, & Treasure, 2008), in exchange for neutral responses that refer to the contingencies stipulated in the behavioural contract. Other examples include the following: (i) implementing a pre-meal routine to distract patients away from negative internal states associated with anticipating the effects of eating and reducing anxiety surrounding exposure to food; (ii) increasing predictability and certainty around food whilst maintaining caloric sufficiency to reduce anxiety and increase weight (e.g. fixed meal plan with increased calories over time); and (iii) meal coaching to redirect the patient when anxiety or obsessions occur to reduce food refusal and improve family function. The treatment format and example strategies are described in more detail in the Supporting Information.

Conclusion

Recent neurobiological models of AN suggest that temperament characteristics contribute to the development and maintenance of the illness. Using insights into the pathophysiology of AN to inform the selection of mechanisms to be targeted in treatment will likely improve treatment efficacy. As such, TBT-AN targets key neurobiological mechanisms that contribute to AN symptomatology, such as anxiety, altered reward sensitivity and interoceptive deficits to reduce disordered eating. TBT-AN is designed for individuals with SE-AN and their CA. Treatment is focused both on building awareness of temperament tendencies and teaching constructive ways to make use of and manage associated traits to target AN behaviour, rather than attempting to change or work against temperament. Targeting restrictive eating in AN from a neurobiological perspective allows us to determine whether TBT-AN engages the identified targets and whether target engagement contributes to improved clinical outcome. Preliminary data collected on these approaches (Supporting Information) suggest that they are well accepted by individuals with AN and CA and hold promise for improving symptoms of AN.

Acknowledgements

Support was provided by the Global Foundation for Eating Disorders (GFED), the Price Foundation, the Wismer/Davis Foundations, and the Peterson Family.

REFERENCES

- Anderlüh, M. B., Tchanturia, K., Rabe-Hesketh, S., & Treasure, J. (2003). Childhood obsessive-compulsive personality traits in adult women with eating disorders: Defining a broader eating disorder phenotype. *American Journal of Psychiatry*, *160*, 242–247. doi: 10.1176/appi.ajp.160.2.242
- Anderson, K., Dugas, M., Koerner, N., Radomsky, A., Savard, P., & Turcotte, J. (2012). Interpretive style and intolerance of uncertainty in individuals with anxiety disorders: A focus on generalized anxiety disorder. *Journal of Anxiety Disorders*, *26*, 823–832. doi: 10.1016/j.janxdis.2012.08.003
- Bailer, U. F., Frank, G. K., Henry, S. E., Price, J. C., Meltzer, C. C., Weissfeld, L., et al. (2005). Altered brain serotonin 5-HT_{1A} receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [¹¹C]WAY100635. *Archives of General Psychiatry*, *62*, 1032–1041. doi: 10.1001/archpsyc.62.9.1032
- Bailer, U., Frank, G., Price, J., Meltzer, C., Becker, C., Mathis, C., et al. (2012). Interaction between serotonin transporter and dopamine D2/D3 receptor radioligand measures is associated with harm avoidant symptoms in anorexia and bulimia nervosa. *Journal of Psychiatry & Neuroscience*, *211*, 160–168. doi: 10.1016/j.psychres.2012.06.010
- Bailer, U., Narendran, R., Frankle, W., Himes, M., Duvvuri, V., Mathis, C., et al. (2012). Amphetamine induced dopamine release increases anxiety in individuals recovered from anorexia nervosa. *The International Journal of Eating Disorders*, *45*, 263–271. doi: 10.1002/eat.20937
- Bischoff-Grethe, A., McCurdy, D., Grenesko-Stevens, E., Irvine, L., Wagner, A., Yau W. Y., et al. (2013). Altered brain response to reward and punishment in adolescents with anorexia nervosa. *Psychiatry Research*, *214*, 331–340. doi: 10.1016/j.psychres.2013.07.004
- Bloss, C., Berrettini, W., Bergen, A., Magistretti, P., Duvvuri, V., Strober, M., et al. (2011). Genetic association of recovery from eating disorders: The role of GABA receptor SNPs. *Neuropsychopharmacology*, *36*, 2222–2232. doi: 10.1038/npp.2011.108
- Brauer, L., & de Wit, H. (1996). Subjective responses to D-amphetamine alone and after pimoziide pretreatment in normal, healthy volunteers. *Biological Psychology*, *39*, 26–31. doi: 10.1016/0006-3223(95)00110-7
- Bulik, C., Baucom, D., & Kirby, J. (2012). Treating anorexia nervosa in the couple context. *Journal of Cognitive Psychotherapy*, *26*, 19–33. doi: 10.1891/0889-8391.26.1.19
- Bulik, C., Baucom, D., Kirby, J., & Pisetsky, E. (2011). Uniting couples (in the treatment of) anorexia nervosa (UCAN). *The International Journal of Eating Disorders*, *44*, 19–28. doi: 10.1002/eat.20790
- Bulik, C. M., Berkman, N. D., Brownley, K. A., Sedway, J. A., & Lohr, K. N. (2007). Anorexia nervosa treatment: A systematic review of randomized controlled trials. *The International Journal of Eating Disorders*, *40*, 310–320. doi: 10.1002/eat.20367
- Bulik, C. M., Sullivan, P. F., Fear, J. L., & Pickering, A. (2000). Outcome of anorexia nervosa: Eating attitudes, personality, and parental bonding. *The International Journal of Eating Disorders*, *28*, 139–147. doi: 10.1091/mbc.E09-06-0532
- Cassin, S., & von Ranson, K. (2005). Personality and eating disorders: A decade in review. *Clinical Psychology Review*, *25*, 895–916. doi: 10.1016/j.cpr.2005.04.012
- Cowdrey, F., Park, R., Harmer, C., & McCabe, C. (2011). Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa. *Biological Psychology*, *70*, 736–743. doi: 10.1016/j.biopsycho.2011.05.028
- Craig, A. (2004). Human feelings: Why are some more aware than others? *Trends in Cognitive Sciences*, *8*, 239–241. doi: 10.1016/j.tics.2004.04.004
- Craig, A. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*, 59–70. doi: 10.1038/nrn2555
- Crane, A., Roberts, M., & Treasure, J. (2007). Are obsessive-compulsive personality traits associated with a poor outcome in anorexia nervosa? A systematic review of randomized controlled trials and naturalistic outcome studies. *The International Journal of Eating Disorders*, *40*, 581–588. doi: 10.1002/eat.20419
- Delgado, M., Nystrom, L., Fissel, C., Noll, D., & Fiez, J. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology*, *84*, 3072–3077.
- Dietz, W. (1998). Health consequences of obesity in youth: Childhood predictors of adult disease. *Pediatrics*, *101*, 518–525. doi: ISSN: 0031-4005. Online ISSN: 1098-4275.
- Eagle, D., Wong, J., Allan, M., Mar, A., Theobald, D., & Robbins, T. (2011). Contrasting roles for dopamine D1 and D2 receptor subtypes in the dorsomedial striatum but not the nucleus accumbens core during behavioral inhibition in the stop-signal task in rats. *Journal of Neuroscience*, *31*, 7349–7356. doi: 10.1523/JNEUROSCI.6182-10.2011
- Fassino, S., Piero, A., Gramaglia, C., & Abbate-Daga, G. (2004). Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and obesity. *Psychopathology*, *37*, 168–174.
- Frank, G., Bailer, U. F., Henry, S., 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*, 908–912. doi: 10.1016/j.biopsycho.2005.05.003
- Frank, G., Reynolds, J., Shott, M., Jappe, L., Yang, T., Tregellas, J., et al. (2012). Anorexia nervosa and obesity are associated with opposite brain reward response. *Neuropsychopharmacology*, *37*, 2031–2046. doi: 10.1038/npp.2012.51

- Frank, G., Roblek, T., Shott, M., Jappe, L., Rollin, M., Hagman, J., & Pryor, T. (2012). Heightened fear of uncertainty in anorexia and bulimia nervosa. *The International Journal of Eating Disorders, 45*, 227–232. doi: 10.1002/eat.20929
- Gabbay, F. (2003). Variations in affect following amphetamine and placebo: Markers of stimulant drug preference. *Experimental and Clinical Psychopharmacology, 11*, 91–101. doi: 10.1037/1064-1297.11.1.91
- Gentes, E., & Ruscio, A. (2011). A meta-analysis of the relation of intolerance of uncertainty to symptoms of generalized anxiety disorder, major depressive disorder, and obsessive-compulsive disorder. *Clinical Psychology Review, 31*, 823–933. doi: 10.1016/j.cpr.2011.05.001
- Goddard, E., Salerno, L., Hibbs, R., Raenker, S., Naumann, U., Arcelus, J., et al. (2013). Empirical examination of the interpersonal maintenance model of anorexia nervosa. *The International Journal of Eating Disorders, 46*, 867–874. doi: 10.1002/eat.22172
- Harrison, A., O'Brien, N., Lopez, C., & Treasure, J. (2010). Sensitivity to reward and punishment in eating disorders. *Psychology: Research, 177*, 1–11.
- Hay, P., Touyz, S., & Sud, R. (2012). Treatment for severe and enduring anorexia nervosa: A review. *The Australian and New Zealand Journal of Psychiatry, 46*, 1136–1144. doi: 10.1177/0004867412450469
- Hooley, J., & Hiller, J. (2001). Family relationships and major mental disorder: Risk factors and preventive strategies. In B. R. Sarason, S. Duck (Eds.), *Personal relationships: Implications for clinical and community psychology*. New York: Wiley, pp. 61–87.
- Jimerson, D. C., Wolfe, B. E., Brotman, A. W., & Metzger, E. D. (1996). Medications in the treatment of eating disorders. *The Psychiatric Clinics of North America, 19*, 739–754.
- Kaye, W., & Bailer, U. (2011). Understanding the neural circuitry of appetitive regulation in eating disorders. *Biological Psychology, 70*, 704–705.
- Kaye, W., Bulik, C., Thornton, L., Barbarich, N., Masters, K., Fichter, M., et al. (2004). Comorbidity of anxiety disorders with anorexia and bulimia nervosa. *The American Journal of Psychiatry, 161*, 2215–2221. doi: 10.1176/appi.ajp.161.12.2215
- Kaye, W., Strober, M., & Klump, K. L. (2003). Neurobiology of eating disorders. In A. Martin, L. Scahill, D. S. Charney, & J. F. Leckman (Eds.), *Pediatric psychopharmacology, principles & practice*. New York: Oxford University Press, pp. 224–237.
- Kaye, W., Wierenga, C., Bailer, U., Simmons, A., & Bischoff-Grethe, A. (2013). Nothing tastes as good as skinny feels: The neurobiology of anorexia nervosa. *Trends in Neuroscience: Special Issue on Neural Control of Appetite, 36*, 110–120. doi: 10.1016/j.tins.2013.01.003
- Kaye, W., Wierenga, C., Bailer, U., Simmons, A., Wagner, A., & Bischoff-Grethe, A. (2013). Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? *Biological Psychiatry, 73*, 836–842. doi: 10.1016/j.biopsych.2013.01.002
- Keel, P. K., Mitchell, J. E., Miller, K. B., Davis, T. L., & Crow, S. J. (1999). Long-term outcome of bulimia nervosa. *Archives of General Psychiatry, 56*, 63–69. doi: 10.1001/archpsyc.56.1.63
- Klein, D., & Walsh, B. (2003). Eating disorders. *International Review of Psychiatry, 15*, 205–216. doi: 10.1080/0954026031000136839
- Klump, K., Strober, M., Johnson, C., Thornton, L., Bulik, C., Devlin, B., et al. (2004). Personality characteristics of women before and after recovery from an eating disorder. *Psychiatric Medicine, 34*, 1407–1418. doi: 10.1017/S0033291704002442
- Ladouceur, R., & Gosselin, P., Dugas, M. J. (2000). Experimental manipulation of intolerance of uncertainty: A study of a theoretical model of worry. *Behaviour Research and Therapy, 38*(9), 933–941. doi: 10.1016/S0005-7967(99)00133-3
- Ladouceur, R., Talbot, F., & Dugas, M. (1997). Behavioral expressions of intolerance of uncertainty in worry experimental findings. *Behavior Modification, 21*, 355–371.
- Lilenfeld, L. (2011). Personality and temperament in eating disorders. In W. H. Kaye, R. Adan (Eds.), *Current topics in behavioral neurosciences*, vol. 6. New York: Springer; 3–9. ISBN: 9783642151309.
- Lilenfeld, L., Wonderlich, S., Riso, L. P., Crosby, R., & Mitchell, J. (2006). Eating disorders and personality: A methodological and empirical review. *Clinical Psychology Review, 26*, 299–320. doi: 10.1016/j.cpr.2005.10.003
- Lock, J., Agras, W., Bryson, S., & Kraemer, H. (2005). A comparison of short- and long-term family therapy for adolescent anorexia nervosa. *American Academy of Child and Adolescent Psychiatry, 44*, 632–639. doi: 10.1097/01.chi.0000161647.82775.0a
- Lock, J., & le Grange, D. (2005). Family-based treatment of eating disorders. *The International Journal of Eating Disorders, 37*, S64–S67. doi: 10.1002/eat.20122
- Maxwell, M., Thornton, L., Root, T. L., Pinheiro, A., Strober, M., Brandt, H., et al. (2011). Life beyond the eating disorder: education, relationships, and reproduction. *The International Journal of Eating Disorders, 44*, 225–232. doi: 10.1002/eat.20804
- McKenzie, J. M., & Joyce, P. R. (1992). Hospitalization for anorexia nervosa. *The International Journal of Eating Disorders, 11*, 235–241. doi: 10.1002/1098-108X(199204)11:3<235::AID-EAT2260110306>3.0.CO;2-T
- Merwin, R., Moskovich, A., Wagner, H., Ritschel, L., Craighead, L., & Zucker, N. (2013). Emotion regulation difficulties in anorexia nervosa: Relationship to self-perceived sensory sensitivity. *Cognition & Emotion, 27*, 441–453. doi: 10.1080/02699931.2012.719003
- NICE. (2004). *Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders (Clinical Guideline 9)*. <http://www.nice.org.uk>. London: National Collaborating Centre for Medical Health.
- Nunn, K., Frampton, I., Gordon, I., & Lask, B. (2008). The fault is not in her parents but in her insula—A neurobiological hypothesis of anorexia nervosa. *European Eating Disorders Review, 16*, 355–360. doi: 10.1002/erv.890
- Oberndorfer, T., Frank, G., Fudge, J., Simmons, A., Paulus, M., Wagner, A., et al. (2013). Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. *The American Journal of Psychiatry, 170*, 1143–1151. doi: 10.1176/appi.ajp.2013.11111745
- Oberndorfer, T., Simmons, A., McCurdy, D., Strigo, I., Matthews, S., Yang, T., et al. (2013). Greater anterior insula activation during anticipation of food images in women recovered from anorexia nervosa. *Psychology: Research, 214*, 132–141. doi: 10.1016/j.psychres.2013.06.010
- Papadopoulos, F., Ekblom, A., Brandt, L., & Ekselius, L. (2009). Excess mortality, causes of death and prognostic factors in anorexia nervosa. *The British Journal of Psychiatry, 194*, 10–17. doi: 10.1192/bjp.bp.108.054742
- Pollatos, O., Kurz, A.-L., Albrecht, J., Schreder, T., Kleemann, A., Schopf, V., et al. (2008). Reduced perception of bodily signals in anorexia nervosa. *Eating Behaviors, 9*, 381–388. doi: 10.1016/j.eatbeh.2008.02.001
- Raney, T., Thornton, L., Brandt, H., Crawford, S., Fichter, M., Halmi, K., et al. (2008). Influence of overanxious disorder of childhood on the expression of anorexia nervosa. *The International Journal of Eating Disorders, 41*, 326–332. doi: 10.1002/eat.20508
- Rigaud, D., Pennacchio, H., Bizeul, C., Reveillard, V., & Vergès, B. (2011). Outcome in AN adult patients: A 13-year follow-up in 484 patients. *Diabetes and Metabolism, 37*, 305–311. doi: 10.1016/j.diabet.2010.11.020
- Schmidt, U., & Campbell, I. (2013). Treatment of eating disorders cannot remain 'brainless': The case for brain-directed treatments. *European Eating Disorders Review, 21*, 425–427. doi: 10.1002/erv.2257
- Sepulveda, A., Lopez, C., Todd, G., Whitake, W., & Treasure, J. (2008). An examination of the impact of 'the Maudsley eating disorder collaborative care skills workshops' on the well being of carers: A pilot study. *Social Psychiatry and Psychiatric Epidemiology, 43*, 584–591. doi: 10.1007/s00127-008-0336-y
- Sexton, M., Sunday, S., Hurt, S., & Halmi, K. (1998). The relationship between alexithymia, depression, and axis II psychopathology in eating disorder inpatients. *The International Journal of Eating Disorders, 23*, 277–286. doi: 10.1002/(SICI)1098-108X(199804)23:3<277::AID-EAT5>3.0.CO;2-G
- Simon, N., Montgomery, K., Beas, B., Mitchell, M., LaSarge, C., Mendez, L., et al. (2011). Dopaminergic modulation of risky decision-making. *Journal of Neuroscience, 31*, 17460–17470. doi: 10.1523/JNEUROSCI.3772-11.2011
- Steinglass, J., Albano, A., Simpson, H., Carpenter, K., Schebendach, J., & Attia, E. (2012). Fear of food as a treatment target: Exposure and response prevention for anorexia nervosa in an open series. *The International Journal of Eating Disorders, 45*, 615–621. doi: 10.1002/eat.20936
- Steinglass, J., Albano, A., Simpson, H., Wang, Y., Zou, J., Attia, E., et al. (2014). Confronting fear using exposure and responses prevention for anorexia nervosa: A randomized controlled pilot study. *The International Journal of Eating Disorders, 47*, 174–180. doi: 10.1002/eat.22214
- Steinglass, J., Sysko, R., Mayer, L., Berner, L., Schebendach, J., Wang, Y., et al. (2010). Pre-meal anxiety and food intake in anorexia nervosa. *Appetite, 55*, 214–218. doi: 10.1016/j.appet.2010.05.090
- Steinglass, J. E., Walsh, B. T., & Stern, Y. (2006). Set shifting deficit in anorexia nervosa. *Journal of the International Neuropsychological Society, 12*, 431–435. <http://www.ncbi.nlm.nih.gov/pubmed/16903136>
- Striegel-Moore, R., DeBar, L., Wilson, G., Dickerson, J., Rosselli, F., Perrin, N., et al. (2008). Health services use in eating disorders. *Psychological Medicine, 38*, 465–474. doi: 10.1017/S0033291707001833
- Strigo, I., Matthews, S., Simmons, A., Oberndorfer, T., Reinhardt, L., Klabunde, M., et al. (2013). Altered insula activation during pain anticipation in individuals recovered from anorexia nervosa: Evidence of interoceptive dysregulation. *The International Journal of Eating Disorders, 46*, 23–33. doi: 10.1002/eat.22045
- Touyz, S., Le Grange, D., Lacey, H., Hay, P., Smith, R., Maguire, S., et al. (2013). Treating severe and enduring anorexia nervosa: A randomized controlled trial. *Psychological Medicine, 43*, 2501–2511. doi: 10.1017/S0033291713000949
- Tozzi, F., Sullivan, P., Fear, J., McKenzie, J., & Bulik, C. (2003). Causes and recovery in anorexia nervosa: The patient's perspective. *The International Journal of Eating Disorders, 33*, 143–154. doi: 10.1002/eat.10120
- Treasure, J., Murphy, T., Szmukler, G., Todd, G., Gavan, K., & Joyce, J. (2001). The experience of caregiving for severe mental illness: A comparison between anorexia nervosa and psychosis. *Social Psychiatry and Psychiatric Epidemiology, 36*, 343–347.
- Treasure, J., Sepulveda, A., MacDonald, P., Whitake, W., Lopez, C., Zabala, M., et al. (2008). Interpersonal maintaining factors in eating disorder: Skills sharing interventions for carers. *International Journal of Child and Adolescent Health, 1*, 331–338. ISSN: 01/2008; 4:1939-5930
- Vocks, S., Herpertz, S., Rosenberger, C., Senf, W., & Gizewski, E. (2011). Effects of gustatory stimulation on brain activity during hunger and satiety in females with restricting-type anorexia

- nervosa: An fMRI study. *Journal of Psychiatric Research*, 45, 395–403. doi: 10.1016/j.jpsychires.2010.07.012
- Wagner, A., Aizenstein, H., Frank, G. K., Figurski, J., May, J. C., Putnam, K., et al. (2008). Altered insula response to a taste stimulus in individuals recovered from restricting-type anorexia nervosa. *Neuropsychopharmacology*, 33, 513–523. doi: 10.1038/sj.npp.1301443
- Wagner, A., Aizenstein, H., Venkatraman, M., Fudge, J., May, J., Mazurkewicz, L., et al. (2007). Altered reward processing in women recovered from anorexia nervosa. *The American Journal of Psychiatry*, 164, 1842–1849. doi: 10.1176/appi.ajp.2007.07040575
- Wagner, A., Barbarich, N., Frank, G., Bailer, U., Weissfeld, L., Henry, S., et al. (2006). Personality traits after recovery from eating disorders: Do subtypes differ? *International Journal of Eating Disorders*, 39, 276–284. doi: 10.1002/eat.20251
- Watson, H., & Bulik, C. (2012). Update on the treatment of anorexia nervosa: review of clinical trials, practice guidelines and emerging interventions. *Psychological Medicine*, 43, 2477–2500. doi: 10.1017/S0033291712002620
- Wierenga, C., Bischoff, S., Melrose, J., Irvine, Z., Torres, L., Bailer, U., et al. (In Press). Hunger does not motivate reward in anorexia nervosa. *Biological Psychiatry*.
- Wierenga, C., Bischoff-Grethe, A., Melrose, J., Grenesko-Stevens, E., Irvine, Z., Wagner, A., et al. (2014). Altered BOLD response during inhibitory and error processing in adolescents with anorexia nervosa. *PLoS ONE*, 9, e92017. doi: 10.1371/journal.pone.0092017

Supporting information

Additional supporting information may be found in the online version of this article at publisher's web site.