Brief report

# *Neurobiologically informed treatment for adults with anorexia nervosa: a novel approach to a chronic disorder*

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*Anorexia nervosa (AN) is a severe and debilitating disorder with significant medical and psychological sequelae. To date, there are no effective treatments for adults, resulting in high rates of chronicity, morbidity, and mortality. Recent advances in brain imaging research have led to an improved understanding of etiology and specific neurobiological mechanisms underlying symptoms. Despite this, there are no treatments focused on targeting symptoms using this empirically supported mechanistic understanding of the illness. Updated treatment approaches focused on targeting neurobiological mechanisms underlying core AN symptomatology are necessary to improve treatment outcomes for this population. Neurobiologically Enhanced With Family Eating Disorder Trait Response Treatment (NEW FED TR) is a neurobiologically informed treatment targeting key temperament constructs associated with the illness through the delivery of psychoeducation and skills training to patients and nominated carers.*

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## Introduction

Anorexia nervosa (AN) is a pernicious psychiatric illness associated with significant medical risk[1] and a refractory course. Approximately 50% of individuals develop a chronic and relapsing illness course characterized by significant physical and psychological impairment.[2-6] Given the magnitude of associated medical and psychological sequelae and the risk for prolonged illness, the development of effective treatments is of critical importance. To date, there are no behavioral or psychiatric treatments that have been proven to reverse core symptoms,[7] and currently available treatments for AN adults have failed to demonstrate efficacy.[5,6,8-12] Consequently, AN is associated with costly medical morbidity and high mortality rates.[13-15] There is a critical need for continued research to address the dearth of efficacious treatments for this dangerous illness.

Several psychosocial, behavioral, and pharmacologic interventions have been investigated in adult AN[5,6,8-12]; however, evidence supporting currently available treat-

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ments is weak, and treatment effects, when found, are generally small.[12,16-22] For instance, controlled medication trials examining selective serotonin reuptake inhibitors,[23,24] tricyclic antidepressants,[25-27] and antipsychotic medication[28] tend to be conflicted and uncertain as to whether there are changes in AN symptoms over time. Yet, despite the absence of a strong evidence base for these psychotropic medications, more than 50% of those with AN report the use of medication.[29] With respect to behavioral treatments, some controlled trials indicate that long-term cognitive behavioral therapy may offer some efficacy in assisting with weight restoration,[30,31] although large-scale randomized trials suggest that specialist cognitive and psychodynamic treatments do not differ from treatment as usual in terms of weight restoration.[32] Furthermore, attrition rates are high and the majority of patients remain underweight upon completion of treatment.[33] A landmark study in 2002[34] illustrated that less than half of all those with AN recover. Relative to other psychiatric illnesses, advances in effective treatment approaches have been marginal and there are relatively few randomized controlled trials. The lack of response to currently available treatments suggests that new models of treatment are necessary, and improvements in methods for targeting core AN symptomatology are needed.

Despite the lack of advances in treatments for adult AN, a robust evidence base exists supporting family-based treatment (FBT) for adolescents with AN.[35-38] FBT is a manualized form of specific eating disorder-focused family therapy in which parents are enlisted as the primary agents of change to oversee their adolescents' recovery by ensuring appropriate food intake and other health-oriented behaviors associated with recovery. FBT demonstrates promising empirical evidence, in that up to 70% of patients are weight restored within a year of commencing treatment,[39] and up to 40% of patients report being remitted of cognitive symptoms within a year.[40]

To date, there are no published clinical trials examining the use of FBT in adults. A small case series applying a modification of FBT to adults demonstrated promising outcomes; however, the small sample consisted of young adults under the care of family members[41] FBT may be an appropriate fit for young adults, but because of its reliance on parental control as the primary agent of change, it is less suitable for older adults who are more autonomous and less likely to be under the direct care of family. As such, effective treatments for older individuals who tend to have a longer duration of illness and a greater level of severity continue to be lacking. In summary, treatments are gravely needed for this subpopulation of "severe and enduring" individuals given that chronicity contributes to a poorer prognosis and significant health concerns leading to morbidity and mortality.[2-6] Although the level of parental control prescribed in FBT is likely not well-suited for older adult individuals, elements of FBT should be considered for adult treatments, such as the encouragement of familial support and involvement, albeit in a more developmentally appropriate fashion.

## Using neurobiology to advance treatment

Despite the lack of gains in establishing effective clinical treatments for adult AN, there have been significant advances in our understanding of etiological influences associated with the illness. Genetic studies indicate that heritability accounts for approximately 50% to 80% of the risk of developing an eating disorder.[42] Recent imaging, neurocognitive, and behavioral studies reveal that AN individuals tend to have specific temperament and personality traits related to neural circuit function, which are heavily implicated in the development and maintenance of the disorder.[43,44] Associated traits known to contribute to AN symptomatology include anxiety, negative emotionality, perfectionism, inflexibility, and harm avoidance (HA).[45-49] These temperament traits are interrelated and together contribute to appetite dysregulation and mealtime behavior in AN, suggesting treatments that target these constructs may see improved clinical effects. Inarguably the most critical issue in treating individuals with AN is addressing food refusal and pursuit of emaciation. There is an anxiety-reducing effect of dietary restraint and caloric restriction for AN individuals,[50,51] whereas food consumption stimulates dysphoric mood.[52] Moreover, enhanced inhibition, self-control, and/or an ability to delay reward may help to maintain persistent food restriction.[53] Finally, disturbed interoceptive awareness of satiety or hunger,[54] or even an alteration of primary gustatory processes,[55-57] could play a role in assessing body states and responding to hunger cues. Imaging data further suggest that anticipatory anxiety contributes to restricted eating. For example, individuals with the ability to restrict their eating have an exaggerated anticipatory

response to food cues that is anxious and aversive,[51,55] along with a diminished insular and striatal response to receipt of food.[58] A disturbance of both anticipating and experiencing food stimuli may contribute to restricted eating in AN. This finding is consistent with the notion of reduced reward and/or enhanced satiety signals in regions that compute hunger-satiety homeostasis.

Clinical treatment approaches have not been developed and/or updated to reflect this mechanistic understanding of the disease. To date, the most widely used behavioral treatment models, such as cognitive behavioral therapy (CBT), used to address core AN symptomatology, are adaptations of treatments that were originally developed to address pathology specific to other psychiatric disorders. As such, they do not adequately address the unique and disease-specific mechanisms that underlie AN. These reasons may explain the limited efficacy of currently available treatments.

In order to continue to make advances in AN treatment, a paradigm shift is necessary in which interventions are developed based on empirically supported theoretical models describing underlying neurobiological mechanisms that may contribute to AN pathology and symptomatology. Indeed, a recent shift in psychiatric research has emphasized the exploration of the mechanistic pathways and constructs underpinning psychopathology, as opposed to focusing on a symptom-oriented understanding of psychiatric illness. Treatments constructed using a bottom-up approach, where an understanding of underlying mechanisms inform specific treatment approaches are needed to improve effectiveness, but such treatments are only in early stages of development and testing.[59,60]

The neurobiological features underpinning AN have been comprehensively reviewed by our group.[43,44,50,51] This brief review is focused mainly on the potential application of these findings to the development of new, more effective clinical treatments. In addressing this gulf between evidence illustrating the neurobiological profile of AN, and current treatments designed to target core symptomatology, we have previously provided a preliminary overview of the development of a novel clinical treatment which is rooted in the unique neurobiology of AN. See Kaye et al[61] for this more comprehensive review of theory and application. It is important to emphasize that there is very limited empirical evidence for this new approach. Rather, this paper speculates on constructs, in order to generate new ideas for innovative approaches. It is worth noting that many of these concepts have been incorporated into a brief treatment approach for adolescents with AN which has shown some efficacy in terms of improved long-term outcomes.[62] Still, this current paper articulates hypotheses rather than conclusions regarding treatments for adults with AN. It remains unknown whether this treatment will prove to be effective. But perhaps what is most critical is stimulating the eating disorder field to devise treatments that address contributory neurobiological features.

## NEW FED TR

In response to the critical need for effective treatments in adult AN, we have developed[61] a neurobiologically informed treatment that draws upon the specific etiology characterizing AN. Neurobiologically Enhanced With Family Eating Disorder Trait Response Treatment (NEW FED TR) is a neurobiologically based treatment delivered to individuals with AN and their carers (eg, parents, siblings, spouses/significant others, friends, or anyone else in their support network who they would like to be involved in their recovery) developed to target AN-specific temperament, cognition, and eating behaviors. The comprehensive treatment aims to achieve a reduction in core symptoms by using behavioral approaches to target disease-specific neurobiological mechanisms. The treatment approach is informed by the understanding that underlying traits are stable and pervasive (versus transitory), and thus focuses on teaching AN individuals and their carers to manage AN symptoms by using these traits constructively (versus destructively through the pursuit of emaciation). Neuroimaging findings suggest mechanisms underlying anticipatory anxiety, reward insensitivity, and/or deficits in awareness of homeostatic needs (interoceptive awareness) contribute to AN. These alterations contribute to appetite dysregulation in AN, and are likely related to enhanced executive ability to inhibit incentive motivational drives. As such, they may reflect mechanisms of action to be targeted to regulate eating behavior in AN. NEW FED TR consists of modules aimed at targeting each of these constructs, delivered to both patients and carers. Each module is formatted to deliver: (i) neurobiological psychoeducation aimed at reducing blame and enlisting support; (ii) neurobiological skills training consisting of teaching skills to address deficits and

facilitate constructive methods for using temperament; (iii) carer management strategies consisting of teaching carers effective response and management strategies; and (iv) experiential learning focused on practicing the implementation of skills and strategies in a therapeutic environment. Below we describe key aspects of the treatment in more detail.

**Format**

The treatment is delivered in two segments that are conducted with the patient and nominated carers. The first segment is delivered via an intensive course, with patients and carers receiving 8 to 9 hours of treatment over 5 consecutive days. The 5-day intensive treatment is delivered in a multifamily format, with multiple families attending jointly. This intensive course is then followed by weekly outpatient follow-up sessions focused on monitoring weight and symptoms and facilitating continued practice of skills developed over the intensive 5-day course. The intensive nature of the treatment is intended to establish an ecologically valid meal structure, while allowing for immersive experiential learning, massed practice, and in-vivo therapist-guided training on key factors involved in recovery. Real-time therapist observation and intervention during target events such as mealtimes, acute emotional outbursts, and family interactions allows for both patients and carers to receive applicative, hands-on training and management skills. Tenets of neuroplasticity dictate that increased treatment frequency and intensity are critical components needed to elicit behavior change.[63,64] Treatment models for anxiety indicate that intense, repeated, and focused in vivo practice is key to altering biologically driven avoidance behaviors by maximizing learning through massed practice and allowing close monitoring of compliance.[65-72] The initial intensive course is intended to improve treatment adherence and maximize the possibility of initial success,[71,73] which has been implicated as a prognostic indicator.[74] One potential reason that current treatment methods for adult AN have failed is because a once-weekly treatment format may be ineffective for such a severe and treatment-resistant disorder.

**Neurobiological psychoeducation and skills training**

Neurobiological constructs of interest are based on the temperament profile characteristic of AN and include anxiety, interoceptive awareness, altered reward and punishment sensitivity, and cognitive flexibility. Psychoeducational activities and experiential skills training are used to address each of these mechanisms. Psychoeducation on the neurobiology underlying AN is taught through interactive activities and demonstrations, whose aim to establish a strong foundation of neurobiology as the primary etiological cause of AN. This theoretical framework serves the purpose of both reducing blame and increasing empathy, which is a critical determinant to enlisting carer support. Education on neurobiology as the driving cause of the illness also assists patients in shifting their perspective on aspects of their illness and provides a rationale for deficits related to appetite dysfunction. For example, in one exercise focused on teaching families about deficits in interoceptive awareness, volunteers are blindfolded and asked to find a target across the room. This is intended to demonstrate dysfunction in the insula, which may be implicated in lack of ability to appropriately gauge hunger and satiety. Approaching this deficit with a biologically based rationale assists patients in accepting necessary structure and support from their treatment providers and loved ones. The activities, pioneered by Hill,[75] are highly interactive and may improve retention and impact and are followed by a short didactic explanation of the construct of interest.

Psychoeducational activities are followed by related skills training for each construct. For example, following the psychoeducation activity described above, to address deficits in interoceptive awareness, patients are asked to follow a routine and predictable structure for meals and snacks that specifies specific times, foods, exchanges, and other details involved in mealtimes. Patients are taught and trained to follow the structure as rigidly as possible, relying on external cues due to the absence of internal appetitive cues. A highly predictable and repetitive structure makes use of personality strengths such as enhanced inhibition and self-control associated with AN, and acknowledges deficits in ability to tolerate uncertainty[76] and to shift sets.[77-80] These skills are learned, implemented, and practiced throughout the intensive portion of the program.

**Carer involvement**

It is well-established that family involvement is critical to treatment success, which may explain why treatments for

adolescent AN are more promising than for adults. Considerable data show that 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.[35-37] Implementing standard FBT in adults is difficult because parental authority is diminished. However, there is growing evidence that carer involvement in the treatment of chronic adult AN may be critical and should be a target of treatment,[81,82] though there are no data to date examining whether improving AN/carer interpersonal factors improves patient outcomes.[83] A new couples approach to treating AN (Uniting Couples in the treatment of AN), based on cognitive-behavioral couple therapy, also shows promise to improve communication and reduce marital distress, but data showing clinical outcomes are needed.[84,85] The rationale for parental involvement in adolescent AN is intended to address the motivational deficits inherent in AN and the unique ego-syntonic nature of this illness. Likewise, motivational deficits and ego-syntonicity are issues in adult AN and may be improved by the enlistment of carers to manage and oversee initiation and maintenance of recovery-oriented behaviors in a modified, age-appropriate manner.

NEW FED TR focuses on constructing a structure in which carers are involved. Along with patients, carers are educated about the neurobiology underlying the illness and the most effective ways to respond to and manage symptoms given the personality profile of the patient. Carers are taught skills to reduce the patient's dietary restraint and shape recovery-oriented behavior around meals. Some examples include: (i) implementing a premeal routine to distract patients 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 while maintaining caloric sufficiency to reduce anxiety and increase weight (eg, fixed meal plan with increased calories over time). Such meal coaching directly with carers helps redirect the patient away from rumination when anxiety or obsessions occur. Our clinical experience is that limiting choice has some useful for carers, in terms of reducing anxiety related to change, set-shifting, and anticipation in AN; (iii) implementing a behavioral contract to achieve compliance with weight restoration. The involvement of carers in treatment is intended to address motivational deficits by enlisting them to facilitate compliance with the structure (established in the intensive program) through techniques such as support and encouragement, the delivery of rewards and consequences, and improved awareness of recovery-related requirements.

**Treatment development progress**

A clinical trial is under way to further develop and test the efficacy of the NEW FED TR treatment program. Data collection for this multisite trial is currently in progress, with six intensive multifamily programs scheduled for 2015. A recent paper by our group[61] described in greater detail translational treatment strategies and their respective underlying neurobiological mechanisms. The article illustrates examples of clinical tools for targeted constructs drawing from manualized treatment strategies developed and tested in our clinical laboratory. Additionally, we report on preliminary methods and results of a proof-of-concept pilot study intended to test carer involvement and key components of NEW FED TR. In this pilot study, patients and their carers received four sessions of neurobiology skills training and psychoeducation in a multi-family group. Pre-post results are promising, with the treatment demonstrating excellent feasibility and acceptability, and improved carer-patient communication and self-efficacy.[61]

## Conclusion

This is the first intervention that establishes a behavioral treatment framework for AN based on empirically validated neurobiological mechanisms underlying the illness. NEW FED TR is a modular treatment focused on improving AN symptoms through a mechanistic approach that includes psychoeducation, skills training, experiential learning, and the enlistment of carers in the management of recovery. Treatment approaches acknowledge core temperamental traits of individuals with AN, thereby improving the clinical utility of these strategies, while maximizing feasibility and adherence. This treatment reflects a paradigm shift for clinical treatment efforts in AN, in which basic neuroscience research is translated and integrated into clinical treatments. However, it should be underscored that controlled empirical data are required to support the core components of this novel approach, and as such, continued treatment development efforts are under way to collect data on this treatment approach. ❑

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## *Tratamiento neurobiológicamente informado para adultos con anorexia nerviosa: una nueva aproximación a un trastorno crónico*

*La anorexia nerviosa (AN) es un trastorno grave y debilitante con importantes secuelas médicas y psicológicas. A la fecha no existen tratamientos efectivos para adultos, lo que lleva a altas frecuencias de cronicidad, morbilidad y mortalidad. Avances recientes en la investigación imaginológica han conducido a un progreso en la comprensión de la etiología y de los mecanismos neurobiológicos específicos de los síntomas subyacentes. A pesar de esto, no existen tratamientos enfocados en los síntomas blanco que utilicen esta comprensión mecanicista con un sustento empírico de la enfermedad. Para mejorar los resultados terapéuticos para esta población es necesario que las aproximaciones terapéuticas actuales se enfoquen en los mecanismos neurobiológicos blanco a la base de la sintomatología central de la AN. El NEW FED TR (Neurobiologically Enhanced With Family Eating Disorder Trait Response Treatment) es un tratamiento neurobiológicamente informado que apunta a constructos temperamentales clave asociados con la enfermedad a través de la entrega de psicoeducación y entrenamiento en herramientas para pacientes y cuidadores designados.*

## *Traitement de l'anorexie mentale chez l'adulte : nouvelle approche neurobiologique d'une maladie chronique*

*L'anorexie mentale est une maladie sévère et invalidante aux séquelles médicales et psychologiques importantes. À ce jour, il n'existe pas de traitement efficace chez l'adulte ; les taux de chronicité, morbidité et mortalité sont donc élevés. Des avancées récentes de la recherche en imagerie cérébrale ont permis de mieux comprendre l'étiologie et les mécanismes neurobiologiques spécifiques à l'origine des symptômes. Mais malgré cela, aucun traitement ciblant les symptômes et fondé sur cette compréhension mécanistique de la maladie sur des bases empiriques n'a vu le jour. Améliorer les résultats des traitements pour cette population nécessite d'actualiser ceux qui ciblent les mécanismes neurobiologiques au cœur de l'anorexie mentale. Le NEW FED TR (*Neurobiologically Enhanced With Family Eating Disorder Trait Response Treatment*) est un programme thérapeutique neurobiologique ciblant les concepts de personnalité clés associés à la maladie en faisant bénéficier les patients et les soignants désignés de mesures psychoéducatives et d'acquisition de compétences.*



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