Restless Activation and Drive for Activity in Anorexia Nervosa May Reflect a Disorder of Energy Homeostasis

Regina C. Casper, MD*

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Introduction

Anorexia nervosa (AN), an uncommon disorder of voluntary food restriction emerging during adolescence, is a condition known in Western Europe for at least 500 years, if not longer. Although AN is currently categorized as an eating disorder, "anorexia" or "loss of appetite" are infrequent. AN is also an intensely personal disorder in that the person with AN concentrates most of his/her thoughts, emotions, and actions on food avoidance and weight loss.

The etiology of AN remains obscure. There is good agreement that AN constitutes a clinical entity and that it does not develop in the context of another psychiatric disorder. Nevertheless, co-morbid psychiatric disorders are frequently associated with AN and they have an impact on the severity and duration of AN. Importantly, twin and family studies point to a significant genetic component in AN with twin-based heritability estimates ranging from 50 to 80%.[1] So far, neither genome-wide linkage studies or candidate gene studies, nor genome-wide association studies (GWAS) have reported incontrovertible findings.[1]

The occurrence of AN in other cultures has renewed the interest in taking a fresh look at the clinical phenomenology of AN. Indeed, research aimed at identifying and refining new phenotypes might provide a link to genetic studies and open avenues for exploring and understanding the pathology of the disorder.

The Long Reported Symptoms of "A Relatively Extraordinary Degree of Physical and Mental Activity" in AN

A century ago, physicians, whose main diagnostic tool was clinical observation, identified some hallmark features of AN. Gull wrote in 1873 "the patient complained of no pain, but was restless and active. This was in fact a striking expression of the nervous state, for it seemed hardly possible, that a body so wasted could undergo the exercise which seemed agreeable" (for most references in the text, please see Ref. 2.

A "remarkable strikingly disproportionate abundance of physical and mental energy" remained a distinct ingredient of the phenomenology of AN in the early 20th century. Numerous studies in recent decades have focused on the frequency of behavior, termed variously "hyperactivity" or "excessive exercise" by interviewing patients, through self-rating scales and through retrospective reviews of medical records. Differences in methodologies and patient populations which have resulted in inconsistent findings of excessive exercise in AN with prevalence rates ranging from 30 to 80% were recently critically reviewed.[3] From a developmental perspective, a reported predisposition to greater than average activity levels in childhood in nearly half of adolescents with AN is relevant.

Equally, if not more, remarkable than excessive exercise is the fact that persons with AN appear to display a normal, sometimes a slightly higher than normal, baseline physical activity level. Clinical descriptions mention a "persistent wish to be on the move" and an "internal urge toward increased activity."

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*Correspondence to: R. Casper. E-mail: rcasper@stanford.edu
Department of Psychiatry, Stanford University School of Medicine, Stanford, California, 94305

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This tendency of AN patients to be active contrasts sharply with the slowing of movements observed in prolonged starvation.

Keyes et al.[4] were the first investigators to study systematically the cascade of physiological and physical changes in response to caloric undernutrition under controlled conditions in the Minnesota Experiments. A 25% weight loss of original body weight induced a significant reduction in the metabolic rate, led to bradycardia, hypotension, hypothermia, loss of sexual interest, increasing muscular weakness, reduced motivation, and energy as well as a decrease in spontaneous and self initiated activity. A few men reported a short-lived sense of quickening; with progressive semi-starvation all men reported "general slowing down, tiredness, and lack of energy." The experiments demonstrated that the body's physiological and molecular adaptations to caloric under-nutrition serve one purpose, to cope with decreased energy availability by conserving energy.

"Restless Activation" and "Drive for Activity" in AN Seem to be the Expression of a Specific Trait Related to a Disturbance in the Mechanisms Regulating Energy Balance

In light of these observations, normal activity and energy levels and continued alertness in persons with AN, whose weight loss frequently exceeds 25% of normal weight, appear inexplicable. The first idea worth researching then would be that such "physical and mental energy preserved in the presence of physical and physiological signs of starvation" might constitute a fundamental characteristic, a phenotype, determined by both genetic and environmental influences. Its clinical expression seems to be that persons with AN feel restless and active. The terms "restless activation" and "drive for activity" describe these sensations. The preserved physical and mental energy appears to allow the person to exercise.

Within this conceptual framework, a second hypothesis worth investigating can be generated, specifically that a pattern of continued normal, sometimes higher than normal, activity levels without signs of fatigue on muscle exertion in AN points to a disturbance in energy homeostasis.

Energy homeostasis is maintained by neurons throughout the CNS that sense hormonal and metabolic signals of systemic energy status and relay this information to secondary neurons that regulate physiological processes so as to maintain energy balance. The strongest experimental evidence supporting normal or higher than expected daily energy levels in AN comes from measurements of total energy expenditure (TEE) using the doubly labeled water method, the most reliable and valid method currently available that provides estimates of habitual energy expenditure over a time period of 14 days.

Total energy expenditure (TEE) is composed of the resting metabolic rate (RMR), the energy expended in activity, and the dietary-induced thermogenesis. Four studies (see Pirke et al. 1991, Casper et al. 1991 in Refs. 2,5,6) concur in finding TEE in anorexia nervosa not to be different from normal weight healthy age-matched controls, whereas two studies of older and chronically ill AN patients[7,8] observed lower than normal TEE.

These observations need to be replicated. They ought to be supplemented by data from other objective, less labor-intensive, methods using devices that measure motion and actual physical activity levels, preferably before hospital admission when movements are not restricted.

A third source of information would be the experiences of persons with AN. Self-ratings and observer-ratings can measure "restless activation" through items such as being fidgety, feeling restless, feeling active, strong, alert, motivated, a sense of liveliness, feelings of elation, and through ratings of fatigue, weakness, and loss of energy. The "drive for activity" can be assessed as the desire to move and an inability to sit still. Concomitantly, body weight, nutritional intake, degree of hunger, eating disorder symptoms, including intense fear of/desire for weight gain and the full profile of psychological symptoms, especially anxiety and depression, as well as co-morbid psychiatric disorders need to be recorded. A self-rating instrument with acceptable reliability and validity would be the International Physical Activity Questionnaire.[9]

Possible Factors and Genetic Components in the Postulated Up-Regulation of Energy Levels Under Catabolic Conditions in AN

Priority ought to be given to research exploring systems mobilized during the body's adaptation to caloric restriction in AN. Studies on leptin, an adipocyte-secreted hormone involved in energy homeostasis which acts as a signal from the periphery to the brain conveying information about the amount of energy available, have shown an inverse relationship between plasma leptin

levels and symptoms of motor restlessness and physical activity, indicating a positive association between "restless activation" and the caloric deficit in AN.[10]

Determining specific genetic changes or altered regulation of gene expression that may be triggered by any of the numerous adaptations during caloric deprivation and which might contribute to resetting energy levels in AN is extraordinarily complex. Concerning possible candidates, exposed during lipolysis, Yoon et al.[11] have recently identified genetic variations in extracellular nicotinamide phosphoribosyltransferase (eNAMPT), the key nicotinamide adenine dinucleotide (NAD+) biosynthetic enzyme, secreted by adipose tissue which is an important modulator for maintaining normal hypothalamic NAD+ levels, SIRT1 activity, and physical activity, particularly in response to fasting.

Another type of variation may involve missense mutations in the estrogen related receptor α (ESRRA) gene and the transcriptional repressor histone deacetylase 4 gene (HDAC4) identified by Cui et al.[12] that segregated with AN. ESRRA participates in energy balance and metabolism and is upregulated by exercise and calorie restriction in peripheral tissues.[12] Furthermore, altered mitochondrial gene expression of evolutionary conserved genes, in line with the theory of activity-anorexia ensuring survival, perhaps by increasing muscle work efficiency through changes in fuel utilization, may be involved. Alternatively, a polygenic pattern with genes of small effect might modulate re-setting energy homeostasis in AN.

In conclusion, we propose as a hypothesis that an abnormal response of the body's energy regulation to severe under-nutrition and weight loss manifested in the symptoms of "restless activation" and "drive for activity" are fundamental elements of the pathology of AN. Future research will be required to establish the validity of the concepts of "restless activation" and "drive for activity" in AN and to explore the phenomenon of "physical and mental energy preserved in the presence of weight loss and under-nutrition in AN." If validated, this clinical phenotype will prove useful for identifying the biological pathways and genetic regulation of energy homeostasis not only in AN, but also under normal conditions.

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