REGULAR ARTICLE

Heat Reversal of Activity-Based Anorexia: Implications for the Treatment of Anorexia Nervosa

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ABSTRACT

Objective: Activity-based anorexia (ABA) provides an animal model of anorexia nervosa (AN). In this model, rats given restricted access to food but unrestricted access to activity wheels, run excessively while reducing food intake, lose a sizeable percentage of body weight, become hypothermic, and can fail to recover unless removed from these conditions.

Method: Once rats had lost 20% of body weight under standard ABA conditions, they were assigned to one of two ambient temperature (AT) conditions.

Results: Increased AT reduced running rates and led to weight gain in active rats. The effect of increasing AT on food intake was dependent on whether the rats were sedentary or active. Although warming reduced food intake in the sedentary rats their body weight remained stable, whereas in active rats increased AT did not reduce food intake and weight gain gradually rose.

Conclusion: From a translational perspective, these findings offer a fresh perspective to the disorder, and underscore the need for further studies to assess the effects of heat treatment in patients as an innovative adjunctive treatment for anorexia nervosa. © 2008 by Wiley Periodicals, Inc.

Keywords: activity-based anorexia; anorexia nervosa; heat treatment; self-starvation; rats; hyperactivity; translational research

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Introduction

Anorexia nervosa (AN) is a serious disorder which has proven difficult to treat either psychologically or pharmacologically.[1] The absence of an effective treatment for AN may be the consequence of how the disorder has been conceptualized in the last 40 years, primarily as a psychological construct of body image disturbances.[2] According to this view, excessive physical activity and the diverse behaviors habitually subsumed under the term hyperactivity are usually conceived in terms of willful strategies to lose weight by patients.[3] This notion is depicted, for example, with respect to strenuous exercising, by two items in the Eating Attitudes Test, EAT,[4] which is one of the inventories most frequently employed for the self-reporting of symptoms and concerns characteristic of eating disorders: *Exercise strenuously to burn off calories* (item 16), and *Think about burning up calories when I exercise* (item 22), retained in the shorter EAT-26, as item 12.[5] Historically, except in rare instances,[6] hyperactivity has received a marginal relevance in the different conceptualizations of the disorder. However, in the last decade neurobiological factors underlying this behavior[7–9] have received greater attention by researchers who are inclined to reconsider the significance of this paradoxical behavior.[10] This viewpoint, which underlines the role of increased physical activity in the development and maintenance of the disorder, has been substantiated by research with an animal model analogous to the human disorder known as Activity-Based Anorexia (ABA).[11]

Although ABA, due its very nature as an animal model, is inherently incapable of matching the mental processes which characterize AN, its analogy rests on the parallel between certain aspects of the human disorder and those displayed by rats submitted to food restriction while having free access to a running wheel. Under such conditions, within a few days, running progressively

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escalates, they self-starve (eat less than sedentary rats during the same feeding period), show marked body weight loss, hypothermia, and disruption of the estrous cycle, an ABA outcome which can lead to death unless the animals are removed from the experimental arrangement.[12,13] This animal model has advanced our understanding of the interaction between starvation and hyperactivity, and some pharmacological interventions have been moderately successful in partially preventing the development of the ABA outcome. These studies have focused on well characterized neuroendocrine systems involved in energy homeostasis, either on peripheral signaling to the hypothalamus, as in the case of the hormone leptin secreted by adipocytes,[14,15] or on central systems such as the melanocortin (MC),[16,17] and serotoninergic (5-HT)[18–20] systems. However, research using the ABA model has yet to identify a pharmacological agent that will aid rats to recover once running escalates and weight loss exceeds 20% of baseline body weight. Hence, a further understanding of how the standard ABA outcome can be reversed may aid the management of the human disorder.

Various explanations have been advanced as to why animals increase running activity in spite of restricted food supply. Some authors interpret excessive running as a form of foraging behavior[21] others explain it as a result of various physiological mechanisms involving the activation of dopaminergic reinforcing pathways,[22] or even as a form of auto-addiction to increased secretion of endogenous opiates produced by running.[23] An alternative view suggests that excessive running in ABA rats is a form of thermoregulatory behavior in response to the hypothermia resulting from the restricted feeding schedule and subsequent weight loss.[13] Evidence supporting this hypothesis comes from the finding that ABA rats prefer access to a warm plate to running in the wheel,[24] and that high AT prevents ABA-development (Ref. 25, Experiment 1).

Previous research designed to evaluate the effects of increased (AT) on rats exposed to the ABA procedure showed that, once the animals had already been exposed to the ABA conditions at a neutral temperature (20°C), switching the AT to 27°C only had a transient effect on weight loss (Ref. 25, Experiment 2). This study, however, had two main drawbacks: (a) The equipment did not allow for the individual adjustment of AT thus, and AT was adjusted on a group basis. (b) The highest temperature setting of 27°C was probably insufficient as this is in the lower range of the thermoneutral zone for rats.

The purpose of the present study was to assess the potential for heat to reverse the ABA outcome once running has become excessive with appreciable weight lost. The study seeks to continue the line of investigation of the previously mentioned work and to improve the experimental design by controlling the individual AT for each rat, and providing higher AT settings (32°C).

Method

A total of 48 male Sprague-Dawley rats (40 day-old, weight range 164–186 g) acquired from the University Animal Resources Centre were kept for 3 days in the colony room with food and water ad libitum on a 12 h light-dark cycle, with lights on from 08:00 to 20:00 h and ambient temperature was set at 21°C. While in the colony room rats were weighed daily. The ethics committee on the use and care of animals of Santiago de Compostela University approved all described procedures. All experiments were carried out in accordance with the European Communities Council Directive of 24 November 1986 and D.L. of 27 January 1992 no. 116 (86/609/EEC). All efforts were made to minimize animal suffering and to reduce the number of animals used.

The laboratory contained 8 Wahman-type activity wheels (1.12 m circumference, 10 cm-wide running surface of 10 mm wire mesh bounded by clear Plexiglas walls). These were attached to acrylic cages ($28 \times 28 \times 14$ cm^3). Wheels and cages were placed inside wooden incubators ($60 \times 60 \times 60$ cm^3) with polycarbonate roofs, provided with a 150 W heat wave lamp, connected to a thermostat and a probe positioned at the level of the animal, which allowed individual control of ambient temperature for each animal. An equal number of same size ($28 \times 28 \times 14$ cm^3) acrylic cages were employed for sedentary animals.

Three consecutive batches of 16 rats were assigned to two weight matched groups; an active ($n = 24$), and inactive ($n = 24$) conditions. Rats in the active condition were housed in the cages attached to the running wheels inside the incubators and given access to the running wheels for 2 h per day for a 3-day period. Inactive rats remained in their cages, also placed inside an incubator. Thus, from now onward the terms active and inactive will designate animals or groups of animals with and without access to a running wheel respectively. During this pre-experimental period and for the rest of the experiment all rats were weighed between 12:00 and 13:00 h each day, and the temperature in the incubators for all animals was set at 21°C.

The ABA procedure started (Day 0) with the removal of food at 14:30 h both for active and inactive groups. At the

same time, the doors to the wheels were opened for the active rats. From Day 1 onwards, all rats were given access to food from 13:00 to 14:30 h. Food intake was measured by weighing the food at the beginning and end of every 1.5 h feeding period. Rats were also weighed daily at 12:00 h (as they were on Day 0). The doors to the wheels were closed during this feeding period. This phase continued for each active rat until it reached an initial criterion of 80% of Day 0 body weight. Once an active animal reached the body weight loss criterion (BWLC), it was assigned to one of the two groups, an Active-High AT group in which the thermostat of the incubator was changed to 32°C, or an Active-Neutral AT group in which ambient temperature was maintained unchanged at 21°C, matched on days to criterion by allocating the first rat to the AT 32°C condition, the second to the AT 21°C condition, the third to the AT 32°C condition, the fourth to the AT 21°C condition, and so on. An equivalent number of inactive animals, previously pair-matched on initial body weight, were yoked to the Active animals to experience the same change in AT, thus forming two inactive groups, an Inactive-High AT group (32°C), and an Inactive-Neutral AT group (21°C). These conditions were maintained until rats reached either the recovery criterion, which was defined as body weight on any particular day, Day *n,* greater than the weight of the animal 4 days before, Day $n-4$, as is standard for ABA experiments since the pioneering work of Routtenberg and Kuznesof in 1967,[12] or the removal criterion which was defined as body weight under 75% of body weight on Day 0. The outcomes for the animals whose weight neither fell below the removal criterion nor increased to the recovery criterion were classified as intermediate. The experiment was terminated after 15 days.

Five dependent variables were analyzed: body weight, food intake, wheel turns, days to BWLC, and recovery/removal outcome. Body weight, food intake, and wheel turns were analyzed using analysis of variance (ANOVA), with AT and activity conditions as independent factors, and with repeated measures over the days until the first rat was removed (trend analysis). Two-tailed *t*-tests were used to assess any group differences in initial measures. Days to BWLC were examined using non-parametric analysis (Mann-Whitney U-test). An α-rate of 0.05 was used for all analyses.

Results

Only five of the 24 rats in the active condition failed to reach the 20% BWLC. These five were discarded as well as their yoked partners in the Inactive group. The remaining 19 rats reached the BWLC in a median of 6 days (range 4–9 days) and were allocated to either the high AT group ($n = 10$) or the neutral AT group ($n = 9$). These groups did not differ with respect to the number of days required to reach the 20% BWLC (High AT, median 6 days; Neutral AT, median 7 days, Mann-Whitney $U(9,10) = 29$, $p = .18$). The yoked inactive animals were also divided into two groups and these experienced the same changes in AT as the active animals. Retrospectively, after discarding the active animals that did not reach the 20% BWLC and their yoked Inactive partners, the resulting four groups did not differ in body weight on Day 0, with mean and SEM body weights as follows: Active-High AT, 224.2 ± 2.5 g; Active-Neutral AT, 217.7 ± 3 g; Inactive-High AT, 227.1 ± 2.5 g; and Inactive-Neutral AT 224 ± 2.9 g.

Phase I

First, we will present the results for the first phase when all the animals from the active and inactive conditions were housed at an AT of 21°C. With respect to running activity of the active animals, the top panel of **Figure 1** shows the running distance covered during the 22.5 h period of wheel access. These data are plotted in relation to the time required for each individual rat in the active condition to reach the 20% BWLC. Given that the animals met the criterion on different days, a complete set of data for the entire group of animals was only available for four days before the criterion day as some animals reached the 20% BWLC after 4 days. However, in the figures always mean and SEM values are represented for whole groups. Thus, only four points on the abscissa of **Figure 1** are shown for the first phase (i.e., Day −3, Day −2, Day −1, and criterion day).

Running distance steadily rose for all animals from the first day they had access to the wheel until the day they met the criterion for the change of phase (the greatest proportional increase recorded was from 555 to 8,787 m, and the least from 1050 to 3518 m). The top panel of **Figure 1** shows the daily group averages for running distances during the last 4 days of Phase I.

Nevertheless, a significant difference between the two active groups was observed as the group allocated to the neutral condition ran somewhat more as shown by the mixed ANOVA that detected a group difference, $F(1, 17) = 1.59$, $p < .05$, but no interaction between group and day, $p > .10$.

The lower panel of **Figure 1** shows body weight for all four groups in the Phase I. As expected, weight loss was greater for Active animals than for Inactive animals, $F(1, 36) = 18.87$, $p = .0001$, and the interaction between group and trend was

FIGURE 1. Top panel: Mean (±SEM) running activity over days prior to and after the 20% BWLC, and on the last day of the experiment. Bottom panel: Mean (±SEM) changes over days in bodyweight relative to weight on Day 0 for the same period as top panel. The vertical dotted line indicates the point at which the ambient temperature (AT) was raised to 32°C for the Active-High AT and the Inactive-High AT groups.

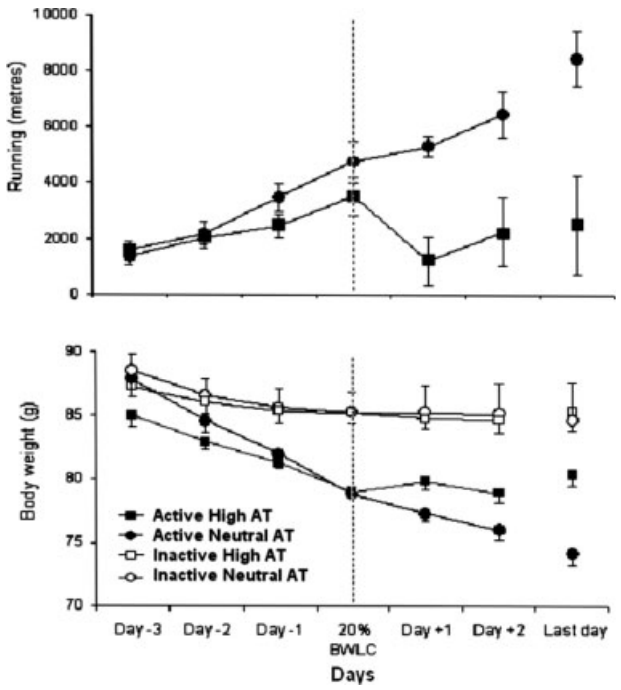
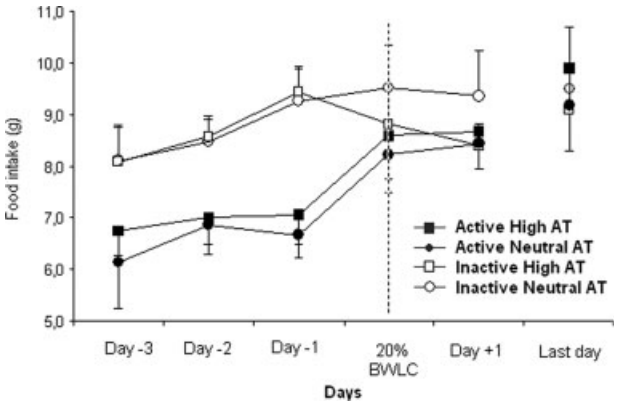


FIGURE 2. Mean (±SEM) food intake over days for active and inactive rats. Note: there are only six points in the abscissa as the experiment finished on the last day after the routine daily weighing, before feeding time. The vertical dotted line indicates the point at which the ambient temperature (AT) was raised to 32°C for the Active-High AT and the Inactive-High AT groups.



significant, $F(3, 108) = 19.172$, $p = .0001$, indicating a faster rate of weight loss for Active animals. However, there was no overall difference in body weight before the 20% BWLC, for animals later allocated to the High and Neutral conditions, $p > .05$. There was also no difference, or interaction with days, between the two inactive groups (both ps $> .05$).

Figure 2 shows food intake. Phase I extends over the first three points given that the change in AT was performed after the weighing session but prior to the meal session (see method section). Thus, food intake on criterion day (20% BWLC) was a "warmed meal session" corresponding to Phase 2. As expected from previous ABA experiments, food intake during the Phase 1 for active rats was less than for inactive rats, $F(1, 36) = 19{,}63$, $p = .0001$, but no interaction was found, $F(2, 72) = 1.821$, $p = .169$. Moreover, in this phase, there was no difference in food intake between the Active and Inactive animals, Fs < 1.

Phase II

The second phase commenced when active rats were assigned to a high or neutral AT group on reaching the 20% body weight loss criterion and extended until animals met either the removal or recovering criterion (see Method). Similarly, an equivalent number of yoked Inactive counterparts were assigned to a High or Neutral AT groups. Only three points are shown on the abscissa for the second phase, since four rats in the Active-Neutral group met the removal criterion after 3 days.

As for running activity, rats maintained at a constant temperature of 21°C displayed a twofold increase in running distance, whereas animals warmed to 32°C reduced running activity. A repeated measures ANOVA revealed that over days rats maintained at 21°C ran more than animals kept at 32°C, $F(1,17) = 15.56$, $p = .001$. As illustrated in the top panel of **Figure 1**, by the last day, Neutral AT animals ran on average three times as much as High AT rats, $t(17) = 3{,}17$, $p = .006$.

In terms of body weight, see the lower panel of **Figure 1**, neutral AT active rats continued to lose weight. ANOVA with repeated measures of the weight data shown in the lower panel of **Figure 1** for Phase 2 confirmed that the body weight of Active-High AT animals was greater than the weight of Active-Neutral AT animals, $F(1,17) = 21.86$, $p = .0001$, and that this difference gradually increased over days, $F(2, 34) = 10.72$, $p = .0001$. As for the Inactive animals, there were neither overall differences between the two groups nor a significant interaction with days (both Fs < 1).

A total of 8 out of 9 animals of the Active-Neutral AT group had to be removed from the experiment as they surpassed the 25% body weight loss criterion (median 4 days, range 3–7 days). In marked contrast, all warmed Active animals gained weight

with a 100% of them reaching the recovery criterion by which rats were judged to have begun to recover body weight, (median 5 days, range 3–9 days), Fisher exact test, $p < .0001$. With reference to the inactive rats, only one inactive animal—from the neutral AT group—reached the removal criterion before the end of the experiment, whereas, as 2 rats from the neutral AT and 2 from the high AT group failed to stabilize and were classed as intermediate. Thus, the percentage of inactive rats reaching the recovery criterion was 67% for animals kept at 21°C and 80% for those animals warmed to 32°C.

With respect to food intake, as shown in **Figure 2**, no differences between active and inactive animals were observed given that food intake for active animals steadily rose whereas intake for inactive animals leveled off, $F(1, 36) = 0.167$, $p = .685$.

However, there were differences in food intake for active and inactive animals following increased AT. Thus, though the food intake of Active-High AT rats continued to gradually increase over days across the two phases, the change in AT depressed food intake in the Inactive-High AT animals. A comparison of food intake for the first 24 h under the warmer AT (from 21° to 32°), yielded a significant interaction, i.e., whereas the increased AT depressed the food intake of Inactive rats, intake for Active rats increased, $F(1, 18) = 5{,}17$ $p = .04$. These different trends in food intake continued for the second day of raised AT, i.e., the interaction for these 3 days (Day −1, BWLC Day and Day +1) remained significant $F(3, 36) = 5.38$, $p = .009$, but disappeared by the Last Day. Interestingly, the reduction in food intake in the inactive rats was not accompanied by weight loss in these animals as compared to the inactive rats maintained at 21°C, as is clearly depicted in the bottom panel of **Figure 1**.

Conclusion

These findings indicate increased AT can both reduce wheel running and increase body weight after 20% weight loss has occurred, even when access to food remains restricted and access to wheel running unrestricted. To our knowledge, there are no previous reports in the literature of such a reversal in the trend in body weight loss induced by the ABA procedure similar to that displayed by the warmed rats in our study. Since 1967, the low rate of animal survival after a 20% of body weight loss resulting from exposure to the ABA procedure has been continuously reported, i.e., the weight of animals continued to decline unless they were removed from the experimental arrangement.[12,13] Thus, the meaning of the recovery criterion should be understood in terms of the reversal in the tendency to lose weight under these life threatening conditions. For this reason, if an animal gained weight in line with the recovery criterion (see methods section), it was considered in a process of weight recovery. Obviously, animals reaching the recovery criterion did not match their previous baseline bodyweight in such a short time span but, to avoid unnecessary suffering, the animals were withdrawn from the experiment upon reaching the recovery criterion. In all likelihood, this modulating effect of AT on ABA has remained elusive due to the fact that ambient temperature has been a neglected area of research in ABA until recently.[13]

It is also worth noting that warming depressed food intake in inactive animals in comparison with inactive animals kept at 21°C. However, despite the reduced food intake, body weight was parallel to that of the Inactive rats kept at 21°C. This result is consistent with previous findings with females of a different strain, Wistar hooded rats (Ref. 25, Experiment 3) where, once female rats had lost 20% of body weight, denial of wheel access at room temperature (22°C) was not sufficient to keep the rats alive. Raising the AT (29.5°C); however, diminished the rate of weight loss and even allowed weight recovery even though the recovering animals ingested significantly less food than the animals kept at 22°C. A plausible explanation for this outcome may lie in the buffering effect of high AT over metabolic demands for maintaining body temperature in the Inactive animals in such a way that the energy savings would allow them to maintain body weight in spite of their reduced food intake.

In contrast, no depressed food intake was observed for the warmed Active rats (see Fig. 2). Moreover, all of the warmed active animal gained weight and recovered (Fig. 1, bottom panel), which was probably due to the fall in energy expenditure by reduced running (Fig. 1, top panel). Bearing in mind this effect of warming for the active and inactive rats, one is compelled to consider the repercussions for the refeeding process in the treatment of AN patients. Hence, from a translational perspective, the supply of heat to AN patients may aid to (a) control hyperactivity,[26] which has an intrinsic reinforcing value for AN patients[27] and poses a threat to weight restoration; and (b) in accordance with the present findings, permit the use of lower caloric supplementations during refeeding without affecting the rate of weight gain, thus reducing the

hormonal and psychological side effects linked to the increased thermic effect of food and its uncomfortable consequences for malnourished patients.[28–30]

Notwithstanding, a number of limitations of this study should be addressed. First, though a: "substantial homology exists across mammalian species in the functional organization of the weight-regulatory system across mammalians" (Ref. 31, p. 661), ABA is a poor model of the higher cognitive processes involved in the supposedly voluntarily food restraint in AN controlled by brain areas involved in cognition, especially the right prefrontal cortex.[32] Nevertheless, the increased running in active rats was unforced, and their lower food intake during meal times with respect to the inactive rats (compare food intake of active versus inactive rats during Phase I in the Fig. 2) was not imposed by the experimental conditions. Thus, the prefix "self" in the term "self-starvation" is equivocally employed in the description of reduced food intake in the rat as it does not refer to a voluntary decision by the rat. Likewise, when applied to humans, the term "self-starvation" presupposes the "wilful" restriction of food intake which may be misleading as this behavior may be beyond the voluntary control of patients. It is also worth noting that rats recover when removed from the experiment and are provided continuous access to food, or that weight loss is only transient if access to the activity wheel is under food ad libitum[33,34] whereas human patients self-starve in the context of abundant food supply.

A second limitation of the study is that it does not provide evidence of the mechanism of action through which a straightforward experimental manipulation such as the increase of ambient temperature produced the previously described behavioral changes in the rats. However, the findings invite one to speculate on the role of body temperature in the whole process of deterioration and recovery from ABA. Rats submitted to ABA become hypothermic as weight loss advances due to increased running and insufficient food consumption; and, although bouts of running increase body temperature, in the long run activity accelerates further body weight loss.[13] However, if given the possibility of gaining heat from a warming source, rats display a different behavioral thermoregulation pattern as they prefer to remain still over a warming plate instead of running on the wheel and thus do not become hypothermic.[24] Furthermore, increased body temperature has been reported in some treatments that increase survival in ABA, such as olanzapine[35] and the Agouti-related protein, AgRP, an endogenous antagonist of the MC system.[16,17] Interestingly, leptin also prevented hypothermia in rats but its additional food intake suppression aggravated weight loss and survival was impossible.[15]

Because of the integrated, nonlinear nature of energy homeostasis neurocircuitry, the most up-to-date efforts to find a single peptide or hormone for ABA recovery have been fruitless.[31] An example of the complexity and redundant nature of neural networks controlling food intake and energy homeostasis, has been presented in a recent publication where ABA rats were treated with a potent orexigenic peptide, neuropeptide Y which, instead of helping rats to recover, increased running activity and reduced food intake further aggravating weight loss.[36] In this context, the beneficial effects of warming ABA rats both for the prevention[25] and reversal of full-blown ABA outstrips those attained by other treatments such as fluoxetine,[37] and the atypical antipsychotic, olanzapine,[35] which have been shown to date to be largely unsuccessful in improving the human disorder.[38–40] Other pharmacological agents, such as AgRP, and leptin have not yet been tested in AN patients. However, in the case of leptin, its utility as a potential therapeutic agent in AN has led to some concern[41] because of its negative impact on food intake. Although body temperature was not measured in our study, the results are consistent with the hypothesis that body temperature is an important parameter in activity-based anorexia, hence hypothermia in AN should be given more attention in future research and treatment.

The development and testing of relevant animal models is in line with translational approaches designed to improve our understanding of the mechanisms underlying anorexia nervosa.[42] In this context, the utility of animal models is not so much an issue of homology or analogy, but as a means of generating new hypothesis and improving treatments).[43] In this sense, the present study strives to bridge the gap ever since Gull's recommendation in 1873 for the application of external heat to patients in his seminal paper in which the term "anorexia nervosa" was coined.[44] Interestingly, this recommendation was based on animal studies, mainly birds, performed by the Swiss physician, Chossat.[45] However, though Gull identified excessive activity as a relevant sign in the disorder, his recommendation for heat supply was not targeted at this remarkable clinical sign. This connection was first established in a article reporting three different strategies for providing heat as a specific strategy to help patients control excessive physical activity.[26]

Although it would be premature to draw firm conclusions from the findings of our study, they underscore the need for further research and offer new avenues on the use of heat as an adjunctive treatment for AN.[46,47]

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