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► To cite this version:

Laura Di Lodovico, Hanna Hatteea, Céline Couton, Philibert Duriez, Janet Treasure, et al.. Physical exercise-related endophenotypes in anorexia nervosa. *International Journal of Eating Disorders*, 2021, Online ahead of print. 10.1002/eat.23503 . inserm-03170394

HAL Id: inserm-03170394

<https://inserm.hal.science/inserm-03170394>

Submitted on 16 Mar 2021

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Physical exercise-related endophenotypes in Anorexia Nervosa

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Short running Title: Physical exercise endophenotypes in Anorexia Nervosa

Trial registration number: NCT02995226

Word count

- Abstract : 227 words

- Main text : 2559 words

Statements

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Acknowledgements

Laura Di Lodovico and Hanna Hatteea equally contributed to the realization of this paper.

Statement of ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This protocol was approved by the Île-de-France III Ethics Committee and the CNIL (Commission Nationale de l'Informatique et des Libertés). Written informed consent was obtained from each participant before inclusion.

Disclosure statement

The authors have no conflicts of interest to declare.

Funding sources

This study received a grant research from the “Fondation de l'Avenir” [Grant number: AP-RMA-16-040].

Janet Treasure acknowledges financial support from the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health award to the South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry, King's College London.

Author contributions

Laura Di Lodovico: original draft preparation, writing and editing, visualization, formal analysis, investigation, data curation.

Hanna Hatteea: conceptualization, methodology, investigation, data curation.

Céline Couton : investigation, data curation.

Philibert Duriez: investigation and supervision.

Janet Treasure: review and editing.

Philip Gorwood: conceptualization, methodology, project administration, supervision, formal analysis, resources, funding acquisition, review and editing.

Abstract

BACKGROUND

The persistence of physical exercise in Anorexia Nervosa (AN) despite underweight and its maintaining factors are poorly understood. The aim of this study was to explore the attitudes towards physical exercise and its effects on emotions, cognitive functioning and body image perception in patients with AN, and to search for exercise-related endophenotypes of the pathology.

METHODS

Physical exercise dependence, quantity and dysregulation were assessed by the Exercise Dependence Scale (EDS), the Godin Leisure Time Exercise Questionnaire (GLTEQ) and a standardized effort test in 88 patients with AN, 30 unaffected relatives and 89 healthy controls. Changes in positive and negative affect, cognitive rigidity, and body image distortion were measured before and after the effort test in the three groups.

RESULTS

Patients with AN had higher scores on the EDS and the GLTEQ and used more effort in the standardized effort test. These three measures of physical exercise correlated with negative emotions at baseline. After the effort test, patients with AN had marked emotional improvement, a moderate increase in body image distortion and a small increase in cognitive rigidity compared to HC. Unaffected relatives also had a significant post-exercise increase of positive emotion.

CONCLUSIONS

The mood-related drive for physical exercise has the characteristics of an endophenotype of the disorder. Excessive and driven physical exercise may be state-associated features of AN, driven by the positive effect on emotional wellbeing.

Keywords: Anorexia Nervosa, Physical Exercise, Endophenotype, Emotions, Body Image.

Anorexia Nervosa (AN) is characterized by persistent restriction of energy intake leading to significantly low body weight, a fear of becoming fat and a distortion of body image (American Psychiatric Association, 2013). Besides food restriction, starvation and purging behaviours, strategies to control weight and shape encompass an excessive and inappropriate practice of physical exercise (Dalle Grave, Calugi, & Marchesini, 2008; Meyer, Taranis, Goodwin, & Haycraft, 2011; Rizk et al., 2015).

A paradoxical increase in motor activity, in the context of the frailty associated with illness progression, has been found in up to 85% of patients with AN (Rizk et al., 2015; Sauchelli et al., 2015; Stiles-Shields, Bamford, Lock, & Le Grange, 2015). The unique character of this persistent drive to physical exercise leads to the hypothesis that driven (i.e. intense and compulsive) exercise constitutes an endophenotype of the disorder (Casper, 2016; Stiles-Shields et al., 2011). This hypothesis is further supported by the fact that the polygenic risk score (PRS) of anorexia nervosa significantly correlates ($r=0.17$; $p=10^{-4}$) with the PRS of physical activity (Watson et al., 2019).

The mechanism underpinning the maintenance of excessive physical exercise at advanced stages of AN is unknown. One hypothesis is that the mood regulating and anxiolytic properties of physical exercise may be involved (Dishman, 1985; Gümmer et al., 2015; Keyes et al., 2015). Other explanatory factors include enhanced cognitive rigidity (Di Lodovico & Gorwood, 2019) leading to highly stereotyped exercise routines, obsessive-compulsiveness (Halmi et al., 2005; Shroff et al., 2006) and an alteration of the reward system towards exercise and food restriction (Giel et al., 2013; O'Hara, Campbell, & Schmidt, 2015). These findings are integrated into the cognitive-behavioural model proposed by Meyer et al. (Meyer et al., 2011). In this model mood dysregulation, cognitive rigidity and distortion of body image are involved in a vicious circle whereby physical exercise is used as a strategy to cope with negative emotions and negative body perceptions.

The persistence of high motivation to exercise after weight restoration suggests that the tendency towards excessive physical exercise might be a state-independent, clinical feature of AN pathology (Klein et al., 2010; Shroff et al., 2006). The possible familial, endophenotype nature of this trait has not been studied. Endophenotypes are primarily state-independent, heritable subclinical traits associated with illness in the population, tending to co-segregate with illness within families and thus found in non-affected family members at higher rates than in the general population (Gottesman & Gould, 2003).

In the present study, the hypotheses tested were that patients with AN would show (1) higher levels of excessive and driven physical exercise compared with healthy controls, that (2) physical effort would increase positive emotions, and be associated with changes in cognitive rigidity and body image distortion (3), and that these effects have endophenotypic characteristics, i.e. are greater in unaffected relatives of patients with AN than in healthy controls.

Materials and Methods

Participants

The present study utilizes data collected as part of a monocentric open trial (NCT02995226). Consecutively admitted patients with AN, first-degree unaffected relatives (UR) and healthy controls (HC) were offered the opportunity to participate in this study. In total, 207 participants were included in three groups by parallel assignment: 1) AN (n=88, including 68 inpatients and 20 outpatients), 2) UR (n=30), all unrelated to the patients included, and 3) HC (n=89).

Inclusion criteria for the AN group were: female sex, age between 18 - 50 years, Body Mass Index (BMI) between 14 and 17.5 kg/m², and diagnosis of AN according to the DSM-5 criteria (American Psychiatric Association, 2013). The Eating Disorder Inventory-2 and the MINI (Mini-International Neuropsychiatric Interview) 6.0.0 for DSM-IV (Sheehan et al., 1998) were performed by trained psychologists or psychiatrists.

Inclusion criteria for UR and HC were: female sex, age between 18 - 50 years, BMI > 17.5 kg/m², and no personal history of eating disorder.

Exclusion criteria for all groups were: contraindications to the practice of an intensive sport, personal history of stroke, phlebitis, hypertension and/or heart attack, surgical, musculoskeletal, osteoarticular and/or neurological pathology, a first degree family history of stroke at the age of <45 years, a first degree familial history of heart attack and/or sudden death at the age of <55 years, and the existence of severe psychiatric diagnoses screened by the MINI (lifetime and/or current mood and/or psychotic disorders).

Personal history and/or a current diagnosis of eating disorders according to the MINI and/or the EDI-2 represented an exclusion criterion for the UR and HC groups.

All study procedures were approved by the Île-de-France III Ethics Committee and the *Commission Nationale de l'Informatique et des Libertés*. In accordance with the

Helsinki declaration, written informed consent was obtained from each participant before inclusion.

Instruments

Eating Disorder Inventory-2 (EDI-2). The EDI-2 (Crikquillon-Doublet, Divac, Gaillac, Dardennes, & Guelfi, 1995; Garner, 1991) explores attitudinal and behavioural dimensions relevant to eating disorders. Internal consistency is $>.80$ in patients with AN for the eight EDI original scales (Garner, Olmstead, & Polivy, 1983), $.65$ to $.75$ for the three additional scales (Eberenz & Gleaves, 1994), and $>.60$ in HC (Garner et al., 1983).

Exercise Dependence Scale-R (EDS-R). The EDS-R (Downs, Hausenblas, & Nigg, 2004) is a 21-item assessment of symptoms of exercise dependence based on the DSM-IV criteria for substance dependence. Higher scores indicate more symptoms of exercise dependence (Hausenblas & Downs, 2002). The French version of the EDS-R preserves the structural validity of the original scale and shows acceptable internal consistency, with Cronbach's alphas ranging from $.75$ to $.89$ (Kern, 2007).

Godin Leisure Time Exercise Questionnaire (GLTEQ). The GLTEQ (Godin & Shephard, 1997) allows a quantitative estimate of the average physical exercise practised over a 7-day period (Amireault & Godin, 2015). To ensure the interpretability of the GLTEQ for inpatients with AN, the latter were asked to rate the amount of physical exercise performed during the week preceding the admission at the unit.

Standardized effort test. A standardized effort test was performed by each participant on a bicycle connected to a computer by a TACX hometrainer® software. The standardized effort test is designed to obtain the same load of effort from each participant. During the standardized effort test, heart rate, power (watts), and speed (km/h) were recorded every 30 seconds. There were three phases in this test (Figure 1). In the "spontaneous effort" phase, participants were asked to ride for 1 kilometre at the speed they would subjectively feel as "pleasurable". Next, in the "maximum effort phase", the power of the device automatically rose 30 watts every 2 minutes until the workload became unbearable: the power of the last segment completed corresponded to the maximum aerobic power (MAP). The "imposed effort phase" was a 15-minute ride at 50% of the MAP reached in the second phase. The "effort dysregulation index" was calculated as the percentage of MAP delivered during the "spontaneous effort" phase (figure 1). The higher this percentage, the smaller the subjective difference between "pleasurable" and "maximum" effort, i.e. pleasure linked to physical effort. Baseline glycaemia and time after the last meal were also recorded as potential confounding factors (Kennedy & Scholey, 2000).

Wisconsin Card Sorting Test (WCST). The WCST (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) entails matching presented cards with one of four multidimensional category cards according to implicit, changing rules (Tchanturia et al., 2012). The proxy measure of cognitive rigidity was the percentage of perseverative errors. In order to limit the learning effect the 64-item-version (Kongs, Thompson, Iverson, & Heaton, 2000) was split in half to measure performance before and after the effort test.

Body image distortion assessment. Patients were invited to choose the silhouette that most closely represented their perceived body image among ten female silhouettes, each corresponding to a specific BMI (Mouchès, 1992). Body image distortion was calculated as the difference between the BMI of the silhouette chosen and real BMI (Sala et al., 2012). The order of the images was randomised before and after the exercise to avoid a practice effect.

Positive and Negative Affect Schedule (PANAS). The 10-item version of the PANAS validated in French (Gaudreau, Sanchez, & Blondin, 2006) assesses momentary positive and negative affect on a 5-point Likert scale from “not at all” to “extremely”. The two scales show a good internal consistency with a Cronbach’s alpha $>.90$ for positive scale and $>.80$ for negative items (Gaudreau et al., 2006). The correlation between the two scales is invariably low ($-.15$) (Watson, Clark, & Tellegen, 1988).

Statistical analysis

All data were preliminarily assessed for parametric distribution by the Kolmogorov-Smirnov test.

Student tests for independent samples were employed for inter-group comparisons, in order to assess differences between patients with AN and HC and between HC and UR in the three measures of physical exercise and in the effects on the variables assessed before and after the standardized effort test. To fulfil the criteria for an endophenotype, a variable should be associated with target illness, and be more common in UR than in HC (Gottesman & Gould, 2003) with an effect size of at least 50% of that of the difference between AN and HC (Iacono, Malone, & Vrieze, 2017).

Bivariate correlation analyses were employed separately in the AN, HC and UR groups to assess the relationships between physical exercise measures and emotional state (PANAS), body image distortion and perseverative errors as an index of rigidity (WCST).

An analysis of covariance (ANCOVA) was run to rule out the influence of potentially confounding, uncontrolled variables on the differences found in the variables of interest

between UR and HC, in order to confirm their endophenotypic nature.

All tests were performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Macintosh, Version 21.0. Armonk, NY: IBM Corp).

Results

Group characteristics

Patients with AN were similar in age to HC. UR were older since mothers were included. AN and UR groups had higher body image distortion and lower positive emotions than HC at baseline (table 1).

Characteristics of physical exercise

Patients with AN had higher amounts of weekly exercise, exercise dependence and effort dysregulation indexes than HC. Effect sizes by Cohen's *d* are shown in table 1. The amounts of weekly exercise in AN inpatients (prior to admission) and outpatients were comparable (51.53 ± 31.41 vs 54.90 ± 28.62 METs, $t=.43$; $df=86$; $p=.67$; $d=.11$).

UR had lower exercise levels and dependence, but higher, non-significant ($d=.13$) effort dysregulation indexes than HC (table 1).

The relationship between physical exercise and emotions, cognitive rigidity and body image distortion

In patients with AN, following the experimental effort test, there was a large increase of positive emotions, moderate increases of body image distortion and decreases of negative emotions, and small increase of cognitive rigidity, when compared to HC. See table 1 for effect sizes. Post-exercise increases of positive emotion and body image distortion were uncorrelated ($r=.15$; $p=.18$).

In UR, following the effort test, there was a significant increase of positive emotions compared to HC, with an effect size larger than 50% of that of the difference between AN and HC (table 1). This remained higher after controlling for age and time from last meal ($F(1,117)=6.89$; $p=.01$).

In patients with AN, negative emotions at baseline were significantly correlated with the three measures of physical exercise, and these correlations did not lose statistical significance when the analyses were repeated after excluding the 10 patients diagnosed with depression ($r=.27$; $p=.02$ for the EDS, $r=.31$; $p<.01$ for the GLTEQ and $r=.23$; $p=.04$ for the effort dysregulation index). Body image distortion was positively correlated with the amount of exercise practiced (all correlations are reported in table 2).

In UR, only a positive correlation between body image distortion and the EDS score was found.

Discussion

This study explored the nature of physical exercise in AN, and its relationship with positive and negative emotions, cognitive rigidity and body image distortion. We also explored the familial nature of this relationship to examine for potential endophenotypes.

A tendency to excessive and driven exercise significantly distinguished patients with AN from HC. A strong relationship was found between negative emotions and a more intensive frequency, dependence and dysregulation of physical exercise in AN, suggesting a possible “anti-depressive” drive of physical exercise. This finding was further confirmed by a significant increase of positive emotions after a single bout of exercise in patients but also in UR, fulfilling the criteria of an endophenotype (Gottesman & Gould, 2003). Body image distortion was increased after exercise in patients with AN only, supporting a state-related relationship between body image distortion and physical exercise in AN.

The finding of more pronounced amounts and drive for physical exercise in AN is in line with the literature. High amounts of exercise (Bratland-Sanda et al., 2009), higher levels of exercise dependence (Di Lodovico & Gorwood, 2019), and a stronger willingness to work for the opportunity to exercise (Klein et al., 2010) could be explained by a tendency for AN patients to perceive exercise-related stimuli as more rewarding and pleasant (Giel et al., 2013; Kullmann et al., 2014).

In previous research, negative affect regulation was presented as the main reason for exercise in patients with AN (Bratland-Sanda et al., 2009), higher levels of negative emotions were described in patients who exercise excessively (Shroff et al., 2006), and physical exercise abuse was identified as a predictor of emotional instability in AN (Selby et al., 2015). Our results demonstrate that the positive emotional consequence of physical exercise in AN has the features of an endophenotype. This positive reinforcement (Klein et al., 2010; Walsh, 2013) may lead to the addictive properties of physical exercise in AN (Karr et al., 2017; Klein et al., 2004).

Although positive emotion improved after exercise, body image perception worsened, probably because of abnormal interoception in AN (Jacquemot & Park, 2020). Taken together, the two divergent perceptions of feeling better because of positive emotions and having greater body image distortion might explain the vicious circle that maintains the drive for exercise in patients with AN (Dalle Grave et al., 2008; Hagman et al., 2015).

Several limitations are present in this study. The drive to exercise was not compared in patients with restricting type vs bingeing-purging type, nor in inpatients vs outpatients. Nevertheless, previous studies found comparable attitudes towards exercise between these subgroups (Di Lodovico & Gorwood, 2019; Keyes et al., 2015). This research lacks an assessment of anxious and depressive symptomatology, as subclinical depressive elements could have influenced the PANAS at baseline. Nevertheless, this chance was limited by screening mood disorders and repeating the analyses after excluding the ten patients diagnosed with depression. Potential confounders such as the smaller size and older age of the UR group may have influenced some exercise-related findings. To address this limitation, we controlled those that were statistically different between groups (such as age and time from last meal) in an analysis of covariance, and we analysed all physical efforts parameters according to each participant baseline MAP, therefore controlling for its variability.

The main strengths of this study are the use of an experimental approach, testing a direct effect of physical exercise on the main factors involved in its onset and maintenance, and the assessment of these same effects in UR, exploring for the first time exercise-related endophenotypes in AN.

Conclusion

The mood-enhancing effect of physical exercise could represent an endophenotype of AN, suggesting how and why exercise becomes a dominant form of mood regulation. However, the increased body image distortion following exercise may allow this behaviour to become compulsive. Alternative mood-regulating strategies may be needed to break this vicious circle.

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Figure Legends

Fig. 1. Design of the study testing positive and negative emotions, cognitive flexibility and body image distortion in patients with anorexia nervosa (AN), healthy controls (HC) and unaffected relatives (UR), at baseline (before exercise) and after a bout of physical exercise (after physical effort).

Table Legends

Table 1. Inter-group comparison at baseline, during and after a standardized effort test, of 88 patients with anorexia nervosa (AN), 30 unaffected relatives (UR) and 89 healthy controls (HC).

Table 2. Bivariate correlations between physical exercise measures and emotional status, body image perception and cognitive rigidity in a group of 88 patients with Anorexia Nervosa (AN), 30 Unaffected Relatives (UR) and 89 Healthy Controls (HC). Correlations were calculated separately for each group. Asterisks indicate statistically significant correlations.

Before physical effort → ← Standardized physical effort → ← After physical effort

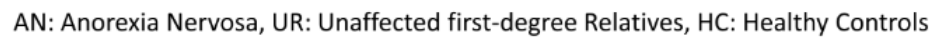


Table 1: Inter-group comparison at baseline, during and after a standardized effort test, of 88 patients with anorexia nervosa (AN), 30 unaffected relatives (UR) and 89 healthy controls (HC).

	AN (n=88)	UR (n=30)	HC (n=89)	AN vs UR				AN vs HC				HC vs UR			
				t	DF	p	Cohen's d	t	DF	p	Cohen's d	t	DF	p	Cohen's d
Baseline characteristics and performances															
Age (years)	26.83 ± 7.57	34.53 ± 11.85	27.46 ± 5.93	-3.33	116	<.01	0.87	.62	175	.54	0.09	-3.13	117	<.01	0.90
BMI (kg/m²)	16.17 ± .99	21.64 ± 2.10	21.82 ± 2.34	-13.75	116	<.01	4.03	15.72	175	<.01	2.35	.34	117	.73	0.06
Baseline glycaemia (g/l)	.98 ± .21	.96 ± .10	.95 ± .15	.44	116	.66	0.07	.87	173	.39	0.13	-.48	116	.62	0.09
Time from last meal (min)	259.39 ± 838.49	122.83 ± 6.39	167.43 ± 164.69	1.52	115	.13	0.19	1.00	174	.32	0.15	2.55	117	.01	0.31
EDI-2 total score	91.07 ± 48.00	21.60 ± 16.98	25.54 ± 20.46	11.56	115	<.01	1.64	11.73	174	<.01	1.78	1.04	117	.30	0.20
EDS score	61.16 ± 27.48	31.73 ± 8.19	39.52 ± 18.45	8.95	116	<.01	0.45	6.37	175	<.01	0.96	2.23	118	.03	0.45
GLTEQ total score	52.30 ± 30.67	28.57 ± 18.63	44.93 ± 24.00	5.04	116	<.01	0.72	1.78	175	.04	0.27	3.85	117	<.01	0.72
Baseline PANAS for positive emotions	10.80 ± 3.21	13.00 ± 2.96	14.92 ± 3.19	-3.45	116	<.01	0.70	8.57	175	<.01	1.29	3.01	117	<.01	0.61
Baseline PANAS for negative emotions	13.63 ± 4.52	8.83 ± 2.48	8.24 ± 2.43	7.25	116	<.01	1.17	9.86	175	<.01	1.49	-1.15	117	.25	0.24
Baseline WCST number of perseverative errors	3.13 ± 2.51	3.07 ± 4.26	2.78 ± 2.39	.08	96	.93	0.02	.82	131	.41	0.38	.34	93	.73	0.09
Baseline body image distortion (kg/m²)	5.08 ± 3.23	2.35 ± 2.32	1.07 ± 2.93	5.00	116	<.01	0.90	8.66	175	<.01	1.30	-2.45	117	.02	0.46
Standardized effort test															
Maximum aerobic power (MAP)	112.27 ± 34.99	139.00 ± 29.64	151.00 ± 32.94	-4.07	116	<.01	0.79	8.30	175	<.01	1.24	1.48	117	.14	0.56
Spontaneous effort average power	38.49 ± 17.96	40.80 ± 13.17	44.15 ± 17.41	.75	116	.45	0.14	2.13	175	.03	0.32	1.10	117	.27	0.20
Effort dysregulation index (average spontaneous power/MAP)	35.08 ± 15.38%	30.15 ± 10.22%	28.52 ± 13.05%	1.98	116	.05	0.34	3.05	175	<.01	0.46	.70	117	.24	0.13
Changes induced by physical effort															
PANAS positive emotions after-before effort	2.69 ± 3.52	1.97 ± 2.52	.52 ± 2.65	1.22	116	.22	0.55	4.65	175	<.01	0.70	2.69	117	<.01	0.55
PANAS negative emotions after-before effort	-.12 ± 2.88	.20 ± 2.04	.85 ± 2.12	.67	116	.50	0.31	2.57	175	.01	0.39	1.50	117	.14	0.31
WCST number of perseverative errors after - before effort	.22 ± 3.36	-.60 ± 4.10	-0.95 ± 2.37	.96	96	.34	0.12	2.33	130	.02	0.40	.44	93	.66	0.12
Perceived body image after - before effort (kg/m2)	.50 ± 1.54	-.01 ± 1.22	.12 ± 1.51	1.82	116	.07	0.09	1.66	174	.04	0.25	.45	117	.65	0.09

AN= Anorexia Nervosa; UR= Unaffected Relatives; HC= Healthy Controls; BMI= Body Mass Index; EDI-2= Eating Disorder Inventory-2; EDS= Exercise Dependence Scale; GLTEQ= Godin Leisure Time Exercise Questionnaire; PANAS= Positive And Negative Affect Schedule; WCST= Wisconsin Card Sorting Test.

Table 2: Bivariate correlations between physical exercise measures and emotional status, body image perception and cognitive rigidity in a group of 88 patients with Anorexia Nervosa (AN), 30 Unaffected Relatives (UR) and 89 Healthy Controls (HC). Correlations were calculated separately for each group. Asterisks indicate statistically significant correlations.

Exercise measures	PANAS baseline positive emotions			PANAS baseline negative emotions		WCST perseverative errors at baseline		Body image distortion at baseline	
	<i>n</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
EDS score									
AN	88	-.15	.15	.27*	.01	.02	.86	.08	.88
UR	30	-.20	.28	-.01	.95	-.10	.58	.04*	.03
HC	89	.29*	<.01	-.04	.74	-.04	.78	.07	.52
GLTEQ score									
AN	88	-.20	.06	.30*	<.01	-.09	.86	.29*	<.01
UR	30	.11	.56	-.07	.71	-.27	.15	-.25	.19
HC	89	.27*	.01	.02	.83	.02	.84	.15	.17
Effort dysregulation index									
AN	88	-.12	.25	.23*	.03	.02	.85	.06	.56
UR	30	-.09	.63	.09	.64	.29	.12	.31	.09
HC	89	-.05	.63	-.05	.62	.05	.67	<.01	.98

AN= Anorexia Nervosa; UR= Unaffected Relatives; HC= Healthy Controls; PANAS= Positive and Negative Affect Schedule; WCST= Wisconsin Card Sorting Test; EDS= Exercise Dependence Scale; GLTEQ= Godin Leisure Time Exercise Questionnaire.