

Wearable physical activity monitoring in inpatients with Anorexia Nervosa - a longitudinal examination

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Abstract

Maladaptive exercise is a clinically relevant but heterogeneously expressed feature of anorexia nervosa (AN). This longitudinal study investigated objectively measured PA patterns in female adolescents with AN compared to a clinical control group with depressive disorders (CD) and healthy controls (HC) and examined their course across inpatient treatment and follow-up (on average 10 months in total).

Seventy-one female adolescents (AN: $n = 28$; CD: $n = 18$; HC: $n = 25$) were assessed at inpatient hospital admission, discharge, and six-month follow-up. Physical activity (PA) was continuously recorded over three days per assessment using wearable inertial sensors and cardiac monitoring. Heart rate (HR), heart rate variability (HRV), acceleration, angular velocity, and combined metabolic equivalent (MET) estimates were derived using a data-driven, multimodal approach. Clinical, anthropometric, psychometric, and hormonal (leptin, ghrelin) data were collected. Linear mixed models and correlation analyses were applied.

At admission, adolescents with AN showed significantly lower overall PA and metabolic equivalent (MET) values compared to both control groups, potentially reflecting restrictive inpatient conditions and physical condition. These group differences resolved over treatment, indicating a degree of PA comparable to control groups by discharge, which persisted at follow-up. Subjectively, adolescents with AN reported higher PA-related stress at all time points and higher perceived PA at follow-up. Acceleration – increase in movement velocity – correlated with self-reported PA at admission, particularly in AN, whereas leptin and ghrelin showed no consistent associations with objective PA measures.

Overall, PA in adolescent AN appears strongly context-dependent and increases during structured inpatient treatment. Multimodal sensor-based assessment provides valuable insights into PA regulation and may support future individualized interventions and relapse monitoring.

1. Introduction

Exercise and physical activity are increasingly recognized as important factors in the development, manifestation, and treatment of mental disorders (1). Depression is a common and disabling disorder in adolescents. Regular physical activity (PA) and structured exercise have been shown in epidemiological studies and large RCTs to reduce depressive symptoms and can serve as an effective strategy to prevent and treat depression (2). Thus, PA is closely linked to psychopathology in adolescents, but the direction and nature of this relationship may differ between psychiatric disorders.

Another mental condition with typical onset in adolescence is Anorexia Nervosa (AN) which is characterized by significantly low body weight, persistent behaviors to prevent weight restoration, and an excessive preoccupation with body weight or shape (3). A common symptom, especially in the active subtype, is maladaptive exercise (ME, (4)) which is highly prevalent (with rates ranging between 31 and 81%) in AN patients (5)

There is no common definition of ME, but similarities between ME patterns and the characteristics of compulsive behaviors have been discussed (4). To better understand the extent and clinical relevance of ME, the degree and manifestation of physical activity (PA) can be assessed using objective methods such as actigraphy, including measurements obtained from multisensory portable devices (5–7). In individuals with AN, ME may represent both a symptom of the disorder and an important consideration during treatment, as it can affect nutritional status, recovery processes, and psychological outcomes (8, 9).

ME is an important prognostic factor in AN (10). Some studies have reported an association between higher or compulsive levels of PA and poorer treatment outcomes (11–13), whereas others have found no clear association between PA levels and treatment or recovery outcomes (14, 15). Beyond its potential relevance for treatment outcomes, PA in AN has also been associated with alterations in metabolic and hormonal markers. In patients with AN, the level of PA (operationalized by daily step counts) was negatively correlated with plasma kisspeptin levels and positively correlated with plasma ghrelin levels (6). Especially leptin levels seem to inform us about the propensity of a person to develop a high extent of PA (15, 16). There is an observed association between PA levels and nutritional intake in AN, with higher activity levels being linked to lower energy consumption (8). However, given that much of the available evidence is based on cross-sectional studies, the directionality and causality of this relationship remain unclear. Similar associations between PA and nutritional intake have also been reported in individuals without eating disorders (17). Somatic consequences of ME in eating disorders include, among others, decreased bone mineral density, cardiovascular complications such as arrhythmias and myocardial fibrosis, hormonal imbalance, hypo- or hyperthermia, kidney and metabolic stress, muscle wasting and decreased strength (18).

The pathophysiological mechanisms and psychological functions of ME in individuals with AN are not fully understood: it may involve both compulsive exercise and exercise dependence, although these constructs reflect partially distinct mechanisms. Compulsive exercise is primarily characterized by a need to exercise to reduce distressing emotions, such as guilt or anxiety associated with not exercising, whereas exercise dependence is associated with tolerance to exercise-related effects and avoidance of withdrawal symptoms (19). In addition, exercise-related cues and information may be perceived as particularly rewarding by individuals with AN, potentially reinforcing persistent exercise behaviours (20). Over the course of illness, these reinforcing processes may contribute to physical activity becoming increasingly habitual, automatic, and difficult to control and therefore exacerbate the condition (21). ME could be used as a deliberate strategy to lose weight, but has also been discussed as an emotion regulation strategy. In line with this, Kolar et al. found that PA was associated with changes in negative affect in adolescents with AN, suggesting that PA may also serve an emotion-regulatory function in this population (22). As altered affect regulation is also a central feature of affective disorders, PA may therefore reflect both disorder-specific mechanisms in AN and more general associations with psychopathology. Further, repetitive movements such as foot fidgeting may indicate attempts to alleviate stress, particularly in anticipation of eating-related events (23). A study that aimed to specifically measure this “non-exercise” PA (i.e., fidgeting behavior) found increased levels when

comparing AN inpatients to control participants during quiet, seated situations (24). The relationship between the extent of PA and treatment outcome in AN patients is complex with contradicting study results (21, 25). While most research in AN has focused on maladaptive forms of exercise, it is well established that adaptive exercise during the course of treatment can promote positive outcomes in those with an eating disorder (26). With regard to the significance of PA during treatment of AN, a paradigm shift has emerged, moving away from traditional approaches that promoted complete abstinence from PA including exercise and sport. Current evidence suggests that appropriately supervised and nutritionally supported PA can be safely integrated into treatment and may support recovery (27). Accordingly, guidelines from the American Psychiatric Association now recommend the gradual reintroduction of PA based on an individual's physical and psychological status, with recent reviews outlining key markers to guide this process throughout treatment (28).

The relationship between ME and eating disorders is multifaceted, requiring careful consideration of individual differences and psychological factors (29). By detecting and classifying movement patterns, it may be possible to identify associations between specific movement behaviors and potentially stressful situations or times of the day, and to investigate longitudinal changes during disease progression and treatment. Consistent with this approach, an inverse association was observed between illness duration and PA, which may reflect reduced physical capacity and lower activity levels in patients with a longer illness duration and poorer physical condition (30). In some studies, ME has been observed during inpatient treatment of AN: prior studies have shown that even under PA restricted inpatient conditions, there is a high variance in PA amongst patients with AN (10, 15, 31). In one study, although patients with AN and controls showed similar average daily step counts and total distance, step-count variability was substantially greater in patients with AN. They showed lower daily average PA and spent more time in very low and low PA levels than controls, while physical inactivity levels were similar (7).

Even under treatment programs that restrict PA, adolescents and adults with AN show considerable variability in activity levels. Kostrzewa and Van Elburg (10) found in a longitudinal study that some inpatients exhibited high PA at admission, which decreased over time, while others with low PA increased their activity during treatment, illustrating divergent trajectories. Leptin levels were highly variable, particularly elevated in the small high-PA group, but did not show a significant association with PA or normalize at follow-up (10). Kemmer and Correll (19) reported similar patterns, with high light-intensity PA at admission associated with lower BMI and lower inpatient BMI gain, whereas moderate-to-vigorous PA levels were comparable between adult patients and controls, but fewer AN patients displayed high PA. Overall, these studies highlight that variability in PA among inpatients with AN is substantial and may influence treatment outcomes. In adolescents, as opposed to adults with AN during treatment, more time spent in sedentary activities and lower levels of light, moderate, and moderate-to-vigorous PA have been observed (27).

Various assessment methods of PA have been reported (21, 27). Physiological markers such as heart rate (HR) and heart rate variability (HRV), which have previously been used primarily in stress research, are often included when determining PA levels (23). Recent research has demonstrated that HR is

decreased and HRV is consistently elevated in patients with AN compared to healthy controls (31, 32). Beyond cardiac markers, activity monitoring has emerged as a promising avenue for identifying behavioral patterns associated with ME. Motion data may reveal the extent, but also the temporal distribution and nature of PA. Metabolic equivalent (MET) is a crucial concept in understanding PA levels. MET quantifies the energy cost of physical activities relative to resting metabolic rate, with 1 MET representing the energy expenditure at rest (29). This corresponds to an oxygen uptake of approximately 3.5 ml O₂ per kilogram of body weight per minute (3.5 ml O₂/kg/min). Physiological and biomedical parameters like HR, acceleration (Acc – rate of increase in movement velocity), and angular velocity (Angular vel., rate of change in angular position) are commonly used as proxies or inputs to estimate energy expenditure, since MET itself is directly tied to oxygen consumption, which is harder to measure directly (34).

Taken together, the available evidence suggests that PA in AN is not simply a measure of general activity, but may reflect a combination of disorder-specific factors, including maladaptive exercise, altered energy regulation, emotion regulation, and the physiological consequences of malnutrition. At the same time, PA is also associated with psychopathology more broadly, including depressive symptoms. Therefore, comparing adolescents with AN not only with healthy adolescents but also with adolescents receiving psychiatric treatment for other disorders can help to determine whether differences in PA are relatively specific to AN or reflect more general effects of psychiatric illness and inpatient treatment. A clinical control group is therefore particularly relevant for interpreting the extent and course of PA in AN. However, it should be mentioned that there have been recent findings of elevated ED psychopathology in different psychiatric disorders (59, 60). In our related study adolescents with AN and those with depression and high body dissatisfaction showed similar ED psychopathology in terms of body dissatisfaction, drive for thinness and body image avoidance (61). In this context, the present study aimed to characterize objectively measured PA in adolescents with AN and to determine whether their PA patterns differ from those of adolescents with depressive symptoms and other psychiatric disorders (CD) and healthy controls (HC). In addition to differences between groups, the longitudinal assessment at admission, discharge, and 6-month follow-up allowed us to examine whether PA changes with treatment and whether the trajectory differs between AN and other psychiatric conditions.

Although much of the literature in AN has focused on ME, ME and overall PA should not be considered synonymous. ME refers to problematic or dysfunctional exercise behavior, whereas objectively measured PA captures the overall amount, intensity, and temporal pattern of movement, including both adaptive and maladaptive activity. In the present study, we primarily focus on objectively measured PA rather than attempting to diagnose or quantify ME, together with self-report measures of aspects of stress and suppression of PA.

Using an approach involving physiological parameters as described above and measuring PA at three time points (hospital admission, discharge and 6-month-catamnesis), we hypothesized based on previous findings:

- At admission and discharge, adolescents with AN would show lower levels of objectively measured PA than HC.
- At admission and discharge, adolescents with other psychiatric disorders (CD) would show higher levels of PA than adolescents with AN, but lower levels than HC ($AN < CD < HC$).
- At 6-month follow-up, adolescents with AN would show higher levels of PA than adolescents with other psychiatric disorders and HC ($AN > CD/HC$).
- Across all three assessment time points, objectively measured PA would be associated with leptin and ghrelin levels.
- Exploratorily, we would examine associations between BMI, self-reported PA, and objectively measured PA.

Given that PA is influenced by both psychopathology and the treatment setting, we expected adolescents with AN to show distinct activity patterns during inpatient treatment because of AN-specific factors and greater activity restrictions related to nutritional rehabilitation, whereas adolescents with other psychiatric disorders would be subject to fewer activity-related restrictions; following discharge, when these treatment-related restrictions are reduced, we expected PA in AN to increase and potentially exceed that of the control groups.

2. Methods

2.1. Study design and procedure:

The current data were collected within the FRAnconian Longitudinal study of Anorexia Nervosa in Adolescents (FRALANA, registered trial with Deutsches Register Klinische Studien, trial ID: DRKS00024675 | April 28th, 2021).

For intra-individual assessments of treatment course and relevant influencing factors, data were collected at three measurement time points from female adolescents with AN, a clinical control group with depression (CD), and a healthy control group (HC):

T1: hospital admission (AN and CD groups)

T2: discharge (AN and CD groups), T1 + 4 months (HC group)

T3: catamnesis (T2 + 6 months)

Each evaluation included three days of RR-interval monitoring as well as the recording of movement profiles

The inpatient treatment program was a multidisciplinary program covered by the German health insurance at a child and adolescent psychiatric hospital. The staff consists of psychiatrists and other physicians, psychologists and other therapists (creative therapists, occupational therapists), nurses,

dietitians, physiotherapists and social workers. An integrative and system-oriented approach aims at recovery of weight, eating behavior and associated psychological issues such as body image concerns, emotion regulation, social skills, school and family issues. In a behavioral therapy-oriented stepped care approach a weight gain of 0.5–1.0 kg/week and a target weight corresponding to the 25th BMI age percentile is aimed for in accordance with the S3-Guideline for the Treatment of Eating Disorders (35, 36). This is achieved through a high level of meal supervision at the beginning of treatment that gradually decreases, as well as an initially high level of restriction of patients' PA that is gradually reduced (e.g. increasing time slots when patients are allowed to leave the ward or spend probational leave days at home or attend their own school as opposed to the clinic school). Dependent on successful weight gain, patients are given strict resting hours of one hour after each mealtime. PA is limited to walking around freely on the ward (1st week of treatment) and later a 10-min walk a day (2nd week of treatment) with increasing time up to 2 hours/day outside the ward. There is no mandatory bed rest. Patients with successful weight gain > 500 g the previous week who are clinically stable may take part in group activities outside the wards and a sports programme (1 hr/week + 15 mins each morning). Total treatment duration is usually about 4–5 months.

The inpatient treatment program for the CD group was similar to that of the AN group and was also covered by the German health insurance. The treatment is conducted on an open ward and follows a behavioral-therapy-oriented, multimodal approach at a child and adolescent psychiatric hospital. It combines individual and group psychotherapy with movement therapy, creative and occupational therapy, psychoeducation, structured daily activities, and social or family-focused interventions and psychopharmacological therapy, when indicated. The aim is to reduce depressive symptoms, strengthen coping and emotion regulation skills, restore daily functioning, and support a sustainable return to home, school, and social life with a total treatment duration of usually about 3 months.

2.2. Participants:

A total of 71 female adolescents between the ages of 12.0 and 17.8 years were included in the current analyses. All participants in the clinical groups (AN and CD) were treated in an inpatient psychiatric treatment setting for children and adolescents at the University Hospital Erlangen. Admission to the hospital occurred based on clinical guidelines and clinical expertise by experienced child and adolescent psychiatrists and psychotherapists (35, 37). Reasons included, e.g., severe ED psychopathology and dangerously low weight for AN patients, or severe depressive symptoms accompanied by significant functional impairment and suicidal thoughts/ behaviour for patients with depression. All of them underwent a multimodal treatment programme according to S3 clinical guidelines based on their primary psychiatric diagnosis.

Inclusion criteria for the AN group were:

- a diagnosis of AN (typical or atypical) according to ICD-10 criteria, assessed by an experienced child psychiatrist or psychologist

Inclusion criteria for the CD group were:

- a diagnosis of a psychiatric mood disorder other than an ED (depressive episode (ICD-10 F32.x or F33.x), emotional disorder with depressive symptoms (F93.x), adjustment disorder with depressive symptoms (F43.2x) or dysthymia (F34.1)), but no comorbid ED
- a body weight corresponding to a Body Mass Index (BMI) $\geq$ 10th BMI age percentile

Antidepressant or antipsychotic medication was allowed for participants in the clinical groups; exclusion criteria for all groups were acute psychotic symptoms, use of illegal substances, medication with sedating effects, chronic somatic diseases, intellectual disability (IQ < 85) and insufficient understanding of the German language.

The HC group comprised $n = 25$ individuals who were recruited from the general population through personal contact and public notifications on hospital grounds. Participants in the HC group had to not have any psychiatric diagnosis at the time they entered the study.

A study assistant informed participants and their parents or legal guardians about the process and purpose of the study and explained each step in detail. Subsequently, all participants and their parents or legal guardians had to provide informed consent before participating in the study.

The groups did not differ in age, but differed significantly regarding BMI SDS with the AN group having significantly lower BMI SDS than the other two groups (see table 1).

[Insert table 1 here]

2.3. Data collection

2.3.1. Demographics and Psychopathology

Demographic features, such as age, height and weight, were taken from participants' hospital files or determined at the study appointment (for the HC group and the catamnesis), respectively. Similarly, an interview was conducted to assess prior physical and psychological conditions and medication usage (see table 2).

[Insert table 2 here]

A psychometric interview (38, 39) was conducted. Eating disorder (ED) psychopathology was assessed with the self-report Eating Disorder Inventory (40). The total score and the subscale 'drive for thinness' were used for analyses, with higher scores implicating higher psychopathology.

The current weight and height, from which the BMI was calculated, were recorded. Body Mass Index Standard Deviation Scores (BMI SDS) were calculated from height and weight as they have emerged as a more suitable metric for characterizing underweight adolescents compared to BMI percentiles. This is due to several specific aspects, including accuracy and ease of interpretation (41, 42).

2.3.2. Objective PA assessment

This study focuses specifically on cardiac data and inertial measurement unit (IMU) sensor data. The IMU data was obtained using two Shimmer IMU sensors (Shimmer Sensing Inc., Dublin, Ireland) placed on the participants' ankles. Cardiac rate data were collected using a chest strap sensor device (Polar H10, Polar Electro Oy, Kempele, Finland) positioned around the torso and a smartwatch (V800, Polar Electro Oy, Kempele, Finland) worn on the wrist. The IMU sensors record 3-axes based acceleration (speed of moving up/ down, left/ right, front/back), as well as 3-axes based gyroscope (rotation speed and angular velocity). This allows for a precise recording of movement. Cardiac rate data (HR and HRV) were recorded using the abovementioned chest strap and corresponding smartwatch to also make the measurements as precise as possible. The data were later used to calculate METs; see section 2.4.2 "PA estimation". Previous studies (e.g. 7, 8, 10, 12) have used similar methods and devices (such as the SenseWear-Armband (BodyMedia, Inc., Pittsburgh, PA) or the Actiheart (CamNtech, Cambridge, UK)) to collect data and subsequently calculate METs. Sensor data were collected for 3 subsequent days at each time point T1-T3. In order to avoid effects of social desirability, participants were informed that PA data would not be accessible for the treatment team and the extent of PA would not have any consequences for their treatment.

2.3.3. Subjective PA assessment

Participants were asked to rate their own PA level and urge to move via a questionnaire containing the following assessments:

- Extent of PA: Assessment of the own level of activity compared to same-age peers – very low, low, similar, high or very high – on a Likert scale from 1 (very low) to 5 (very high)
- Distress: Assessment of feelings of marked stress or discomfort if participants are not able to exercise in a certain situation on a Likert scale from 1 (not at all) to 5 (very strongly)
- Constant PA: Assessment of constant PA even in situations or at times when it seems inappropriate (e.g., during school hours or during meals) on a Likert scale from 1 (not at all) to 5 (very strongly)
- Suppression: Assessment of the extent to which participants are trying to suppress PA on a Likert scale from 1 (not at all) to 5 (very strongly)

The questions relating to stress, constant PA and suppression are thought to be representative of the maladaptive nature of PA and were derived from current literature and questionnaires on ME in EDs 45, 46, 47).

2.3.4. Blood samples

A venous blood sample was collected to determine plasma levels of leptin and ghrelin. The blood samples were taken at a standardized time (between 8 and 9 am) in a fasting state. For participants undergoing inpatient treatment, the blood sample was taken with their routine blood check. HC participants had blood samples taken only at time point T1 due to ethical considerations.

2.4. Data analysis

2.4.1. Movement data preprocessing

Accelerometer, gyroscope and heart rate sensor data were preprocessed for the analysis of PA patterns. All data pre-processing was performed using Python (V. 3.12). Noise and artefacts were removed from the accelerometer and gyroscope data according to established processes by (44, 48). Outliers were removed from the heart rate sensor data and missing data points were interpolated. Subsequently, average values for one-minute windows were created according to (43).

Raw accelerometer (Acc in m/s^2) and gyroscope data (Angular vel. in $^\circ/\text{s}$) from individual x-, y-, z-axes were converted to their Euclidean norm following (43, 44) and filtered with a 0.7 Hz high-pass filter to attenuate low-frequency noise and suppress gravity-induced artefacts. The normalization mitigates the influence of device orientation and ensures that subsequent analyses remain unbiased by sensor placement. Preliminary results in a specific context in subjects with paraplegia suggest that acceleration metrics may have a stronger and more consistent correlation with energy expenditure compared to Angular vel. metrics, which are more sensitive to posture changes or rotation-heavy activities (48).

In addition, instantaneous HR were calculated from the HRV (recorded R-R intervals (RRI)) according to $HR = \frac{60,000}{NN}$, where NN represents the normal-to-normal intervals (NNI) in milliseconds (49). To convert RRI to NNI, three preprocessing steps were applied using the hrv-analysis algorithm library inside Python [<https://github.com/Aura-healthcare/hrv-analysis>]: (1) Outlier removal, (2) interpolation and (3) ectopic beats elimination. Outliers were deleted according to the outlier processing method of Gaussian distribution with three standard deviations empirically selected as the thresholds (upper threshold was 99.73% and the lower threshold was 0.27%), empty values were filled using quadratic interpolation and the Malik rule was applied to delete ectopic beats (50). Subsequently, all data was segmented into non-overlapping one-minute windows following (43). Within each window, the average value of the sensor readings was calculated to provide a measure of overall signal magnitude for subsequent PA analysis.

After the described preprocessing steps, all patients with incomplete or missing data were excluded. A session was included in the analysis if both heart and inertial measurements had been recorded for at least 8 hours, with a maximum recording time per day from waking up until going to bed. An overview of the remaining number of participants with valid data at each time point per group are shown in Table 3. $N = 8$ adolescents were not included due to incomplete data sets. For some participants, valid data were not available for all three measurement days. Reasons were premature discontinuation/withdrawal from the study, discontinuation of recording due to removal of the sensor or hardware or software malfunctions, including cases where timestamp information is missing from sensor recordings

2.4.2. PA estimation

Sensor data was separated into three categories after preprocessing: high, medium and low physical activity. This was derived by utilizing value thresholds from the literature (51, 52), as well as combined data results, to create modality-specific percentile thresholds to incorporate both cardiac and movement data. Subsequently, MET equivalent estimates were determined based on values from the literature (56).

To estimate activity intensity from multimodal sensor signals, we divided the preprocessed data into three activity categories (high, medium and low). The thresholds were calculated from literature values, e.g., typical resting HR is usually between 60–80 beats per minute (bpm) (51, 52). Thus, we used 80 bpm to separate low (rest/very light) from medium (light/typical daily) activity. For the remaining low and high thresholds, percentile thresholds were determined empirically from the combined data of all groups (AN, HC, and DC) to provide common decision boundaries. The chosen percentiles were selected to (i) capture clear low and high regimes visible in the distributions while (ii) retaining sufficient sample size per category and (iii) reducing sensitivity to outliers. Because inertial (accelerometer/gyroscope) and cardiac (HR/HRV) signals differ markedly in scale and distribution, modality-specific percentile thresholds were used. Standardized accelerometry cut-points established for conventional hip- or wrist-worn accelerometers in healthy adult populations are not directly transferable to the present ankle-mounted multimodal IMU setup, preprocessing pipeline and clinical population, as activity thresholds are known to depend on sensor placement, preprocessing procedures, and study population characteristics (53–55). For the accelerometer and gyroscope data, the 95th and 60th percentiles were defined as thresholds for high and low activity, respectively (see Fig. 1A and B). For HR, the 90th and 10th percentiles were applied (see Fig. 1C and D). Since high HRV correlates with low HR and low PA, the percentile values for HRV were inverted relative to those for HR, resulting in 90th and 10th percentiles to define high and low HRV, respectively.

The method offers an effective way to categorize activity based on the distribution of the data (see Fig. 1 for an example).

Figure 1. Illustration of percentile thresholds

[Insert Fig. 1 here]

Notes. Illustration of percentile thresholds for normalized acceleration (A), normalized angular velocity (B), HR (C), and HRV of one participant.

MET-equivalent estimates were then derived by mapping the categorized activity levels to established MET values (3 MET for the cut-off between low and medium PA, 6 MET for the cut-off between medium and high PA (56). With two fixed values for METs, the remaining values were determined using linear regression. To combine modality-specific MET-equivalent estimates across sensors, equal weighting (25% each) was applied to accelerometer, gyroscope, HR, and HRV signals, adapted from (57), to derive a composite activity intensity estimate while avoiding overemphasis of a single sensor modality:

$$\text{MET} = (0.25 \times \text{MET}_{\text{Acc}}) + (0.25 \times \text{MET}_{\text{Gyro}}) + (0.25 \times \text{MET}_{\text{HR}}) + (0.25 \times \text{MET}_{\text{HRV}}).$$

2.4.3. Blood sample analysis

The plasma serum levels of the specified biomarkers were quantified using matched enzyme-linked immunosorbent assay kits (Ghrelin: human ghrelin (total) EZGRT-89K, Merck, Darmstadt, Germany; Leptin: leptin sensitive ELISA, MD53011, IBL International, Hamburg, Germany). The instructions provided by the manufacturer were followed. The blood samples were collected in 2.7 ml EDTA tubes and immediately cooled. Within 30 minutes, the samples were centrifuged at $2000 \times g$ for 10 minutes at 4°C . The plasma was then aliquoted, and the aliquots were stored at -80°C . The serum concentration of each biomarker was measured twice using the Benchmark Plus™ Microplate Spectrophotometer (Bio Rad Laboratories GmbH, USA). The mean and coefficient of variation (CV) were calculated from the two measurements. The plasma concentration in the samples was determined using a standard curve. Samples with a CV greater than 20% were excluded from the analyses, as were values greater than 2.5 standard deviations (SD) from the group mean.

2.4.4. Statistical analysis

Statistical analyses for this section were conducted using IBM SPSS Version 28.0.0.0, with an alpha level of 0.05 applied to determine significance.

Descriptive group differences (AN vs. CD vs. HC) regarding age, BMI SDS, EDI total score, EDI drive for thinness subscale, treatment duration (for AN and CD groups), self-report PA questionnaires and differences in leptin and ghrelin serum levels (for HC only available at T1) were tested by (pairwise) t-tests or chi-squared tests. For t-tests, Cohen's d was used as effect size measure (58).

Linear mixed model analyses were performed. Group (AN/CD/HC), time point (T1-T3), as well as the interaction between these were used as fixed effects. The individual intercept of the participants was used as the random effect. The dependent variable consisted of the different parameters in question: HR, HRV, Acc, Angular Velocity (Angular vel.), mean MET value, low PA, medium PA, high PA. Bonferroni correction was applied to adjust for multiple testing with $\alpha' = .05/(3*8) = .00208$. Leptin and ghrelin levels were analysed in an exploratory manner as the HC group did not have blood samples taken at T2 and T3 (see supplemental material). Bonferroni correction was not applied to these analyses, as they were of an exploratory nature.

Age, BMI SDS, leptin, ghrelin, ED psychopathology and self-assessments of PA were investigated as possible confounding factors by testing for correlations with the PA outcome variables (HR, HRV, Acc, Angular vel., MET, low PA, medium PA, high PA) using Pearson correlation (r) for each time point T1-T3 across groups and for the AN group separately. Bonferroni correction was employed for multiple testing. Due to missing data points, sample size differed between analyses. No consistent significances were found, so these variables were not included as covariates.

To evaluate the relationship between peptide hormone levels and PA as well as (in an exploratory manner) between BMI SDS and self-assessment of extent of PA, correlation analyses were conducted.

Pearson correlation (r) for each time point T1-T3 across groups and for the AN group separately. Bonferroni correction was employed for multiple testing. A new level of significance of α' (T1)=.05/(3*4)=.00417 and α' (T2 and T3, total sample)=.05/(3*2)=.00833 (as ghrelin and leptin were not analyzed for all groups at T2 and T3) was set. Correlations for the AN group were analyzed separately in order to elucidate within-group effects.

3. Results

3.1. Psychopathology and subjective PA

The AN and CD groups showed similar scores regarding ED psychopathology (EDI total score) and drive for thinness (EDI subscale) which differed significantly from the HC group at all time points. Regarding PA self-assessment, participants with AN reported a higher extent of PA than the other two groups at T3 and a higher stress level regarding PA than the HC group at all time points. Both clinical groups reported higher suppression of PA at time point T1. For an overview of assessments see table 4.

[Insert table 4 here]

3.2. LMM analysis of PA parameters and peptide hormones

Regarding the single HR and PA parameters, no significant effects could be determined via linear mixed models (LMM) analysis. For the combined parameters regarding levels of PA, the LMM analysis for high PA showed a significant group*time point interaction, as the AN group had significantly lower values of high PA at T1 than the other two groups did. The values of the AN group assimilated to the values of the other groups at T2 and T3. Similarly, a trend for a group*time point interaction was observed for mean MET. Again, the AN group had significantly lower values at T1 which had assimilated at T2 and T3. For a detailed overview on LMM results see table 5. For the single parameters across time points see Fig. 2.

[Insert table 5 here]

Figure 2. Box plots of movement data, cardiac data, and PA data.

[Insert Fig. 2 here]

Notes. Box plots showing movement data, cardiac data, and PA data across time points T1-T3 for the three groups (AN: patients with AN, HC: healthy control group, CD: adolescents with depressive symptoms and other psychiatric disorders). The center line indicates the median, boxes represent the interquartile range (25th to 75th percentile), whiskers extend to the most extreme data points within 1.5× the interquartile range, and points denote outliers.

LMMs were also calculated for ghrelin and leptin levels to determine group differences and time course in an exploratory manner. An exploratory approach was particularly important due to the HC group not having blood samples taken at T2 and T3. The results showed significant differences between groups,

time points, as well as group and time point interactions for both leptin and ghrelin. Specifically, Leptin levels were lower for the AN group at T1, compared to the HC and DC groups, which had similar leptin levels at T1. Leptin levels of the AN group then increased to a similar level as the HC group at T2, while leptin levels of the DC group surpassed leptin levels of HC and AN at T2. At T3, leptin levels stayed similar to T2 in all groups. Ghrelin levels in the AN and in the DC groups were higher than in the HC group at T1. Ghrelin levels in the AN group then decreased to a similar level as the HC group at T2, while ghrelin levels in the DC group stayed similar to T1. At T3, ghrelin levels in the AN group increased again, while they decreased in the DC group, reaching a similar level to the HC group. Please see supplementary material (table S1 and figure S1) for the full results.

3.3. Correlation analysis

Using α' , the following correlations were found:

Time point T1:

For the total sample:

- Between BMI SDS and HR ($r=.437, p=.001$)
- Between BMI SDS and HRV ($r=-.490, p<.001$)
- Between BMI SDS and high PA ($r=.365, p=.004$)
- Between EDI (total score) and HR ($r=.408, p=.002$)
- Between EDI (total score) and low PA ($r=-.381, p=.002$)
- Between EDI (drive for thinness) and HR ($r=.424, p=.002$)
- Between self-assessment of extent of PA and Acc ($r=.429, p=.003$)

For the AN group only:

- Between self-assessment of extent of PA and Acc ($r=.636, p=.003$)
- Between self-assessment of extent of PA and high PA ($r=.668, p=.001$)
- Between self-assessment of constant PA and Acc ($r=.625, p=.003$)

Time point T2:

For the total sample: no significant correlations between peptide hormones, BMI SDS, self-assessment and sensor data.

For the AN group:

- Between BMI-SDS and low PA ($r=-.716, p=.006$)
- Between BMI-SDS and mean PA ($r=.752, p=.003$)

For the full results table of the correlations, please see tables S2 and S3.

Time point T3:

For the total sample and the AN group: no significant correlations between peptide hormones, BMI SDS, self-assessment and sensor data.

3.4. Participant numbers

Participants numbers differed between analyses based on available data points. A total of 32 participants dropped out of the study: 14 participants dropped out during or after T1 ($n_{AN} = 8$, $n_{DC} = 3$, $n_{HC} = 3$) and 18 participants dropped out after T2 ($n_{AN} = 10$, $n_{DC} = 5$, $n_{HC} = 3$). Reasons for discontinuation included discharge against medical advice ($n_{AN} = 6$, $n_{DC} = 1$), inability to contact participants ($n_{AN} = 2$, $n_{DC} = 1$, $n_{HC} = 1$), relocation ($n_{AN} = 1$, $n_{DC} = 2$), anxiety ($n_{AN} = 2$), feeling overwhelmed ($n_{AN} = 2$), hospitalization at another facility ($n_{AN} = 1$), discomfort with data collection ($n_{HC} = 1$), lack of time ($n_{HC} = 1$), lack of motivation ($n_{DC} = 1$), being taken into protective custody ($n_{DC} = 1$), as well as unknown reasons ($n_{AN} = 4$, $n_{DC} = 2$, $n_{HC} = 3$). Hence, participants who withdrew from the study were more often in the AN group than in the other two groups, and they dropped out of treatment, were not reachable, or associated negative feelings with participation more frequently. Another eight participants were excluded due to receiving an ED diagnosis during treatment ($n_{atypical\ AN} = 6$; $n_{bulimia\ nervosa} = 2$) after they had already completed part(s) of the study.

4. Discussion

The examination of PA patterns among inpatients with AN revealed differential effects over the course of treatment and during follow-up. In accordance with our expectations we found lower levels of high PA in patients with AN at admission compared to healthy controls and adolescents with depressive symptoms and other psychiatric disorders. Sedentary behavior among patients with AN at the beginning of treatment is common due to restrictions imposed by the behavioral clinical programme itself (62). Efforts by the clinical staff to prevent high levels of PA and treatment plans aim to reduce ME, especially in adolescents with AN with severe underweight and partly medical issues involving, e.g., the cardiovascular system. In a comprehensive review, lower PA levels in adolescents than in adults, particularly during treatment, were attributed to the greater daily demands of adulthood as well as to differences in treatment approaches, with adolescents typically receiving more structured and closely supervised care than adults (26, 63).

Other possible explanations for reduced high PA at the beginning of treatment are physical weakness and other physical symptoms such as low blood pressure and dizziness due to emaciation. Hence, the finding of predominantly low levels of PA at the beginning of treatment is in accordance with other studies looking at PA in the course of inpatient and day clinic treatment (15, 64). These findings may primarily reflect the constraints and characteristics of the inpatient setting rather than participants' motivation or desire to engage in PA. Therefore, this study demonstrates the feasibility of applying the

methods used to capture physical activity behavior in an inpatient population. Due to those limited opportunities for PA in a standardized treatment programme, it would have been interesting to observe patients with AN during a time span before inpatient admission. However, admission is often urgent when patients present with a very low body weight and recruitment would be much more difficult than during inpatient treatment.

When looking at the single parameters, it is important to shed light on a methodological aspect: in our analysis, HR has an important influence, as MET data were calculated via equal weighting of 25% for each sensor. As HR is inherently low and HRV is, according to a considerable body of research (31, 65) – although still not fully conclusive – larger in AN than in HC, the parameters Acc and Angular vel. seem more suitable to predict PA independently of the actual physical state. Accordingly, the reported MET values should be interpreted as relative MET-equivalent estimates reflecting composite activity intensity derived from combined inertial and cardiac sensor signals rather than validated measurements of energy expenditure. Equal weighting was applied as a pragmatic strategy to integrate complementary physiological and movement-related information while avoiding overemphasis of any single sensor signal. This is underlined by the correlation between BMI SDS and HR in our sample at admission (time point T1). Acc, which measures changes in velocity along a straight line, is generally considered a good general-purpose indicator of actual PA (see, e.g., a study comparing various accelerometer-based metrics and their relation to estimated oxygen consumption during PA (66)). Preliminary results in a specific context in subjects with paraplegia suggest that acceleration metrics may have a stronger and more consistent correlation with energy expenditure compared to Angular vel. metrics, which are more sensitive to posture changes or rotation-heavy activities (66). At admission, our participants' self-assessment of PA correlated with the parameter Acc, an interesting concordance of subjective and objective perception as opposed to the other parameters. Interestingly, our two clinical groups were highly similar with regard to ED psychopathology and – except for one difference at the follow-up assessment (T3) – self-reported PA.

As an additional research question, which was not examined in other studies looking at PA in AN (15, 63), our design allowed us to also look at PA in inpatients with depressive symptoms of other psychiatric disorders as a clinical control group. Those patients were treated in the same hospital, but their treatment programme did not involve as many restrictions as that for patients with AN: they were allowed to spend more time outside of the ward and were – given they were not underweight or otherwise in a critical medical state – encouraged from the beginning of treatment to take part in sports (once a week in the treatment programme) and other activities involving movement, such as walks in nature. The adolescents in the CD group were all suffering from depressive symptoms (diagnoses including major depression, emotional or adjustment disorder). In adolescents with depression, research focusing on PA levels over the course of treatment is limited. However, broader studies on adolescents with and without depressive symptoms provide insight into general activity patterns. In a Swedish cohort study on leisure time PA, those adolescents who were physically inactive during leisure time reported feelings of depression more frequently (12%), compared to 5% among those engaging in daily or weekly PA (67). Similarly, Chinese adolescents with a high level of PA had significantly lower odds of depression

compared to their inactive peers (68). Findings of the ALSPAC cohort study, which utilized accelerometers to objectively measure PA, indicated that higher total PA was associated with reduced odds of depressive symptoms (69). So, it could be expected that adolescents hospitalized for depressive symptoms may exhibit even lower baseline PA levels due to the severity of their condition. Discussing the range of aspects of PA in adolescents with depression and other psychiatric disorders would be beyond the scope of this paper focussing on PA in AN; nevertheless, it is worth mentioning that the AN group and the CD group did not show any notable difference in the parameter Acc at admission in our study, given that Acc is likely the most accurate indicator of actual PA (see above).

At discharge, which typically occurred with a BMI within the normal healthy range (provided treatment was not discontinued against professional advice), the AN group still exhibited elevated ED psychopathology compared with the control group. Regarding PA parameters, group differences were no longer detectable with the available data. This is contradictory to a review of prior studies using different, only partly objective measures of PA showing a higher level of PA in patients with AN across different treatment stages compared to healthy individuals (21) and, specifically, results of a still elevated number of daily steps, moderate and vigorous physical activity duration and energy after AN treatment (10). Nonetheless, it is important to note that, although inpatients approaching discharge typically have considerable freedom and numerous opportunities to leave the ward, attend their regular school, and spend entire days and nights at home, adolescents in the AN and CD groups were still receiving inpatient treatment and were therefore not fully able to independently determine all aspects of their daily activities. Sedentary activities on the ward such as therapy sessions which patients were required to attend and rest periods still covered a considerable amount of time (several hours/day) and sports activities, especially for patients with AN, were limited in accordance with the treatment plan and weight. An alternative explanation to the restrictions imposed by the inpatient setting could be that the adolescents might have been more cautious, and parents and other carers might have discouraged patients from ME exercise due to psychoeducation on its negative effects during treatment. Nevertheless, the finding that ME, as captured by combined sensor measurements, was not significantly elevated in patients with AN could be interpreted as a potentially favorable indicator of treatment outcome. It is in line with a long term study on AN inpatients in which adolescents with high levels of PA and those with low levels of PA at the beginning of treatment showed a similar extent of PA at treatment discharge without a correlation with treatment outcome (15). However, only accelerometry data were used in that study. At 6-months follow-up, in a comparatively small patient group with data from all measurements, we found no significant group differences regarding the single parameters. In the AN group, some parameters showed a U shape (ghrelin, HRV) or an inverse U shape (leptin, HR, mean MET), respectively, across the three time points which hints toward a slight relapse regarding physiological parameters (see Fig. 2). However, this observation was not reflected in the statistical results. A longer observation span would be interesting to determine a potential predictive value of the single parameters for ED relapse (e.g. twelve months as in 15) or to look at subgroups with higher vs. lower PA at follow-up.

In this context, neuropeptides leptin and ghrelin levels developed in an expected course over the different measurement time points: leptin showed increasing and ghrelin decreasing levels, across the three time

points signifying trend for an inverted U-curve while the ghrelin levels of the AN group showed a trend for a U-curve, similar to prior studies (70–72). Nevertheless, there are reports of contradictory results: ghrelin values were stable e.g. in Kostrzewa, Van Elburg (15), and a recent meta-analysis on the course of leptin levels suggested persistent low leptin levels during recovery (73). However, the majority of the previous literature and recent longitudinal data including adolescents and young adults suggest that the endocrine abnormalities observed in acute anorexia nervosa, including reduced leptin and elevated ghrelin levels, as well as associated alterations in brain structure, are largely reversible with weight restoration (74). Correlations between reduced leptin and a higher urge for PA have been found (7, 75). In our data, no correlations of leptin or ghrelin with any of the HR and movement parameters were seen, neither in the total group nor within the AN group. The absence of associations between leptin/ghrelin concentrations and these parameters does not necessarily indicate that PA is unrelated to appetite regulation. Rather, in adolescents, circulating appetite-related hormones may be more strongly influenced by pubertal maturation, recent energy intake and overall energy availability than by PA alone (76, 77). Regarding the relation between PA and BMI in AN populations, results are similarly inconsistent, with some studies finding no and some a positive correlation (21). In our study, BMI SDS was correlated with HR at admission in the total sample, but not in the AN group when considered separately. Overall, we found fewer correlations of biological parameters and PA levels in our sample of adolescents with AN and depressive disorders, respectively, than expected.

Limitations:

Several limitations of this study relate to methodological aspects of the study design and the challenges inherent in conducting research with a particularly vulnerable population. Blood samples of HC participants were only obtained at T1 due to ethical concerns, so potential alterations in leptin or ghrelin levels over the course of time could not be considered in that group. A substantial limitation was the high rate of drop-outs due to various reasons (e.g., leaving treatment against medical advice, inability to reach participants after discharge, etc.; see section 3.4).

Moreover, sensor data and HR data collection was difficult in some participants. In spite of detailed instructions, the equipment was sometimes not worn properly and also had to be taken off, e.g., during water activities such as swimming and showering. Especially for the HC group, the correct application could not consistently be monitored. Additionally, the comparison of results across studies investigating PA is difficult due to a high diversity of devices and methods used to measure PA and inconsistent definitions of PA levels (59). Examining the data, we were unable to discern specific movement types among participants. Although inertial sensor-based measures such as step counts may provide complementary information on locomotor activity, the present study focused on deriving overall activity intensity estimates from combined inertial and cardiac sensor signals. Future studies may benefit from integrating validated gait- and step-detection algorithms to further characterize locomotion-specific activity patterns. It would have been interesting to distinguish patterns such as foot fidgeting, but this might be reflected similarly to whole body movements when sensors are worn around the ankle.

Therefore, more specific devices are needed, e.g., a shoe-based sensor (23) or sensors distributed across different locations of the body.

Strengths of the current study are the inclusion of two control groups to compare PA to healthy adolescents, but also to adolescents with other diagnoses in an inpatient setting and the longitudinal design with a follow-up, as well as the range of parameters measured.

Recommendations for future research:

For future studies, longer follow-up periods would be interesting to examine potential indicators of relapse or long-term recovery. To better understand and address the needs of hospitalized adolescents, future studies should investigate potential benefits of integrating tailored PA programs into treatment plans and use sensor technology to evaluate these and other ED treatment programs. It would also be interesting to use advanced sensor technology (small unobtrusive sensors worn at different parts of the body) to better differentiate the characteristics of different movement patterns as potential functional correlates of psychopathological and biological parameters.

Conclusion

Participants in the AN group initially showed lower high PA levels than the two control groups, but this difference had converged by T2 and T3. Significant differences were found in the exploratory analysis of leptin and ghrelin levels across groups and time points. The study faced a number of limitations and future studies should include longer follow-up periods and more advanced sensor technology.

Abbreviations

Acc Acceleration

AN Anorexia nervosa

Angular vel. Angular velocity

BMI Body mass index

BMI SDS Body mass index standard deviation scores

CD Control group with depressive disorders

CV Coefficient of variation

ED Eating disorder

HC Healthy controls

HLP High-level physical activity

HR Heart rate

HRV Heart rate variability

IMU Inertial measurement unit

LMM Linear mixed models

LPA Light physical activity

MET Combined metabolic equivalent

MPA Moderate physical activity

NNI Normal-to-normal intervals

PA Physical activity

PTSD Post-traumatic stress disorder

RRI R-R intervals

SB Sedentary behavior

SD Standard deviations

SSRI Selective serotonin reuptake inhibitor

T1 – T3 Time point 1–3

VPA Vigorous physical activity

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Friedrich-Alexander-University Erlangen Nuremberg (reference number [257_20B]). All participants and their parents or legal guardians provided informed consent before participating in the study.

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No funding was received.

Author Contribution

L.S. contributed to the investigation, formal analysis, visualization, and project administration and was involved in writing the manuscript, including review and editing. L.U. contributed to validation, formal analysis, and visualization and participated in reviewing and editing the manuscript. V.S. contributed to the conceptualization and methodology of the study, as well as to the investigation and project administration. O.A. and O.K. contributed to the conceptualization of the project and provided resources. S.H. contributed to the conceptualization and methodology of the study, investigation, formal analysis, visualization, and project administration. S.H. also prepared the original draft of the manuscript and contributed to its review and editing. All authors read and approved the final manuscript.

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Data Availability

The data generated and analyzed during the current study are not publicly available because they comprise patient data, which, although anonymized, are subject to confidentiality and data protection considerations. The data are available from the corresponding author upon reasonable request, subject to appropriate ethical and data protection requirements.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

Image not available with this version

Figure 1

Figure 1. Illustration of percentile thresholds

Notes. Illustration of percentile thresholds for normalized acceleration (A), normalized angular velocity (B), HR (C), and HRV of one participant.

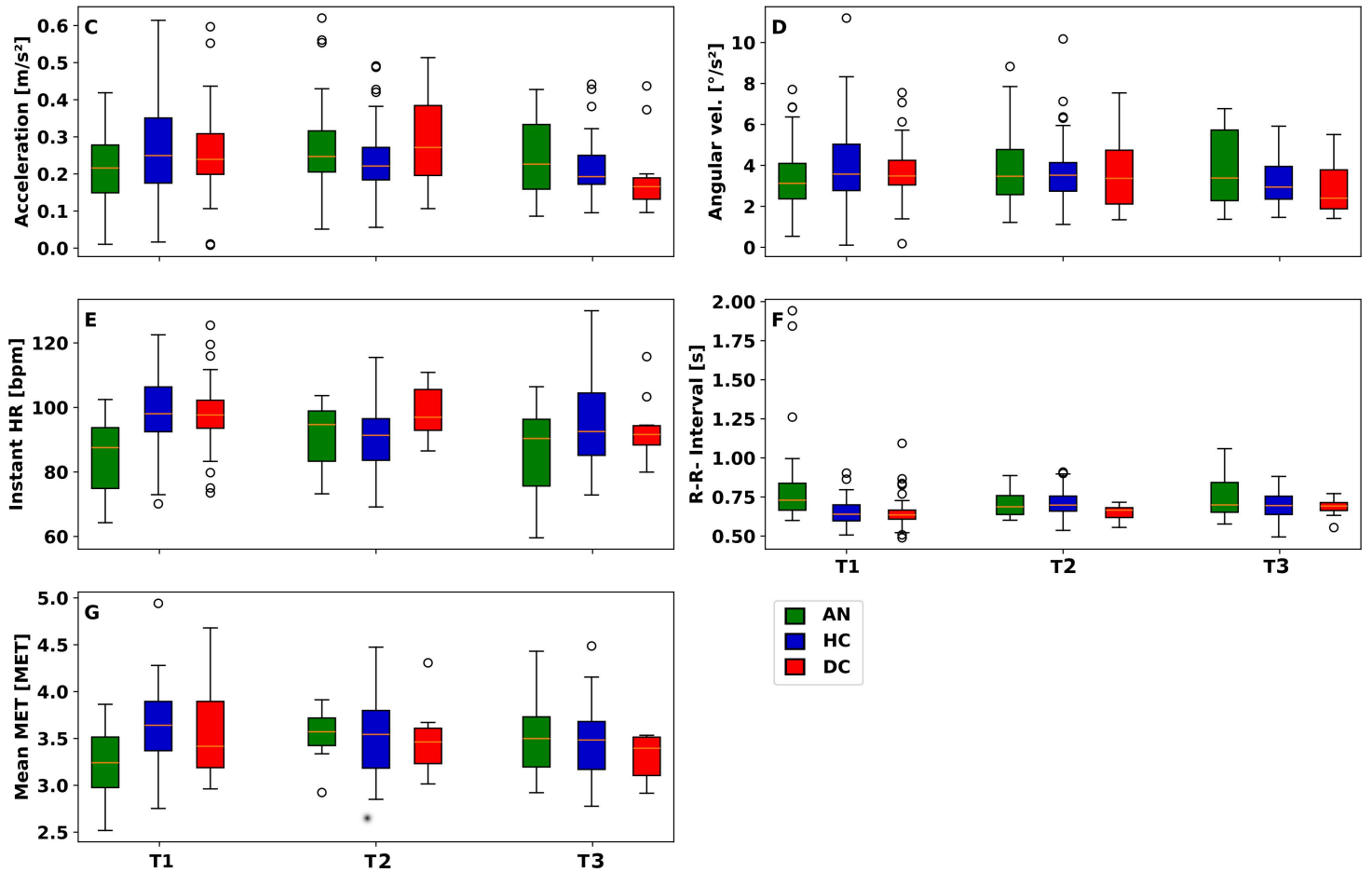


Figure 2

Figure 2. Box plots of movement data, cardiac data, and PA data.

Notes. Box plots showing movement data, cardiac data, and PA data across time points T1-T3 for the three groups (AN: patients with AN, HC: healthy control group, CD: adolescents with depressive symptoms and other psychiatric disorders). The center line indicates the median, boxes represent the interquartile range (25th to 75th percentile), whiskers extend to the most extreme data points within 1.5× the interquartile range, and points denote outliers.

Supplementary Files

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