



# Low Fasting Oxytocin Levels Are Associated With Psychopathology in Weight-Recovered Anorexia Nervosa

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**Abstract:**

Anorexia nervosa (AN), a psychiatric disorder characterized by restriction of food intake despite severe weight loss, is associated with increased comorbid anxiety and depression. Secretion of oxytocin, an appetite-regulating neurohormone with anxiolytic and antidepressant properties, is abnormal in AN. The link between oxytocin levels and psychopathology in AN has not been well explored. We performed a cross-sectional study of 80 women ages 18-45 years old [(20 AN, 26 weight recovered AN (ANWR) and 34 healthy controls (HC)] investigating the relationship between basal oxytocin levels and disordered eating psychopathology, anxiety, and depressive symptoms. Fasting serum oxytocin levels were obtained and the following self-report measures were used to assess psychopathology: Eating Disorder Examination Questionnaire, State Trait Anxiety Inventory, and Beck Depression Inventory – II. We found that fasting oxytocin levels were low in ANWR compared to HC ( $p=0.0004$ ). In ANWR but not AN, oxytocin was negatively associated with disordered eating psychopathology ( $r=-0.39$ ,  $p=0.0496$ ) and anxiety symptoms (state anxiety:  $r=-0.53$ ,  $p=0.006$ ; trait anxiety:  $r=-0.49$ ,  $p=0.01$ ). Furthermore, ANWR with significant disordered eating psychopathology, anxiety symptoms, or depressive symptoms had lower oxytocin levels compared to those with minimal or no symptoms. We conclude that dysregulation of oxytocin pathways may contribute to persistent psychopathology after weight recovery from anorexia nervosa.

## 1. Introduction:

Anorexia nervosa (AN) is a psychiatric disorder affecting mostly young females that is characterized by distorted body image, intense fear of gaining weight, and food restriction despite a very low body mass index (BMI). The estimated incidence of AN is eight per 100,000 persons per year (Hoek, 2006). Comorbid psychiatric disorders are common in AN, with an estimated lifetime prevalence of up to 65% for anxiety disorders and 80% for affective disorders (Herzog, 2007), with these co-morbidities predicting a more severe variant of AN, especially with respect to psychological symptoms and suicide risk (Brand-Gothelf et al., 2014).

Recent evidence suggests that dysregulation of the anorexigenic neurohormone oxytocin may be one of the many factors underlying the psychopathology of AN. In addition to promoting satiety, oxytocin has been linked to disordered eating thoughts and behaviors (Lawson et al., 2012; Kim et al. 2014a) and has been shown to have anxiolytic (Bale et al., 2001; Mantella et al., 2003; Amico et al., 2004; Blume et al., 2008; Yoshida, et al., 2009) and antidepressant (Arletti and Bertolini, 1987; Matsushita, et al., 2010) properties. Administration of oxytocin also reduces anxiety and depression behaviors in rodents (Arletti and Bertolini, 1987, Uvnas-Moberg et al., 1994; Windle et al., 1997; Ring et al., 2006; Peters et al., 2014). Pilot studies in humans have demonstrated that intranasal oxytocin reduces amygdala activity and amygdala-midbrain connectivity and may reduce anxiety in response to psychosocial stress (Heinrichs et al., 2003; Kirsch et al, 2005; de Oliveira et al., 2012). A genetic polymorphism of the oxytocin receptor was shown to moderate the association of maternal depression in early childhood and youth depressive symptoms in adolescence (Thompson et al., 2014). Furthermore, peripheral oxytocin levels are low in depressed compared to non-depressed females (Yuen et al., 2014). In fourteen patients with major depression who did not respond to treatment with 40 mg of escitalopram for at least 8 weeks, the addition of 8 international units (IU) of intranasal oxytocin twice per day over four weeks significantly reduced depressive symptoms (Scantamburlo et al., 2014).

Oxytocin secretion is dysregulated in AN, and the pattern of dysregulation and possible connection to comorbid psychopathology in AN is not fully understood. Mean overnight oxytocin levels are low in AN compared to healthy controls (HC) (Lawson et al., 2011), likely as an adaptive response to nutritional deprivation. Limited data exist on oxytocin levels in subjects who have weight recovered from anorexia nervosa (ANWR), with the most recent study showing the persistence of low oxytocin levels in ANWR compared to healthy controls following full ( $100.5 \pm 1.5\%$  ideal body weight (IBW)) and stable ( $37.2 \pm 6.4$  months) weight recovery (Lawson et al., 2012). The significance of low oxytocin levels in ANWR is not well understood, but suggests an underlying dysfunction of oxytocin pathways.

The only study to date examining the relationship between oxytocin and comorbid psychopathology in AN focused on postprandial oxytocin levels. Postprandial oxytocin levels were high in AN and low in ANWR compared to HC (Lawson et al., 2012) and were positively associated with the severity of disordered eating psychopathology across AN and ANWR and fMRI hypoactivation of food motivation neurocircuitry (hypothalamus, amygdala, hippocampus, orbitofrontal cortex and insula in AN and insula in ANWR compared to HC) in response to visual food stimuli (Lawson et al., 2012). Higher postprandial oxytocin levels were associated with increased anxiety and depressive symptoms across AN and ANWR (Lawson et al., 2013). However, in the postprandial state, these changes in oxytocin levels may be directly explained by food intake or psychopathology (stress, anxiety) related to food consumption. Whether abnormal basal fasting levels of oxytocin are related to psychopathology in AN and ANWR has not been explored. Furthermore, the association between oxytocin levels and psychopathology has not been examined separately in AN, where low weight may underlie changes in oxytocin secretion, versus ANWR, where low weight is no longer a factor.

We hypothesized that lower levels of fasting oxytocin would be associated with increased psychopathology in women with AN regardless of weight status, suggesting that low oxytocin levels may contribute to disordered eating psychopathology, anxiety, and depression.

## **2. Methods:**

### **2.1 Subjects:**

We studied 80 women, age 18-45 years: 20 AN, 26 ANWR and 34 HC, recruited from the community through advertisements and referrals from healthcare providers. Women with AN met DSM-5 criteria as determined by the Structured Clinical Interview for DSM Disorders (SCID) (First, 2002), with IBW less than 85% as determined by the 1983 Metropolitan Life tables. Women with ANWR met DSM-5 criteria for AN in the past, with current weight between 90-120% of IBW. Exclusion criteria for AN, ANWR, and HC subjects were current hormone use, pregnancy or breastfeeding, and diabetes mellitus.

HC were 90-120% of IBW with regular menstrual cycles and no pubertal delay. These subjects had no past or present eating disorder histories as assessed by the SCID and no history of excessive exercise within the last three months (having run more than 25 miles or exercised more than ten hours in any one week).

### **2.2 Procedures:**

This study was approved by the Partners Human Research Committee. Written informed consent was obtained prior to the subject visit.

During the study visit, a complete medical history (including eating disorder, weight, menstrual, and medication histories), physical examination, and urine pregnancy test were performed. Height, metabolic weight, and elbow breadth were measured by research dieticians, and BMI and %IBW were calculated. We obtained BMI by dividing weight in kilograms by the square of height in meters. Frame size was determined by comparing elbow breadth to race-specific norms derived from the US Health and Nutritional Examination Survey-I (Frisancho and Flegel, 1983). We used the Eating Disorder Examination Questionnaire (EDEQ) (Fairburn and Beglin, 1994), State-Trait Anxiety Inventory (STAI

State and Trait) (Spielberger, 1987), and Beck Depression Inventory (BDI-II) (Beck, 1996a) to assess psychopathology. Fasting serum was drawn for oxytocin.

### **2.3 Assessment of Psychopathology:**

The EDEQ is a well-validated self report measure comprising of 28 items based on the Eating Disorder Examination Interview (Fairburn and Beglin, 1994). It is used to assess attitudes and behaviors related to eating patterns and body image over the past 28 days. Four scales are derived: dietary restraint (EDEQ-DR), eating concern (EDEQ-EC), shape concern (EDEQ-SC), and weight concern (EDEQ-WC). A global score (EDEQ-GS) can be calculated to render a dimensional assessment of eating disorder psychopathology. EDEQ scores of 1 standard deviation (SD) above the mean were considered significant for active disordered eating psychopathology in our analysis. Note that published EDEQ-GS scores are available for a number of different healthy populations, and the mean values for EDEQ-GS for these groups differ, with mean + 1 SD values ranging from 1.9 to 3.0 (Luce et al., 2008; Mond et al., 2010; Aardoom et al., 2012; Kelly et al., 2012; Nakai et al., 2014). We considered the general Dutch female population sample, with mean + 1 SD of 1.9 (Aardoom et al., 2012), and the US undergraduate women sample, with mean + 1 SD of 2.91 (Luce et al., 2008) to be most similar to our sample; thus, we decided upon the EDEQ-GS cutoff value of 2.5 to represent a cutoff of approximately 1 SD > mean.

The STAI is a well-validated, reliable instrument for assessing anxiety symptoms. The state scale assesses how subjects feel “right now, at this moment,” and the trait scale assesses how they feel “generally” (Spielberger 1987). Scores of > 46 on the state scale and > 45 on the trait scale (1 SD > mean) were considered significant for active anxiety in our analysis (Vautier, 2004).

The BDI-II is a validated, reliable questionnaire for assessing symptoms of depression. It assesses the severity of depression over the prior two weeks, using DSM-IV criteria (Beck, 1996a). The following cutoffs were used: 0-13 minimal depressive symptoms, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression (Beck et al., 1996b).

## 2.4 Biochemical Analysis:

Serum was stored in a  $-80^{\circ}\text{C}$  freezer until analysis. Oxytocin was measured in unextracted serum by ELISA (Assay Designs, Inc., Ann Arbor, MI, USA) as reported (Lawson et al., 2015). The limit of detection (lowest concentration distinguishable from zero with 95% confidence) was 12.5 pg/mL. In-house QCs had a mean of 152 and 338 pg/mL, respectively and a between-assay coefficient of variation of 15 and 18%, respectively.

## 2.5 Data Analysis:

JMP Pro statistical discovery software (version 11) was used for statistical analyses. Clinical characteristics, oxytocin levels, and psychopathology were compared using Fisher's Least Significant Difference Test. Additional correction for multiple comparisons is not indicated when this method is used for 3-group comparisons (Meier, 2006). Given evidence that oxytocin levels may be different between the binge/purge and restricting subtypes of AN (Demitrack et al., 1990), secondary post-hoc analyses excluded patients with binge/purge subtype. Oxytocin levels were compared across AN, ANWR, and HC only in subjects with restricting subtype of AN. We also controlled for potential confounders using multivariate least-square analyses. Pearson's correlations were used to investigate associations between oxytocin levels and psychopathology separately in AN and ANWR groups. Statistical significance was defined as a 2-tailed  $p$  value  $\leq 0.05$ . Data are reported as mean  $\pm$  standard error of the mean (SEM).

To investigate oxytocin levels in ANWR with vs. without significant disordered eating psychopathology, we divided ANWR into subjects with EDEQ-GS  $\leq 2.5$  (approximately 1 SD  $>$  mean for healthy age-matched population) vs. subjects with EDEQ-GS  $> 2.5$ , and then compared mean oxytocin values in these groups using Student's T-test.

We performed similar analyses with STAI State, STAI Trait, and BDI-II scales. ANWR were divided into subgroups based on predetermined cutoffs, and the fasting oxytocin values were compared

between these subgroups. For the STAI, scores of  $> 46$  on State scale and  $> 45$  on Trait scale (1 SD  $>$  mean) were used as the cutoff values to represent active anxiety (Vautier, 2004; Lawson et al., 2013). For the BDI-II, we used a cutoff of  $\leq 13$  to represent the group with no/minimal depressive symptoms and  $BDI > 14$  to represent the group with evidence of clinical depression (Beck et al., 1996b)



### **3. Results:**

#### **3.1 Subject Characteristics:**

Table 1 presents subject characteristics. Mean age was  $23.9 \pm 0.6$  years and did not differ across groups. Per study design, weight, BMI, and %IBW were low in AN compared to ANWR and HC, but did not significantly differ between ANWR and HC. Mean number of months since weight recovery reported by ANWR was  $37.2 \pm 6.4$ , with values ranging from 5 to 94 months. Two out of 20 AN (10%) reported significant current bingeing/purging behavior (subject 1 with 4 bingeing/0 purging episodes, subject 2 with 4 bingeing/1 purging episodes over the past 28 days). Three out of 26 ANWR (12%) reported significant current bingeing/purging behavior (subject 1 with 10 bingeing/0 purging episodes, subject 2 with 28 bingeing/28 purging episodes, subject 3 with 3 bingeing/3 purging episodes over the past 28 days). Fourteen out of 20 (70.0%) AN self-reported amenorrhea, compared to 3 out of 26 (11.5%) ANWR and no HC.

#### **3.2 Eating Disorder Psychopathology:**

Figure 1 presents EDEQ scores. Global scores and scores on all subscales were higher in AN and ANWR compared to HC ( $p < 0.0001$ ). While EDEQ-EC scores were higher in AN than ANWR ( $p = 0.01$ ), there were no significant differences in other subscale or global scores between AN and ANWR.

#### **3.3 Anxiety and Depressive Symptoms:**

Figure 2 presents symptoms of anxiety and depression as measured by STAI State, STAI Trait, and BDI-II. Anxiety and depression scores were higher in AN and ANWR compared to HC ( $p < 0.0001$ ), and did not significantly differ between AN and ANWR.

#### **3.4 Oxytocin Levels:**

Fasting serum oxytocin levels are presented in Table 1. Oxytocin levels were low in ANWR compared to HC ( $p=0.0004$ ), and this difference remained significant after controlling for BMI and estrogen status, as assessed by presence or absence of amenorrhea. Levels in AN were intermediate, but differences between AN and HC ( $p=0.08$ ) or AN and ANWR ( $p=0.12$ ) did not achieve statistical significance. When the two AN and three ANWR subjects who reported significant bingeing and/or purging were excluded from the analyses, oxytocin levels remained low in ANWR compared to HC ( $p=0.001$ ).

### **3.5 The Relationship Between Oxytocin and Disordered Eating Psychopathology:**

The relationship between fasting serum oxytocin levels and the severity of disordered eating psychopathology in ANWR is shown in Table 2. Fasting oxytocin levels were negatively associated with EDEQ-WC ( $p=0.04$ ) and global scores ( $p<0.05$ ). The correlations between oxytocin and EDEQ-DR ( $p=0.06$ ), EDEQ-EC ( $p=0.09$ ) and EDEQ-SC ( $p=0.12$ ) subscales were also negative, but did not achieve statistical significance. There were no associations between oxytocin levels and EDEQ scores in AN.

Figure 3 shows mean oxytocin levels in ANWR with vs. without disordered eating psychopathology as determined by EDEQ-GS scores. Fourteen ANWR had  $EDEQ-GS \leq 2.5$  (no significant disordered eating psychopathology) and 12 had  $EDEQ > 2.5$  (significant disordered eating psychopathology). Mean fasting oxytocin levels were lower in those with vs. those without significant disordered eating psychopathology ( $776 \pm 114$  vs.  $1144 \pm 126$  pg/mL,  $p=0.04$ ).

### **3.6 Relationship Between Oxytocin and Anxiety Symptoms:**

The relationship between fasting oxytocin levels and symptoms of anxiety in ANWR is presented in Table 2. Fasting oxytocin levels were negatively associated with STAI State ( $r=-0.53$ ,  $p=0.006$ ) and STAI Trait ( $r=-0.49$ ,  $p=0.01$ ). There were no associations between fasting oxytocin levels and anxiety symptoms in AN.

Figure 4 shows mean oxytocin levels in ANWR with vs. without significant anxiety symptoms. Fifteen ANWR had normal STAI State scores ( $\leq 46$ ) and 11 had abnormal scores ( $>46$ ) indicating significant anxiety symptoms. Mean fasting oxytocin levels were low in ANWR with current anxiety symptoms compared to those with normal STAI State scores ( $685 \pm 130$  vs.  $1186 \pm 98$  pg/mL,  $p=0.004$ ). Ten ANWR had normal STAI Trait scores ( $\leq 45$ ) and 16 had abnormal scores ( $>45$ ). Mean fasting oxytocin levels were low in ANWR with significant trait anxiety symptoms compared to those without ( $812 \pm 118$  vs.  $1233 \pm 106$  pg/mL,  $p=0.02$ ).

### **3.7 Relationship Between Oxytocin and Depressive Symptoms:**

The relationship between fasting oxytocin levels and symptoms of depression in ANWR is shown in Table 2. Fasting oxytocin levels were negatively associated with BDI-II at the trend level ( $r=-0.34$ ,  $p=0.09$ ). There were no associations between fasting oxytocin levels and depressive symptoms overall in AN.

Mean oxytocin levels in ANWR with clinical depressive symptoms (BDI-II 14-63,  $n=13$ ) compared to those with minimal or no depressive symptoms (BDI-II 0-13,  $n=13$ ) are shown in Figure 5. Mean fasting oxytocin levels were low in those with clinical depressive symptoms compared to those with minimal or no symptoms ( $738 \pm 115$  vs.  $1210 \pm 112$  pg/mL,  $p=0.007$ ).

#### 4. Discussion:

To our knowledge, this is the first investigation linking low fasting peripheral oxytocin levels to increased disordered eating psychopathology and symptoms of anxiety and depression in women who have weight-recovered from AN. Importantly, these data suggest that dysregulation of oxytocin pathways in women following weight recovery from AN may relate to persistent psychopathology.

Prior studies demonstrated oxytocin dysregulation in women with active AN. Low nocturnal serum and fasting cerebrospinal fluid (CSF) levels of oxytocin, as well as failure of oxytocin levels to appropriately increase in response to stimulation in AN indicate a possible oxytocin deficiency in the setting of chronic starvation (Demitrack et al., 1990; Chiodera et al., 1991; Lawson et al., 2011). Differences in methylation status of the oxytocin receptor between AN and controls have been reported, although it remains unclear whether these epigenetic differences confer risk or are secondary to the illness (Kim et al., 2014b). There are limited data on oxytocin regulation following weight recovery in AN, with studies to date showing inconclusive results. In a study of 7 women with restricting AN (with 3 subjects followed longitudinally through weight recovery), CSF oxytocin levels normalized following three weeks of weight restoration to  $84.7 \pm 2.0\%$  of average body weight (Demitrack et al., 1990). Chiodera et al. similarly found that oxytocin levels in response to stimulation with insulin or oral ethynylestradiol normalized in seven low weight AN who achieved a mean weight of  $95.3 \pm 1.4\%$  of average body weight over a period of 16-17 weeks (Chiodera et al., 1991). These data suggest that oxytocin secretion may normalize acutely following short-term weight restoration in AN. In contrast, in a study of 13 AN, 9 ANWR ( $98.3 \pm 3.8\%$  IBW, stable for  $44.4 \pm 12.0$  months) and 13 healthy controls, we previously found that fasting and postprandial serum oxytocin levels were low in ANWR compared to controls (Lawson, Holsen et al. 2012). Our data in a larger group of women now confirms low fasting serum oxytocin levels in ANWR following full ( $100.5 \pm 1.5\%$  IBW) and stable ( $37.2 \pm 6.4$  months) weight recovery, independent of BMI or presence/absence of amenorrhea. Whether low oxytocin levels in ANWR represent a trait of AN or a scar from chronic starvation is unknown.

Abnormal oxytocin secretion has previously been linked to disordered eating psychopathology in AN. In a prior study, we found a strong association between postprandial oxytocin levels and EDEQ scores in a group of AN and ANWR. Furthermore, in a visual food-related fMRI paradigm, oxytocin levels accounted for fMRI hypoactivation of brain regions involved in food motivation in AN compared to controls, as well as in ANWR compared to controls (Lawson et al., 2012). Kim et al. recently demonstrated that a single dose of intranasal oxytocin to women with AN reduced selective attention to images of food and fat body parts, indicating that oxytocin administration may improve eating disorder psychopathology (Kim et al. 2014a). We now demonstrate that lower fasting serum oxytocin levels in ANWR are associated with greater severity of disordered eating psychopathology, including higher weight concern and global EDEQ scores. In addition, those ANWR with significant disordered eating psychopathology as assessed by the EDEQ have lower oxytocin levels compared to those without psychopathology. Although we cannot infer causality, these results suggest that oxytocin dysregulation may reflect or contribute to disordered eating psychopathology in ANWR.

Similarly, abnormal oxytocin secretion may in part explain anxiety symptoms in anorexia nervosa. In studies of female oxytocin knockout mice tested in an exposed to psychogenic stressors (EPM) task, the animals spent less time in the open arms of the maze than controls, indicative of greater anxiety-like behavior (Amico et al., 2004), as did wild-type female mice administered an oxytocin receptor antagonist into the lateral ventricles (Mantella et al. 2003). Furthermore, administration of oxytocin into the lateral ventricles of oxytocin deficient mice reduced anxiety-like behaviors (Amico et al., 2004). Treatment of wild type rats with oxytocin, administered peripherally or infused into the central nucleus of the amygdala, also resulted in anxiolytic effects (Uvnas-Moberg et al., 1994; Bale et al., 2001). In humans, lower plasma and CSF oxytocin levels are associated with greater symptoms of anxiety in children as reported by the parent version of the Spence Children's Anxiety Scale (Carson et al., 2014). A single dose of 24 IU of intranasal oxytocin administered to 14 healthy volunteers 50 minutes prior to a public speaking task significantly reduced anticipatory anxiety (de Oliveira et al., 2012). When 16

socially anxious males and 26 healthy controls were administered 24 IU of intranasal oxytocin or placebo, oxytocin administration reduced the difference between socially anxious vs. non-socially anxious subjects in attentional bias for emotional faces as measured by the dot-probe task (Clark-Elford et al., 2014). We previously reported a relationship between postprandial levels of oxytocin and anxiety symptoms in a combined group of AN and ANWR (Lawson et al., 2013). We now show that low fasting peripheral oxytocin levels, which reflect basal unstimulated oxytocin, are associated with more severe anxiety symptoms in ANWR. Furthermore, those ANWR with significant anxiety symptoms as assessed by STAI State and Trait have lower oxytocin levels compared to those without such symptoms, supporting the concept that oxytocin dysregulation following weight recovery in AN may contribute to persistent symptoms of anxiety.

Oxytocin dysregulation may also contribute to depressive symptoms in AN. Depressive disorders are frequently precipitated by stressful social experiences, which activate the HPA axis, and the antidepressant effects of oxytocin may in part stem from its ability to inhibit the HPA axis (Neumann et al., 2000). In wild type mice, mating induces oxytocin release and reduces depression-like behaviors measured by duration of immobility in the forced swim test; this antidepressant effect of mating is absent in oxytocin receptor deficient mice (Matsushita et al., 2010). Intraperitoneal injection of oxytocin in mice has been shown to reduce the duration of immobility, with anti-depressant effects comparable to those of imipramine (Arletti and Bertolini, 1987). In a study of 6 women and 8 men who had failed two different antidepressant classes and did not respond to escitalopram, 16 IU of intranasal oxytocin daily in conjunction with escitalopram resulted in significant improvement in depressive symptoms as early as day 8 of treatment (Scantamburlo et al., 2014). We previously showed a relationship between postprandial oxytocin levels and depressive symptoms in a group of women with AN and ANWR (Lawson et al., 2013). We now demonstrate that ANWR with significant depressive symptoms have lower fasting peripheral oxytocin levels than those with no or minimal depressive symptoms. Whether oxytocin dysregulation leads to depressive symptoms is unknown and warrants investigation.

It is interesting that although we detected correlations between oxytocin and disordered eating psychopathology and anxiety symptoms in ANWR group, these associations were not observed in the AN group. One possibility is that the effects of nutritional depletion and/or other endocrine abnormalities on psychopathology in the setting of starvation outweigh the effects of oxytocin deficiency. Future studies defining the role of oxytocin in disordered eating psychopathology, anxiety, and depression in AN during starvation will be important.

In summary, low fasting oxytocin levels in weight-recovered women with AN are associated with increased severity of disordered eating psychopathology and anxiety symptoms. Furthermore, oxytocin levels are low in those with significant disordered eating psychopathology, anxiety symptoms, or depressive symptoms compared to those without such symptoms. Future studies will be important to investigate whether low oxytocin levels following weight recovery in AN contribute to psychopathology and impact prognosis. Oxytocin pathways may include novel treatment targets in eating disorder patients.

**Acknowledgments:**

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**Table 1. Participant characteristics**

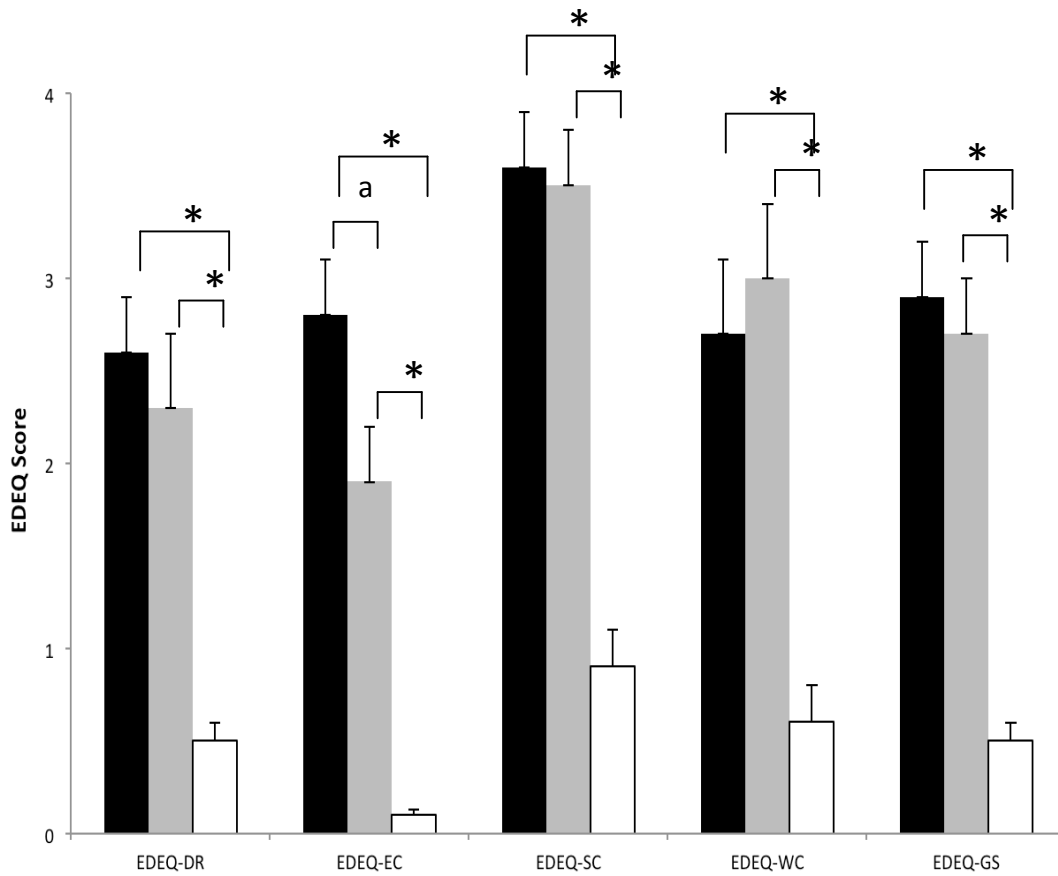
	AN	ANWR	HC	AN vs. ANWR	AN vs. HC	ANWR vs. HC	Overall ANOVA
	Mean $\pm$ SEM			P Value			
Age (years)	23.9 $\pm$ 1.2	23.8 $\pm$ 1.0	23.9 $\pm$ 0.8				1.00
Weight (kg)	46.9 $\pm$ 0.8	61.0 $\pm$ 1.4	61.5 $\pm$ 0.9	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	0.7	<b>&lt;0.0001</b>
Body mass index (kg/m <sup>2</sup> )	17.7 $\pm$ 0.2	22.5 $\pm$ 0.4	22.6 $\pm$ 0.3	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	0.8	<b>&lt;0.0001</b>
% Ideal body weight	80.3 $\pm$ 0.8	100.5 $\pm$ 1.5	101.2 $\pm$ 1.1	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	0.7	<b>&lt;0.0001</b>
Oxytocin (pg/ml)	1230 $\pm$ 82	974 $\pm$ 92	1501 $\pm$ 114	0.12	0.08	<b>0.0004</b>	<b>0.002</b>
EDEQ-DR	2.6 $\pm$ 0.3	2.3 $\pm$ 0.4	0.5 $\pm$ 0.1	0.5	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
EDEQ-EC	2.8 $\pm$ 0.3	1.9 $\pm$ 0.3	0.13 $\pm$ 0.03	<b>0.01</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
EDEQ-SC	3.6 $\pm$ 0.3	3.5 $\pm$ 0.3	0.9 $\pm$ 0.2	0.7	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
EDEQ-WC	2.7 $\pm$ 0.4	3.0 $\pm$ 0.4	0.6 $\pm$ 0.2	0.6	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
EDEQ-GS	2.9 $\pm$ 0.3	2.7 $\pm$ 0.3	0.5 $\pm$ 0.1	0.5	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
STAI State	43.7 $\pm$ 2.5	42.2 $\pm$ 3.2	28.0 $\pm$ 1.4	0.7	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
STAI Trait	53.3 $\pm$ 2.9	47.3 $\pm$ 2.9	31.4 $\pm$ 1.7	0.1	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
BDI-II	18.8 $\pm$ 2.7	15.3 $\pm$ 2.4	3.1 $\pm$ 1.0	0.2	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>

AN, active anorexia nervosa; ANWR, weight recovered anorexia nervosa; HC, healthy control; SEM, standard error of the mean. EDEQ, Eating Disorder Examination Questionnaire; DR, dietary restraint; EC, eating concern; SC, shape concern; WC, weight concern; GS, global score; STAI, State – Trait Anxiety Inventory; BDI, Beck Depression Inventory. Bolded p-value < 0.05.

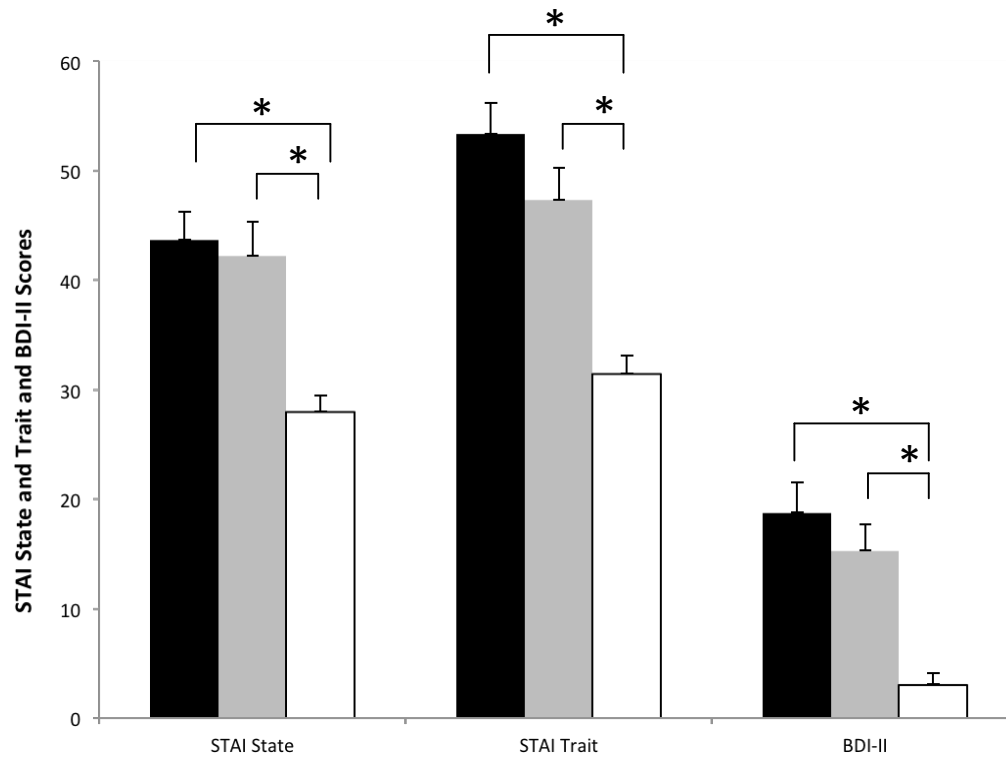
**Table 2. Relationship between oxytocin levels and psychopathology in ANWR**

	Fasting Oxytocin (pg/ml)	
	Correlation Coefficient	P Value
EDEQ-DR	-0.38	0.06
EDEQ-EC	-0.34	0.09
EDEQ-SC	-0.31	0.12
EDEQ-WC	-0.40	<b>0.04</b>
EDEQ-GS	-0.39	<b>0.05</b>
STAI State	-0.53	<b>0.006</b>
STAI Trait	-0.49	<b>0.01</b>
BDI-II Total Score	-0.34	0.09

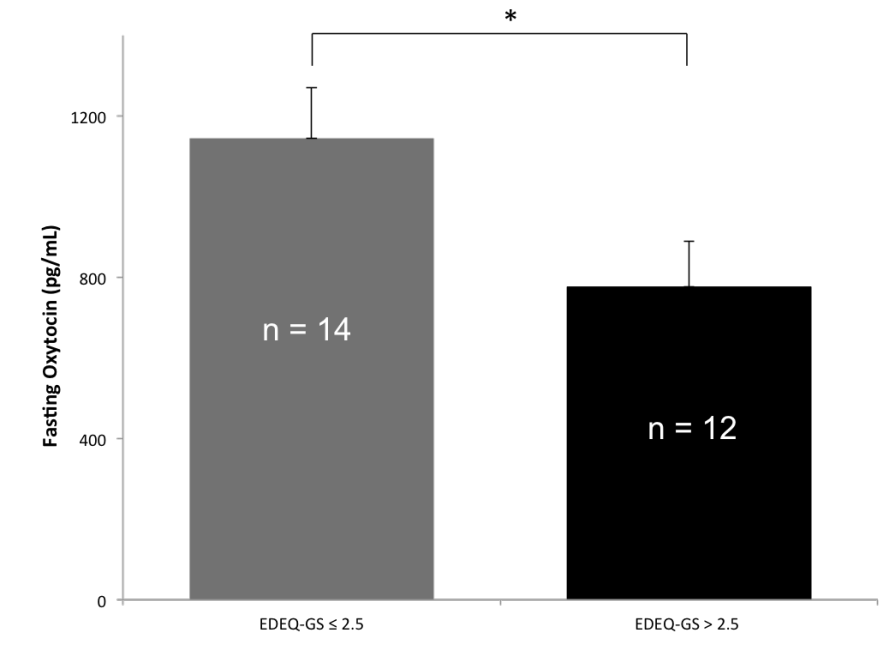
ANWR, weight recovered anorexia nervosa; EDEQ, Eating Disorder Examination Questionnaire; DR, dietary restraint; EC, eating concern; SC, shape concern; WC, weight concern; GS, global score; STAI, State – Trait Anxiety Inventory; BDI, Beck Depression Inventory. Bolded p-value < 0.05.



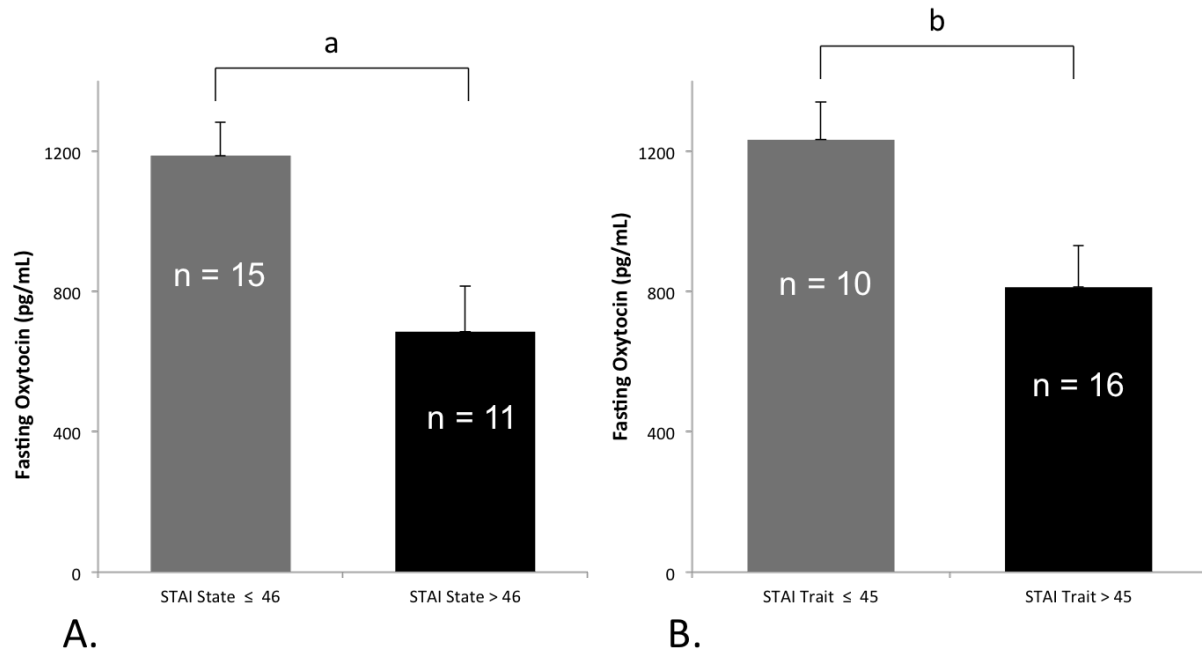
**Figure 1. Disordered eating psychopathology.** EDEQ scores on all subscales and EDEQ-GS were higher in AN and ANWR compared to HC ( $p < 0.0001$ ). EDEQ-EC score was higher in AN than ANWR ( $p = 0.01$ ). Black, AN; grey, ANWR; white, HC. EDEQ, Eating Disorder Examination Questionnaire; DR, dietary restraint; EC, eating concern; SC, shape concern; WC, weight concern; GS, global score. \*,  $p < 0.0001$ . <sup>a</sup>,  $p = 0.01$ .



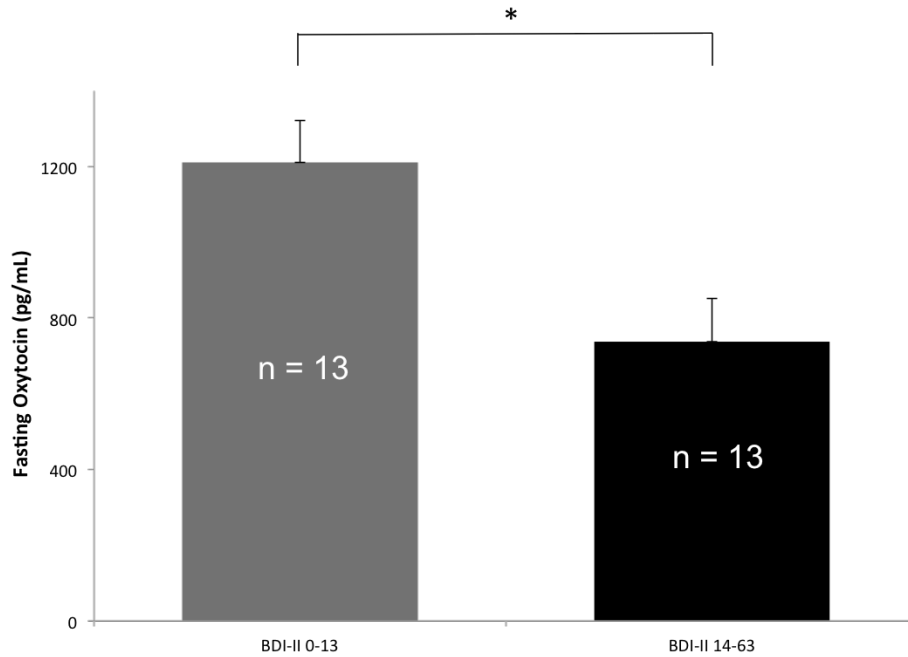
**Figure 2. Anxiety and depressive symptoms.** STAI State and Trait scores and BDI-II scores were higher in AN and ANWR than in HC ( $p < 0.0001$ ). Black, AN; grey, ANWR; White, HC. STAI, State-Trait Anxiety Inventory; BDI-II, Beck Depression Inventory. \*,  $p < 0.0001$ .



**Figure 3. Fasting oxytocin and disordered eating psychopathology in ANWR.** ANWR with EDEQ-GS > 2.5 (significant disordered eating psychopathology) had lower oxytocin levels compared to ANWR with EDEQ-GS ≤ 2.5 (no or minimal disordered eating psychopathology). EDEQ, Eating Disorder Examination Questionnaire; GS, global score. \*, p=0.04.



**Figure 4. Fasting oxytocin and anxiety in ANWR.** **A.** ANWR with STAI State  $> 46$  (significant anxiety symptoms) had lower oxytocin levels compared to ANWR with STAI State  $\leq 46$ . **B.** ANWR with STAI Trait  $> 45$  (significant anxiety symptoms) had lower oxytocin levels compared to ANWR with STAI Trait  $\leq 45$ . STAI, State-Trait Anxiety Inventory. <sup>a</sup>,  $p=0.004$ . <sup>b</sup>,  $p=0.02$ .



**Figure 5. Fasting oxytocin and depressive symptoms in ANWR.** ANWR with BDI-II 14-63 (clinical depressive symptoms) had lower oxytocin levels compared to ANWR with BDI-II 0-13 (minimal or no depressive symptoms). BDI-II, Beck Depression Inventory. \*,  $p=0.007$ .

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