Published in final edited form as:
Biol Psychol. 2009 April ; 81(1): 31–39. doi:10.1016/j.biopsycho.2009.01.004.

Salivary Gonadal and Adrenal Hormone Differences in Boys and Girls With and Without Disruptive Behavior Disorders: Contextual Variants

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Abstract

Hormone differences by psychopathology group and gender may have implications for understanding disruptive behavior disorders (DBD) and complexities of treatment outcomes. Current theoretical models emphasize contextual differences as moderators of hormone-behavior relations. This report examined: a) hormone differences in youth with and without DBD, and b) contextual factors as moderators of behavior problems and hormones. 180 children and adolescents were enrolled (141 boys, mean 9.0 ± 1.7 years). DBD participants met criteria for conduct disorder (CD) and/or oppositional defiant disorder (ODD) (n = 111); 69 were recruited as healthy comparisons (HC). Saliva was collected for testosterone, cortisol, dehydroepiandrosterone and androstenedione. DBD youth had significantly higher androstenedione than the HC group. There was a group by gender interaction for basal cortisol mean with DBD boys and HC girls having lower cortisol. Moderating effects of contextual variables (e.g., family functioning, delinquent peers) were noted for cortisol and adrenal androgens. Findings argue for considering hormones as an influence on DBD beyond simple direct one-to one associations.

Keywords

cortisol; conduct disorder; disruptive behavior disorders; testosterone; adrenal androgens; context

1.0 Introduction

Numerous reports reveal the significant toll that adolescent antisocial behavior takes on society as a whole as well as on families and individuals (Jones, Dodge, Foster, & Nix, 2002). Potential causative factors of antisocial behavior are less well examined. In a few studies, correlates and

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causes of antisocial or disruptive behavior disorders (DBD), notably, oppositional defiant disorder (ODD) and conduct disorder (CD) have been centered on the influence of contextual factors. These include parent psychopathology (Kaplan & Liu, 1999; Tremblay et al., 2004), family/parenting environment including maternal parenting (Frick et al., 1992), hostility (Lahey, Russo, Walker, & Piacentina, 1989; Rey & Plapp, 1990) and parent supervision and/or parenting behaviors and practices (Haapasalo & Tremblay, 1994; Stormshak, Bierman, McMahon, & Lengua, 2000). In all instances, parent psychopathology and negative parenting environments or lack of supervision is related to negative child and adolescent behaviors. Additionally, contextual correlates of DBD or antisocial behaviors include involvement with deviant peers (Burke, Loeber, Lahey, & Rathouz, 2005; Coie & Miller-Johnson, 2001; Dishion, French, & Patterson, 1995; Keenan, Loeber, Zhang, Stouthamer-Loeber, & van Kammen, 1995) or peer rejection (Dodge et al., 2003) where more associations with deviant peers or peer rejection is associated with increased DBD. Stress related to family functioning also affects DBD (Mathijssen, Koot, & Verhuist, 1999); specifically, family dysfunction is a risk for developing externalizing problems. Similarly, socioeconomic status (Loeber, Green, Keenan, & Lahey, 1995; Tremblay et al., 2004) and socioemotional factors, such as impulsivity, and arousal (Lahey, Hart, & Pliszka, 1993; Vanyukov et al., 1993) may influence the onset or persistence of DBD. Importantly, such negative contextual factors typically are more prominent in DBD than non-DBD children (reference withheld to maintain blind).

In addition to contextual factors, biological parameters, including the autonomic nervous system (ANS) and neurotransmitters, also have been examined in relation to DBD, although to a much lesser degree [See reviews (Lorber, 2004; Stoff & Susman, 2005); and other empirical work (Kruesi et al., 1992; Mezzacappa et al., 1997; Raine, 1993; Scarpa & Raine, 2003)]. Such examination is based on the premise that these biological parameters may influence behavior. An increasing number of studies are now focused on neuroendocrine processes in DBD compared to healthy youth [for example, see (van Goozen & Fairchild, 2006)]. Hormones may contribute to variations in DBD phenotype and subsequent outcome of treatment. Further, interindividual differences in hormone levels may be a cause or a consequence of DBD. Specifically, the hormone-related psychobiology of stress has been linked to behavior problems in youth (Stoff & Susman, 2005). Most studies examining DBD or externalizing problems focused on testosterone (T) (Book, Starzyk, & Quinsey, 2001; Granger et al., 2003; Olweus, 1986; Popma et al., 2007; Scerbo & Kolko, 1994; van Bokhoven et al., 2006) and cortisol (McBurnett, Lahey, Rathouz, & Loeber, 2000; Pajer, Gardner, Kirillova, & Vanyukov, 2001; Popma et al., 2007; Susman, Dorn, Inoff-Germain, & Nottelmann, 1997). DBD and externalizing problems have been shown to be related to aggression and low arousal, respectively. However, the direction of these relations is not always uniform [e.g., (Booth, Johnson, Granger, Crouter, & McHale, 2003)] or is not always different from non-DBD participants (Granger et al., 2003; Rowe, Maughan, Worthman, Costello, & Angold, 2004; Van Goozen, Matthys, Cohen-Kettenis, Gispendewied, & Vanegeland, 1998). To our knowledge, examination of disruptive behavior and diurnal changes in hormones, particularly cortisol, has received less attention. Diurnal changes in cortisol may represent a vulnerability to antisocial behavior (Susman et al., 2007) and differences in the typical diurnal pattern of cortisol may also vary with contextual factors (Watamura, Donzella, Alwin, & Gunnar, 2003).

Individual differences in adrenal androgen levels including dehydroepiandrosterone (DHEA), its sulphate (DHEAS) and androstenedione, have received much less attention with regard to DBD. Exceptions include van Goozen and colleagues who reported high DHEAS in DBD boys and no differences in androstenedione between DBD and healthy boys (van Goozen et al., 2000; Van Goozen et al., 1998) and Pajer and colleagues (Pajer et al., 2006) who reported lower cortisol to DHEA ratio in CD girls but no differences in androstendione or DHEAS. Adrenal androgens may be an important mechanism involved in the hormone-behavior

relations as they are the first hormones to change during puberty (e.g., during adrenarche) and are precursors of more potent steroids, specifically, testosterone. With our younger aged youth in the study, those hormones are likely to have just begun to increase. Further, adrenal androgen levels were related to externalizing behavior problems in healthy adolescents (Brooks-Gunn & Warren, 1989; Nottelmann et al., 1987b; Susman, Dorn, & Chrousos, 1991; Udry & Talbert, 1988) but their role in ODD or CD is virtually unknown. Given the paucity of research, it is unclear whether gonadal and adrenal hormones are higher or lower in DBD youth, particularly at young ages.

Models examining the development of antisocial behavior or DBDs have been diverse and generally have examined unitary predictors without accounting for how these predictors are integrated with other key dimensions. To advance the literature regarding hormones and disruptive behavior disorder, a conceptual biopsychosocial model of the development of conduct problems has been articulated (Dodge et al., 2003). Their model included biological predisposition, sociocultural context, as well as parenting and peers as it relates to conduct disorder. Although this model cannot be tested in the cross-sectional analyses at hand, we used components of the model to consider associations between gonadal and adrenal hormones and disruptive behavior. Further we were guided by the notion that gonadal and adrenal hormones may be directly related to DBD but more complex theoretical models now are proposed that consider bidirectional relations moderated by contextual domains (Susman, 1997; Susman, 2006).

In line with the theoretical and empirical literature, we propose that children with ODD or CD will be different from the healthy comparison group on hormone levels but the relation of hormones and disruptive disorders will be moderated by contextual factors. Our selection of contextual factors (e.g., parent and family functioning as well as exposure to delinquent peers) was also based on an ecological perspective suggesting that interventions target these contextual factors to improve the behavior of children and youth (Kazdin, 2005; Kolko, 2002; Nock, 2003). Further, for both researchers and clinicians it is encouraged that risk factors be included in intervention studies so as to understand how the broader social environment can improve the lives of children with DBD (Burke, Loeber, & Birmaher, 2002; Chronis et al., 2003). Therefore we felt it was important to include these contextual domains in our model. The model led to the following aims and hypotheses. The first aim was to assess group differences in adrenal and gonadal hormones in youth with and without DBD. It was hypothesized that cortisol would be lower and T and adrenal androgens higher in those with DBD compared to the HC group. Gender differences also were examined in an exploratory fashion as fewer girls were enrolled. Second, contextual factors previously associated with DBD (parental dysfunction, parenting practices, family conflict, exposure to delinquent peers) were examined as moderators of DBD and hormones. It was hypothesized that family disruption and exposure to delinquent peers in combination with disruptive behavior problems would be related to higher gonadal and adrenal hormone levels given the reported association between higher gonadal and adrenal hormones and aggressive behavior. No identified studies have examined hormones and DBD and the role that family/parenting environment and peer contexts may play in DBD. The study also controlled for potential confounds (e.g., medication, sampling time) and used multiple samples in a unique, randomized clinical trial (RCT) for treatment of DBD. Understanding potential hormone and context factors associated with DBD in developing youth may provide more insight into serious DBD in later adolescence.

2.0 Methods

2.1 Design

Children were recruited to a large, randomized clinical trial designed to treat DBD (reference withheld to maintain blind). Participants were randomized to one of two specialized treatment

protocols applied by research clinicians in either the community or outpatient clinic. An additional group was recruited to serve as a treatment-as-usual (TAU) group. Healthy comparison (HC) participants without DBD were matched to those in all three groups. Since no treatment had taken place at the baseline timepoint, the assignment to treatment groups is not relevant for this paper. This report includes only baseline information and thus groups are defined as DBD versus HC.

2.2 Participants

The study included 180 participants (141 boys, 39 girls), age 6 to 11 years (9.0 ± 1.7). The younger age was chosen to capture early experiences of DBD. Additionally this age represents the youngest likely able to participate in treatment in the clinical trial using cognitive behavioral therapy themselves. Of the 180, there were 111 DBD and 69 HC participants. (See Table 1). Inclusion criteria for DBD were: 1) boys or girls, age 6-11 years, 2) diagnosis of CD or ODD, 3) resided with one or more parent/guardian, 4) intellectual level no more than 2 SD below age norms, 5) parent/guardian consent, 6) not suicidal, psychotic and in no other treatment.

This sub sample was drawn from of the larger parent study (N = 176 DBD; 69 HC) (reference withheld to maintain blind) and represents those with salivary hormone samples. The hormone sub-sample was funded at a later date than the parent study. DBD participants with saliva sampling were no different from the full sample of DBD participants on age, SES, or race. However, significant gender differences ($p = .05$) indicated a higher proportion of girls in the current study (e.g., 21.7%) compared to the subgroup (10.8%) who did not participate in the saliva sub sample. No differences were noted between participant/non-participant groups in externalizing behavior using the Child Behavior Checklist (Achenbach, 1991).

HC group eligibility criteria included: 1) matched on age (± 6 months), gender, race, and SES (± 10 points) (Hollingshead, 1975), 2) no acute or chronic illnesses, 3) no learning disabilities, 4) no current or past DSM-IV diagnoses, 5) resided with at least 1 parent/guardian, 6) intellectual level no more than two SDs below age norms, and 7) parental/guardian consent. The decision to use a HC group without psychopathology was reported to be useful in other studies of disordered versus non-disordered children and adolescents (Birmaher et al., 2004; Williamson, Birmaher, Axelson, Ryan, & Dahl, 2004).

2.3 Procedure

2.31 Recruitment—For the special treatment groups, cases were referred from within and outside the participating institution. Two multiple-gate screening phases were used to determine the DBD sample. First, administration of the clinic screening form was used by phone or face-to-face interview to describe diagnosis, behavioral problems, and treatment needs. Second, a diagnostic assessment was conducted to determine general intellectual level (Kaufman & Kaufman, 1990) and presence of ODD or CD (K-SADS for DSM-IV) (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996). The TAU group was recruited from the only other child/adolescent outpatient clinics affiliated with the institution and located on site, as well as institutions located in a neighboring county, and a large local children's hospital.

The HC group was recruited through the community. The study was approved by the Institutional Review Board of a major research university. All participants were informed of risks, benefits, procedures, and confidentiality. Parents provided consent and children assent.

2.32 General Procedures—Master's level clinicians completed diagnostic interviews. Trained research assistants administered the instruments. Participants were reimbursed for their time. Saliva hormones were collected at four time points. The first two samples were collected during a specific task (e.g., diagnostic interview which varied in time duration). Specifically,

Sample 1 was collected in an outpatient clinic immediately following consent (15-20 min after arrival). Sample 2 was collected immediately following completion of the diagnostic interview. Saliva collection time in the clinic began on average at noon (± 2.4 h) and ranged from 0800h to 1930h. HC participants were seen ± 2 h from their pair-match.[a] Sample 3 was collected the same day immediately before going to sleep and Sample 4 upon awakening the next morning. Participants were instructed not to brush teeth or eat for two hours before each collection and to swish with water prior to passively drooling into collection tubes. Trident Sugarless natural flavor gum was used to stimulate saliva (Granger, Schwartz, Booth, & Arentz, 1999). Samples were stored until assayed at -80° C.

2.4 Psychosocial Measures

2.41 K-SADS—To determine psychiatric disorders, the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (KSADS) for DSM-IV–Present and Lifetime (Kaufman et al., 1996) was used. Interviewers received training from clinicians trained by the authors who developed the revised instrument. Regular review was conducted of inter-rater reliabilities with project diagnosticians and group training that included reliability assessments with other research diagnosticians. For those in the parent study, kappa coefficients were high [CD (k = .76); ODD (k = .70); ADHD (k = .77)].

2.42 DBD Duration—Research assistants reviewed a summary of diagnoses and history completed by the intake clinician. They were verified by the staff physician and project coordinator. The longest disease duration of any DBD was used.

2.43 Medications—Information was collected on current prescription and non-prescription medications. Medications were categorized into major groups (e.g., antibiotics, antidepressants) by a nurse practitioner. Medications were dichotomized into steroid-related versus non-steroid-related medication or no medication, as steroid medications can influence cortisol concentrations. Thirty-three (18.3%) participants were on steroid-related medications within the last 2 weeks.

2.5 Hormone Measures

2.51 Cortisol—Cortisol was used in three ways. First, the mean of samples collected at intake in the clinic (Sample 1, & 2) was used to represent cortisol secretion during a specific task (e.g., the diagnostic interview). The intra-cluster correlation coefficient of the two repeated samples was 0.77 suggesting reasonable reliability using the mean of two samples. Although participants came to the clinic at different times of the day, the majority came between 0900h to 1400h (75.7%). The effect of the sampling time on cortisol was examined using a one-way ANOVA. Results suggest that, if the two participants who came at 0900h, and the two who came at 1700h were excluded, there was not a significant time effect (ANOVA p = 0.33; Kreskas-Wallis p = 0.16). These four participants were retained in the analyses. The second measure of cortisol was the computation of the a.m. and p.m. samples to form a ratio (Sample 4: Sample 3). The ratio allowed for the examination of diurnal changes from morning to evening. The third measure was the difference between the a.m. and p.m samples (Sample 4 – Sample 3). In these latter two measures, time of day is really “consistent” across participants. That is, the relevant point for collection is bedtime and wake-up.

[a]Although it is ideal to enroll participants at the same time of day when collecting hormones, this was not possible as visits for DBD participants were underway before the hormone component was funded. This is an issue for cortisol collected in the lab, in particular. Thus, we carefully controlled for time of day in analyses. (See 2.51 and 3). Additionally, the results section indicates some subgroup analyses that were conducted to confirm our findings.

Samples were assayed in duplicate using highly-sensitive enzyme immunoassays (Salimetrics, PA). The test has a lower limit of sensitivity of .003 ug/dl, a range of sensitivity from .003 to 1.8 ug/dl, and average intra-and inter-assay coefficients of variation 4.8% and 8.8%, respectively. Values from matched serum and saliva samples collected by Salimetrics showed the expected strong linear relationship, r (17) = > .94, p < .0001.

2.52 Androstenedione—Samples 1 and 2 in the lab were pooled and assayed. Androstenedione was measured using a radioimmunoassay kit from ICN Pharmaceuticals, Inc. The detection limit is 0.05 ng/mL and interassay coefficients of variation range between 2.4-2.5%.

2.53 DHEA—Samples 1 and 2 were pooled and assayed using a highly-sensitive enzyme immunoassay (Salimetrics, PA). The test has a lower limit of sensitivity of 10 pg/mL, (range of sensitivity 10.2 to 1000 pg/mL), and average intra-and inter-assay coefficients of variation of 4.9% and 3.45%, respectively. The serum-saliva correlation was r = 0.88 in analyses conducted by Salimetrics.

2.54 Testosterone—Samples were assayed in duplicate using a highly-sensitive enzyme immunoassay (Salimetrics, PA). The test has a lower limit of sensitivity of 1.5 pg/mL, range of sensitivity from 3.7 to 360 pg/mL, and average intra-and inter-assay coefficients of variation are 5.0% and 7.35%, respectively. Clinic Samples 1 and 2 were pooled and assayed. Additionally, a morning sample of T (a.m. T; Sample 4) was utilized.

2.6 Contextual Moderators

2.61 Parental Dysfunction—Two measures were used where one parent (most often mother) served as the reporter. The hostility scale (α = .75) from the Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983) measured parental distress in the past week by asking, “How much were you distressed by: “Feeling easily annoyed or irritated”, “Feeling that most people cannot be trusted”, or “Temper outbursts that you could not control”? Participants responded by answering, “Not at all”, “A little Bit”, “Moderately”, “Quite a bit’, or “Extremely”. A higher score indicates more hostility. A parent also completed the Beck Depression Inventory (BDI) (Beck, Steer, & Garbin, 1988) (α = .88). They were asked to select a statement in each group that best describes how they were feeling in the past week (including today). A sample statement was: “I do not feel sad”, “I feel sad”, “I am sad all the time and I can’t snap out of it”, or “I am so sad or unhappy that I can’t stand it”. A higher score indicates more depressive symptoms.

2.62 Parental Practices—The child completed the 18 item Parent Perception Inventory (PPI) to determine the primary caretaker’s overall parenting practices (Hazzard, Christensen, & Margolin, 1983). The PPI yields parental behaviors that are positive (α= .80) and negative (α= .78). The child is asked to respond to an item such as, “How often does your mom: Take away things when you misbehave (like not letting you watch TV or ride your bike or stay up late or eat desert). A single response of “Never”, “A little”, “Sometimes”, “Pretty much”, “A lot” is then given.

2.63 Family Functioning—The Family Environment Scale (FES) (Moos, Insel, & Humphrey, 1974) was completed by the child to assess family environment relevant to children with DBDs (Dadds, Sanders, Morrison, & Rebgetz, 1992). The FES conflict subscale includes 9 items (α = .50). The child is asked to respond by answering “True” or “False” to such statements as, “We fight a lot in our family” or “Family members are rarely ordered around”. A higher score indicates greater conflict. Second, family stress was measured using the Life Events Checklist (LECL). The LECL was administered to parents to evaluate the child’s

exposure to 46 stressful life events in the past year (Brand & Johnson, 1982). The ratings yield a total positive life change value resulting in a negative to a positive score (higher more positive) and a total negative life change value where higher indicates more negative life changes. Sample items include: “Moving to a new home” or “Getting put in jail”.

2.64 Peers—Exposure to Delinquent Peers was measured using the Peer Delinquency Scale (PDS) (Elliot, Juizinga, & Morse, 1985). The percent of 15 statements endorsed about delinquent activities in his/her peers in the last six months about delinquent peers was utilized ($\alpha = .92$). Sample items include: “Skipped school without an excuse”, “Encouraged you to do something bad”.

2.7 Statistical Analysis

Distributions of hormones and log-transformed hormones were examined by histogram plots and descriptive statistics. The Wilks-Shapiro tested for the normality assumption was met for the AM/PM ratio of cortisol. The natural log transformation was applied to all other hormone measures. The majority of contextual factors were highly skewed with the presence of a few extreme outliers. To avoid strong influences from outliers and to better interpret the effect of contextual factors, all contextual measures were categorized into three groups using quartile (Q) cut-points, i.e. low (<Q1), middle (Q1~Q3) and higher (>Q3) groups. DBD and HC youth were compared on gender, race and steroidal mediation taken using chi-square or Fisher’s exact test; on age, SES and DBD duration using student T-test. Further, DBD and HC youth were compared on distributions of contextual groups stratified by gender, using chi-square or Fisher’s exact test. SES was marginally significant between the DBD and HC youth, thus it was included as a covariate. The additional covariate of time of sampling was included when comparing cortisol in the lab.

Given known gender differences on hormones, gender was included as a main factor in all hypothesis testing. The primary aim to compare group differences between the DBD and HC youth on adrenal and gonadal hormones used a two-way ANCOVA, including DBD and gender as the main factors with adjustment for covariates. Analyses were conducted for each hormone. Finally, multivariate analysis of variance (MANOVA) was used to test for overall group differences between DBD and HC simultaneously on all hormone measures. The secondary aim was to explore contextual modifying effects on hormones. To control for the family-wise type I error within each domain of the contextual variables (family function, parent dysfunction, parental practice and peer exposure), we specified the primary contextual variable (listed first in Table 2) and considered the remaining variables as secondary. For example in the parent dysfunction contextual domain the BDI was the primary variable. A three-way ANCOVA was used, including group (DBD vs. HC), the contextual groups (by quartiles) and gender as main factors, adjusting for covariates. Gender effects, as well as its interaction effect with behavioral and contextual groups were examined. Analyses were conducted using SAS v9.1.

3. Results

Descriptive statistics for demographic variables appear in Table 1. There were no group differences on age, race, or gender. SES was significantly higher in the HC group although that difference (~ 3.5 points) would not put them into a different SES category. Use of steroid-related medication was significantly higher in the DBD group compared to the HC.

The cross-tabulation analyses on the contextual quartile group by DBD and HC stratified by gender is shown in Table 2. The findings indicate there are significant proportional differences in quartiles between DBD and HC youth for both boys and girls for contextual factors of parental dysfunction (BDI total and BSI hostility), peer exposure, and parental practices using the PPI total negative score. For family functioning, the FES conflict scale revealed significant

differences but only for girls whereas total negative life events, as well as the difference between total negative and total positive life events were significantly different between the DBD and HC groups but only in boys.

3.1 DBD vs. HC Differences on Hormones

Table 3 presents means for hormones by group and gender. Salivary hormone concentrations are within in the range of other studies using a similar age group. (See normative information provided by www.salimetrics.com; (Hibel, Granger, Cicchetti, & Rogosch, 2007) (Susman, unpublished data 2008). A two-way ANCOVA suggested a significant difference on androstenedione where DBD participants were higher than HC ($p = 0.018$; LS-Means of log-transformed androstenedione 4.63 +/- 0.05 vs. 4.40 +/- 0.08). No group differences were noted for T, DHEA or cortisol from the two-way ANCOVA results. When considering all hormone measures, MANOVA further identified a significant group difference ($F(9,116)=3.12$, $P = 0.002$) where the DBD group was higher than HC, again highlighting the androstenedione difference.

Gender differences were significant only for the cortisol AM/PM ratio ($p = 0.001$). Girls had a lower ratio than boys indicating that there was less change in level across the day. In addition, a significant gender by group interaction was noted for cortisol mean in the clinic ($p = 0.01$) where DBD boys and HC girls had lower mean cortisol. This suggests that boys and girls may present different patterns when comparing DBD and HC on mean cortisol following a designated task in the clinic setting. No other interaction was noted. MANOVA with all hormones revealed a significant gender effect ($F(9, 116) = 3.66$, $p = 0.0005$), but not a gender by DBD group interaction ($F(9,116) = 1.56$, $p = 0.13$).

3.2 Contextual Group Comparisons and Their Moderating Effects

Potential effects of contextual variables as moderators of group and hormones were examined. Significant interactions are shown in Figure 1 a-d. A three-way ANOVA found a significant group by family functioning (LECL positive) interaction ($p = .02$) on mean cortisol where positive life events moderated the cortisol by group interaction. Cortisol in the DBD group remained quite stable across all quartiles of the positive LECL whereas the HC group had higher mean cortisol in the lowest and highest quartiles of positive life events. Second, there was a group by Parenting Practice (PPI total) interaction ($p = . 02$) with DHEA where DHEA was low in the first quartile and increased in the DBD group as more positive parenting practices increased across quartiles. Alternatively in the HC group DHEA remained high and relatively unchanged in the low and mid quartiles. Third, there was a group by Peers interaction (PDS %) ($p = .01$) where cortisol mean for the DBD group was lowest in the first quartile (low involvement with delinquent peers) and rose in higher quartiles. Alternatively in the HC group, cortisol mean was highest in the first quartile and declined in the quartile groups with more involvement with delinquent peers (middle quartiles). Finally, there was a significant group by Peers interaction (PDS %) ($p = .03$) for androstenedione where the HC group in the lowest quartile (low involvement with delinquent peers) had low androstenedione whereas those in the middle quartiles had higher androstenedione. Androstenedione was only slightly higher in the HC group across quartiles as exposure to delinquent peers increased. The same results hold when adjusted for covariates. These results suggested that the hormone- behavior relation may differ depending on family and peer context.

To further examine our data with respect to the time of day of sampling for cortisol, subgroup analyses were conducted. Two subgroups were specified. The first group included those who had cortisol sampling in the lab after 11 a.m. ($n = 101$). In this case, all previous mean cortisol analyses with interactions remained significant. The second subgroup included those with cortisol sampling in the lab before 11 a.m. ($n = 79$). The group by family functioning (LECL

positive) interaction remained significant (p = .04) whereas the group by Peers (PDS%) interaction showed a trend for significance (p = .09).

4. Discussion

Hormones, behavior, and contextual parameters represent dynamic processes in youth. This study represented a unique opportunity to examine baseline differences in these parameters in a well-characterized sample of boys and girls with DBD enrolled in a RCT. A matched HC group also was included. Multivariate analysis of variance indicated that taken together, the array of hormones showed significant group differences between DBD and healthy comparison youth. Thus, hormone profiles are different depending on the presence of DBD psychopathology.

With respect to hormone differences by group, one must consider that in some cases hormones may act together to alter a behavior. Teasing apart the individual contributions of a single hormone is more difficult. A unique finding was that the DBD group had higher androstenedione compared to the HC group. In older adolescents, higher adrenal androgen levels were related to more negative or acting out behaviors (Brooks-Gunn & Warren, 1989; Nottelmann et al., 1987b; Susman, Inoff-Germain, Nottelmann, & Loriaux, 1987a; Udry, Billy, Morris, Groff, & Raj, 1985; Udry & Talbert, 1988). Androstenedione, a weak adrenal androgen that begins increasing at about age 6-8, is a precursor of T and the main source of androgens prior to gonadarche. In line with earlier literature showing that T is related to aggression, one may expect T as opposed to androstenedione to be related to DBD when gonadal axis activation increases in later puberty. Alternatively, higher androstenedione in DBD participants may further contribute to higher T as the sample ages as greater concentrations of available androstenedione will be converted to T. Importantly we do not include a measure of puberty in our analyses so the progression puberty as a possible confounding influence on DBD is not possible to rule out.

Contrary to our hypothesis, there were no group differences in T, although there was a trend for T to be lower in the DBD group. One explanation for lower T is that DBD youth are experiencing more stress than other youth. Those with DBD are likely living in more stressful conditions, as noted by the family contextual characteristics. Stress can reduce T secretion (Chrousos & Gold, 1992; Susman et al., 1997; Susman, Nottelmann, Inoff-Germain, & Dorn, 1987b), as mediated by glucocorticoids, and thereby may mask T variability in this young age group. In brief, our findings are inconsistent with the literature showing that T has a positive relationship with aggression or antisocial behavior (Book et al., 2001; Dabbs Jr., Jurkovic, & Frady, 1991; Olweus, 1988; Scerbo & Kolko, 1994); primarily in boys.

Cortisol indices generally were not lower in the DBD group contrary to what was expected. There was however, a group by gender interaction for mean cortisol with DBD boys and HC girls showing lower mean cortisol. A caveat is that our sample of girls is small. Therefore, these findings should be evaluated with caution. Since the literature reports lower cortisol in boys with externalizing behavior or DBDs (McBurnett et al., 2000; Susman et al., 1997) and in CD girls (Pajer, Gardner, Rubin, Perel, & Neal, 2001), we conducted post hoc analyses and found mean cortisol was lower in those with ODD compared to the HC group. Additionally, ODD only boys had lower cortisol than ODD girls. These findings may reflect that individuals with low cortisol seek stimulating aggressive-potential situations in an effort to raise cortisol (Raine, 2002). No mean cortisol differences were noted in CD + ODD group perhaps because of the smaller size of this subsample. Differences between CD and ODD groups may be masked by comorbidity of other disorders as comorbidity is often present in youth with CD and ODD.

The direction of the relation between cortisol and antisocial behavior varies across studies. A recent study of children without a diagnosis of DBD reported the same negative association between cortisol and externalizing behaviors (Shirtcliff, Granger, Booth, & Johnson, 2005). Some studies reported no underarousal in the HPA axis in disruptive youth (Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001; McBurnett et al., 2005), yet other studies showed lower basal cortisol and higher cortisol reactivity (Susman et al., 1997) or higher cortisol and more conduct problems (Susman & Ponirakis, 1997; van Bokhoven et al., 2004)}. Higher cortisol also was present in a subsample of boys at the highest 5% of conduct problems (McBurnett et al., 2005). Inconsistencies across studies may be due to age or methodological differences, such the time when cortisol levels were obtained, or results may be confounded by comorbid diagnoses.

Diurnal variability of cortisol (a.m. to p.m. ratio), which notes HPA axis activity differences from wake-up to bedtime, showed no group differences in our sample. We anticipated a more flattened diurnal variability given the reported findings of low cortisol in youth exhibiting conduct disorder symptoms. For example, the response of cortisol to a stressor was lower in those with ODD or those with both ODD and ADHD versus a comparison group or ADHD only group (Snoek, Van Goozen, Matthys, Buitelaar, & van Engeland, 2004). In addition, boys with a lower a.m. to p.m. ratio of cortisol had more attention problems (Susman et al., 2007) and also exhibited less reactivity to a laboratory stressor (Randazzo, Dockray, & Susman, 2007). It should not be surprising that findings for low basal cortisol and low ratios are inconsistent given that cortisol reactivity and diurnal variations in cortisol are controlled by different signals.

Overall, there were fewer group differences in hormones than hypothesized. One reason may be that participants were relatively young and hormones have not yet increased enough to directly or indirectly impact behavior changes in conjunction with their contexts. Additionally, as T has been implicated in aggressive behavior, an increase in T may be a consequence rather than a cause of aggression (Brain & Susman, 1997). Therefore, a longer duration of DBD may be necessary to change hormones, hormone-behavior associations, mediators or moderators. Follow-up visits will be instrumental in determining the effect of DBD duration on hormone concentrations. The group differences in androstenedione may be especially important as the early adrenal androgen rise may initiate and maintain aggression (Ramirez, 2003). Since our DBD group had higher androstenedione than the HC youth, one may expect more aggressive behaviors in future phases of this longitudinal study.

Importantly, contexts that moderated hormone concentrations heretofore have not been described. For example with our Parental Practices domain, DHEA concentrations only varied for the DBD group. DHEA had a different assosciation with parental practices depending upon the group (DBD vs. HC) and it also varied depending on the quartile of negative parenting practices. DHEA was nearly equal in the HC group with the lowest negative parenting and the DBD group in the highest quartile of negative parenting. From the cross sectional design one cannot untangle cause and effect but these differences argue for longitudinal examination for moderators of DBD and DHEA.

For cortisol mean, moderation by two contextual variables also was evident. For example, cortisol mean was relatively consistent in the DBD group across all quartiles in total positive life events whereas cortisol was highest in both the low and high quartiles of the HC group. It may be that positive life events do not alter cortisol in the DBD group. Additionally, the measure of cortisol (mean cortisol in the lab setting) may not be a sensitive indicator of a biological reaction to life events in the DBD group. Alternatively, cortisol was higher in the middle and highest quartiles for exposure to delinquent peers for the DBD group whereas it was lowest in the middle quartiles for the HC. Cortisol appeared to have more variability in

the HC group across quartiles for both contextual factors (positive life events and PDS) although for the latter, there were no HC participants in the highest exposure quartile for delinquent peers.

Regardless of the few group differences in hormone concentrations, it is important to consider hormones as a potential influence on (or consequence of) disruptive behavior in youth, particularly since the overall MANOVA revealed significant group differences. First, the stage of science of hormone-behavior research has gone beyond the simple direct association of one hormone to one behavior (Susman & Ponirakis, 1997; Susman & Rogol, 2004). The picture is more complex than a simple unidirectional or bidirectional model given the importance of mediators in these results. Thus, our findings of contextual variables moderating the hormone and behavior group associations are unique and encouraging. Overall, contextual factors (family functioning and peers) were related to more varied concentrations of cortisol and androstenedione for the HC group whereas parenting was related to more varied concentrations of DHEA in the DBD group. An earlier study reported that the relationship between testosterone and adjustment problems in adolescents varied depending on the quality of the parent-child relationship (Booth et al., 2003). Further, in younger children, cortisol change was higher in negative interactions with parents in those low on ego-resiliency whereas cortisol did not increase in those high on ego-resiliency (Smeekens, Riksen-Walraven, & van Bakel, 2007). Thus, examining the family context is important when considering the role of hormones and DBD.

4.1 Limitations

Limitations in the study are worthy of mentioning. First, multiple tests were conducted. However, to control for family-wise Type I error within each contextual domain, we prioritized one variable whereas the remaining variables were secondary. Since testing for interactions demands is more rigorous in terms of sample size, we also felt that providing the unadjusted *p* values for the reader would be beneficial.

Second, a measure of pubertal development was not included in the analyses. Since the literature reports gender and pubertal stage differences in gonadal and adrenal hormones, the inclusion of pubertal stage might have yielded another potential moderator of group differences. The lack of a measure of pubertal stage reflects the fact that the parent study was conducted in multiple clinics throughout the geographical region and that the study did not focus on puberty. Measures of pubertal maturation have since been added to the study, allowing for future longitudinal analyses to consider the influence of pubertal stage or pubertal timing on DBD and its treatment. However, this does not provide potential correction for the baseline analyses reported here.

Another limitation is that hormone sampling did not occur at the same time of day across all participants. Because the hormone component of the study merged with an existing clinical trial that was underway, we were unable to assess the participants at the same time of day across all sites. We statistically controlled for time of collection, although such a control is not a perfect remedy for the situation. Our analysis yielded time of day as an insignificant covariate for any hormone. Importantly when we also divided our sample into those sampled after 11 a.m. and those sampled before 11 a.m. the results remained significant in all but one case. This change is likely due to reduced power with the much smaller sample size. The 11 a.m. cutoff was based on the literature. Few studies have sampled saliva cortisol across a 24 hr period. An earlier report shows that after cortisol peaks in the early morning it continues to decrease, then plateaus in the afternoon and evening and again begins to rise in the early morning(Weitzman et al., 1971). Two other studies indicated that the steepest decline in morning cortisol was ending at about 11 a.m.(Dorn, Lucke, Loucks, & Berga, 2007; van Poll, Nicolson, & Sulon,

1992). After about 11 a.m. cortisol only fell slightly across our sampling frame until late afternoon to early evening. Thus, the two subgroups were formed.

It should also be noted that the time of day issue applies primarily to cortisol collected in the lab but it is less of an issue for the adrenal androgens and it is not an issue for the ratio of a.m. to p.m. cortisol or morning testosterone as collection time was consistent for those. Further, the HC visit was conducted at a similar time as the matched pair (± 2 hrs) to help adjust for timing of the saliva collection. Finally, future studies could benefit from inclusion of a larger sample of girls. Our percentage of girls in the samples with DBD is comparable to reports in incidence of DBD adding strength to the study. Regardless of these limitations the study yielded unique findings on the psychobiological aspects of DBD and contextual moderators. In addition, the sample of boys with diagnosable DBDs is large and a unique healthy comparison group also is included.

4.2 Conclusions

The current study represents an initial step in understanding the combined influences of multiple biological and social contextual processes involved in DBD. These multivariate findings documenting diagnostic group differences in hormones suggest that future hypotheses be tested longitudinally so as to establish cause-effect relationships between hormones and DBD. Understanding the cause-effect relationship may lead to interventions to prevent or reduce the harmful effects of DBD but until directionality is determined it is not obvious what model of intervention might be most efficacious. These findings show that first, multiple hormones are related to DBD and that diagnostic groups differ in hormone levels. Second, as hypothesized, family and peer contextual factors moderated the relationship between diagnoses and hormone levels. Collectively, the results of this study lend support to the often cited need to consider biopsychosocial models in future research. Specifically, prevention/intervention programs that foster healthy families and positive peer interactions will surely lead to less youth disruptive behaviors and, in turn, may regulate hormone secretion consistent with healthy biological development. Finally, the reader should be cognizant that the complex nature of DBD necessitates more statistical models to include biological and contextual factors. However, each study cannot include all components yet most can contribute in some way, to further understanding DBD. This baseline report provides the first step in examining group differences and biological relationships in a large group of DBD and healthy children and adolescents prior to the instigation of a unique treatment in a clinical trial for DBD across three years.

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Table 1

Means ± standard deviations or frequencies of demographic variables for Disruptive Behavior Disorder (DBD) and Healthy Comparison (HC) Youth

	DBD (n=111)	HC (n=69)	P-value
Male Sex	84 (75.7%)	57 (82.6 %)	0.27[1]
Race			
Caucasian	60 (54.1%)	40 (58.0 %)	0.87[2]
African-American	46 (41.4 %)	26 (37.7 %)	
Hispanic	1 (0.9 %)	0 (0 %)	
Biracial	4(3.6%)	3 (4.3 %)	
Age in years	9.0 ± 1.8	9.2 ± 1.6	0.47[3]
SES	34.5 ± 11.8	38.0 ± 11.0	0.05[3]
Disease Duration (y)	3.2 +/- 1.8	-	-
Steroidal Meds Taken	30 (27.0 %)	3 (4.3 %)	<0.0001[2]

[1] Chi-square test

[2] Fisher Exact test

[3] T-test

SES = socioeconomic status using Hollingshead criteria.

Table 2

Distributions in contextual groups by quartile in Disruptive Behavior Disorder (DBD) and Healthy Comparison (HC) youth by gender

	Contextual Variables	GENDER	DBD			HC			P Value*
			<Q1	Q1-Q3	>Q3	<Q1	Q1-Q3	>Q3	
Parent Dysfunction	BDI Total	M	20.48	44.58	34.94	40.35	49.12	10.53	0.002
		F	11.11	37.04	51.85	50.00	25.00	25.00	0.028
	BSI Hostility	M	32.93	23.17	43.90	68.42	17.54	14.04	<0.001
		F	18.52	48.15	33.33	66.67	16.67	16.67	0.013
Family Functioning	FES Conflict	M	34.52	30.95	34.52	29.82	38.60	31.58	0.637
		F	29.63	22.22	48.15	50.00	50.00	0.00	0.012
	LECL Net Diff Pos & Neg	M	44.58	36.14	19.28	5.26	52.63	42.11	<0.001
		F	48.15	29.63	22.22	16.67	33.33	50.00	0.119
	LECL Total Negative	M	12.05	51.81	36.14	54.39	38.60	7.02	<0.001
		F	29.63	25.93	44.44	41.67	50.00	8.33	0.080
	LECL Total Positive	M	31.33	45.78	22.89	36.84	35.09	28.07	0.449
		F	44.44	37.04	18.52	33.33	25.00	41.67	0.309
Peer Exposure	PDS %	M	8.43	44.58	46.99	78.57	21.43	0.00	<0.001
		F	23.08	50.00	26.92	91.67	8.33	0.00	<0.001
Parental Practices	PPI Total negative	M	14.29	53.57	32.14	42.11	45.61	12.28	<0.001
		F	22.22	37.04	40.74	50.00	50.00	0.00	0.026
	PPI Total Positive	M	23.81	47.62	28.57	31.58	50.88	17.54	0.280
		F	29.63	44.44	25.93	16.67	33.33	50.00	0.326

*P values from Chi-square or Fisher's Exact test comparing DBD and HC children by gender;

BDI = Beck Depression Inventory, BSI = Brief Symptom Inventory, FES = Family Environment Scale, PDS = Peer Delinquency Scale, LECL = Life Events Checklist, PDS = Peer Delinquency Scale, PPI = Parent Perception Inventory.

Table 3

Means and standard deviations of hormone variables by Disruptive Behavior Disorder (DBD) and Healthy Comparison (HC) group and gender

Hormone	Gender	DBD		HC	
Androstenedione (pg/mL)	F	117.8	58.7	96.5	72.4
	M	110.8	53.2	94.6	50.0
Cortisol: mean (μg/dL)	F	0.17	0.16	0.14	0.12
	M	0.13	0.08	0.16	0.08
Cortisol: AM - PM (μg/dL)	F	-0.50	0.34	-0.27	0.94
	M	-0.31	0.32	-0.25	0.54
Cortisol: ratio AM/ PM	F	13.90	11.88	18.39	11.60
	M	9.40	8.03	10.49	8.35
DHEA (pg/mL)	F	46.5	30.2	44.2	26.3
	M	39.5	22.9	51.7	39.6
Testosterone pool (pg/mL)	F	47.2	19.3	53.3	34.2
	M	42.8	23.7	38.8	21.2
Testosterone AM (pg/mL)	F	51.9	22.6	74.9	48.9
	M	50.3	30.8	47.6	30.4

Note: pool = pooled sample of 2 lab collected samples; mean = mean value in 2 lab samples, M = male, F = female