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Hypothalamic-pituitary-adrenal axis dysfunction in non-clinical psychosis

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Abstract

While studies have examined psychosocial stress in non-clinical psychosis (NCP), it is unclear if the elevated cortisol seen in schizophrenia also occurs in this group. Cortisol was sampled in High- and Low-NCP groups and findings of elevated resting cortisol in the former suggest that hypothalamic-pituitary-adrenal-axis dysfunction underlies a psychosis continuum.

Keywords

Hypothalamic-Pituitary-Adrenal Axis; Cortisol; Non-Clinical Psychosis

1. Introduction

Evidence suggests that psychosis occurs across a phenotypic continuum, in which one extreme represents disorders such as schizophrenia, and at the other a subset of the general population that experiences sub-clinical symptoms in the absence of illness (6–8%) (Kelleher and Cannon, 2011). It is clear that non-clinical psychosis (NCP) reflects a constitutional vulnerability as individuals experiencing these symptoms (e.g., fleeting auditory hallucinations) are at increased risk for conversion to a psychotic disorder (Zammit et al., 2009). However, there is a dearth of research aimed at elucidating underlying biological factors. This is a critical line of research, as understanding etiological factors in the absence of significant third variable confounds stands to significantly improve our understanding of the pathogenic processes.

Although it appears that psychosocial stress is a key contributor to NCP (e.g., trauma, social disadvantage, bullying, poor family functioning) (Morgan et al., 2009; Lovatt et al., 2010; Kelleher and Cannon, 2011), and that cortisol abnormalities occur outside of formal

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psychosis (Collip et al., 2011; Mittal and Walker, 2011), there have been no studies designed to investigate biological markers of stress in this population. The present study examines resting cortisol in participants reporting High- and Low-NCP to test the hypothesis that the High-NCP group will exhibit elevated resting cortisol.

2.0 Methods

2.1 Participants

All participants in this Institutional Review Board (IRB) approved study were recruited through the Adolescent Development and Preventive Treatment (ADAPT) program. The under graduate research pool (n=1,248) was administered the Launay-Slade Hallucination Scale (LSHS) (Bentall and Slade, 1985), a questionnaire focusing on symptoms of non-clinical psychosis. The option to participate in the study was made available to those scoring in the top and bottom 10^{th} percentile on the LSHS (≥23 or ≤3). Of those invited (n=250), a total of 72 elected to participate in the present study. To limit potential sampling bias, the available studies were listed as numbers without descriptions, and students were only given study details upon arrival for the consent process (all of the individuals who arrived consented to participate). The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1976) was administered to ensure that participants with elevated psychosis would not be included as this could potentially confound results (no participants were excluded based on this criterion). Individuals who ate, drank, or participated in activity prior to the study (in a manner which could potentially affect cortisol levels) were excluded (n=9) and the final sample consisted of 63 persons (See Table 1).

2.2 Clinical Symptoms

The Launay–Slade Hallucination Scale-Revised (LSHS-R) (Bentall and Slade, 1985)is one of the most widely-used instruments in examining NCP (Johns, 2005; Barkus et al., 2007; Vellante et al., 2012) and the noted screening approach has been used successfully in other related investigations (van't Wout et al., 2004). This well-validated self-report questionnaire measures the prevalence of psychotic-like experiences on a four-item Likert scale ranging from "Never"' to "Nearly Always" (Stefanis et al., 2002). The depressive symptom frequency subscale (comprised of 8 items) of the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002) was used to examine the possibility that symptoms of depression may be driving any group difference findings in cortisol. As noted, the BPRS (Overall and Gorham, 1976) was used to screen the participants in order to control for frankly psychotic symptoms (a score of 4 "moderate" or higher on any item was set as the threshold for exclusion).

2.3 Cortisol

The participants gave three saliva samples over the course of 1.5 hours (every 45-minutes). Based on our prior studies saliva was collected utilizing a passive-drool method (Mittal et al., 2007; Mittal and Walker, 2011). The participants were not exposed to a stressor; the cortisol level indexed represents the participants' cortisol-secretion in the context of the novelty of the assessment. Because diet and exercise have been shown to affect cortisol (Hill et al., 2008), participants were instructed to detail all food and drinks consumed after 6:00pm the day prior to the study and any exercise they had engaged in 2 hours prior to the study (as noted, 9 individuals were excluded on basis on this information). The cortisol samples were stored in a −20C freezer until ready for assay; the Salimetrics High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics, LLC, College Park, PA) was used and following gold standard procedures, samples were subject to duplicate analyses and the average of all points was calculated to yield the resting cortisol variable. Data collection occurred between 9:00am and 5:00pm depending upon the appointment time for the

participant. Utilizing a method adopted by other studies of resting cortisol (Granger et al., 2007; Saxbe and Repetti, 2010), the sampling time of day was treated as a covariate to control for diurnal changes in cortisol.

3. Results

There were no significant differences between High-NCP (n=33) and Low-NCP (n=29) group son demographic characteristics including gender, age, and parental education. The use of contraceptives was tested as a covariate and was not significant in the group comparison analyses (it was subsequently excluded). A comparison between groups for sampling time of day did not approach significance, and the mean starting sample time for both groups centered around 12:00 noon (High-NCP mean=11:54am±2.33 hours; Low-NCP mean=12:24pm±2.73 hours). A Kolmogorov-Smirnov test revealed that the target cortisol variable met assumptions for parametric analyses. Examples of the most endorsed items rated as “certainly applies” include: “In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it” (28.6%);“Sometimes my thoughts seem as real as actual events in my life” (25.4%); and “I often hear a voice speaking my thoughts aloud” (19%). Reflective of the sampling strategy, the High-NCP group showed a significantly higher total score on the LSHS scale when compared to the Low-NCP group, $t(61)=-44.93$, $p\leq 0.01$. The level of NCP symptoms endorsed is comparable to recent reports (Alemany et al., 2011). While the High-NCP group showed significantly elevated frequency of depressive symptomatology when compared with the Low-NCP group, $t(60)=-4.66$, $p\leq 0.01$, there was not a significant association between the depressive symptoms and cortisol level for either group or for the sample.

An ANCOVA was conducted to examine group differences in mean level of resting cortisol, controlling for the sampling time of day. Results indicated that the High-NCP group showed significantly elevated levels when compared to the Low-NCP group, $F(1,60)=13.63$, $p\leq 0.01$. This direction of this finding was replicated in a supplementary analysis including the largest group of subjects who provide a sample at the same time (n=14). Specifically, for the subgroup of the sample who provided saliva assays between 9–10 am, the High-NCP subjects (n=8; mean=0.46, SD=0.22) showed elevated levels of cortisol when compared to the Low-NCP group (n=6; mean=0.36; SD=0.14), $t(12)=-1.07$, $p=0.15$. While this finding includes a small number of participants and is at a trend level, the direction further supports that notion that the result seen for the analysis including the entire sample is not likely the product of a time-of-day confound.

Based on an equation provided by Pruessner and colleagues (2003), mean cortisol values for each of the three sample points were used to calculate the total area under the curve with respect to ground (AUC_g). This method was utilized to supplement the mean cortisol analysis with a richer look at the data, as the measure takes into account both sensitivity (the difference between the single measurements from each other) and intensity (the distance of these measures from ground) (Pruessner et al., 2003). Consistent with the analyses of mean cortisol values, an ANCOVA analysis examining the AUC_g indicated significant elevations in the High-NCP group, $F(1,60)=13.03$, $p\leq 0.01$.

4. Discussion

Present findings support the existing literature suggesting that biological stress dysfunction is critically implicated across the phenotypic continuum of psychosis. It is interesting to consider the results are consistent with a continuum framework, in that the mean cortisol level observed in the High-NCP group rested in between the healthy controls and what has been reported in schizotypal and ultra-high risk samples (Mittal et al., 2007; Walker et al. 2010; Mittal & Walker, 2011). Investigating hypothalamic-pituitary-adrenal (HPA) axis

dysfunction helps to improve understanding of vulnerability in this population and may explain, in part, why a subgroup of NCP individuals eventually develops formal psychosis.

The sizeable effect for biological differences in a non-clinical sample is noteworthy, and suggests that understanding putative vulnerability markers may refine understanding of psychosis. In line with this goal, it is important to consider that cortisol both regulates the stress response and modulates neurodevelopment by triggering gene expression for synaptic pruning and white matter growth (Walker et al., 2008). Further, there is a synergistic relationship between activation of the HPA-axis and activation of dopaminergic circuits implicated in psychosis (Czyrak et al., 2003). For example, researchers utilizing positron emission topography (PET), have observed that stress-induced cortisol elevations are associated with increased subcortical dopamine activity in healthy (Wand et al., 2007) and at-risk participants (Soliman et al., 2008). This is particularly relevant given recent findings that suggest basal salivary cortisol levels are associated with stress sensitivity in ultra-high risk populations (Corcoran et al., 2012; Sugranyes et al., 2012). Consistent with these putative factors, a large study has shown that HPA dysfunction is predictive of eventual conversion among high-risk youth (Walker et al., 2010). In addition, a recent comprehensive review concluded that high-risk individuals show a range of abnormalities in the biological stress system including increased cortisol levels and pituitary volume in addition to reduced hippocampal volumes (Aiello et al., 2012). However, it is also important to consider that this a nuanced literature requiring significantly more investigation. For example, a small study (n=12) has suggested that elevated cortisol levels may not necessarily be directly associated with pathogenic processes, but rather, the depressive symptoms that are common in these high-risk groups (Thompson et al., 2007). With regard to the present study, the non-significant association between depressive symptoms and cortisol levels suggest that depression was not driving the observed group differences in cortisol level.

The current approach has several strengths including screening for formal psychosis and conservative assessment of cortisol (i.e., duplicate analyses, collecting several samples to rule-out artifacts due to the novel environment, controlling for diet/exercise/contraceptives). However, some factors that can affect cortisol were not examined (e.g., night-shift work, gum disease, phase of menstrual cycle). There were also limitations involving self-report measures and the relatively small sample size. While the present approach (sampling for extreme groups) was effective for optimizing the ability to detect subtle effects in a smaller sample, this strategy did not permit for continuous analyses examining relationships between cortisol levels and LSHS scores (as this could confound/inflate findings). A continuous perspective is both more statistically powerful and informative for understanding symptom-cortisol relationships as well as potential mitigating factors (e.g., depression diagnosis, childhood trauma, overall current stress) in the psychosis continuum (Collip et al., 2011). Future larger studies utilizing a different strategy are integral for improving our grasp of this topic. Further, new studies designed to examine the affect of acute stressors in NCP groups also hold promise.

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References

Aiello G, Horowitz M, Hepgul N, Carmine PM, Mondelli V. Stress abnormalities in individuals at risk for psychosis: A review of studies in subjects with familial risk or with “at risk” mental state. Psychoneuroendocrinology. 2012; 37:1600–1613. [PubMed: 22663896]

Alemany S, Arias B, Aguilera M, Villa H, Moya J, Ibanez MI, Vossen H, Gasto C, Ortet G, Fananas L. Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences. British Journal of Psychiatry. 2011; 199:38–42. [PubMed: 21719879]

Barkus E, Stirling J, Hopkins R, McKie S, Lewis S. Cognitive and neural processes in non-clinical auditory hallucinations. British Journal of Psychiatry. 2007; 51:s76–81.

Bentall RP, Slade PD. Reliability of a scale measuring disposition twards hallucination: a brief report. Personality and Individual Differences. 1985; 6:527–529.

Collip D, Nicolson NA, Lardinois M, Lataster T, van Os J, Myin-Germeys I. Daily cortisol, stress reactivity and psychotic experiences in individuals at above average genetic risk for psychosis. Psychological Medecine. 2011; 41:2305–2315.

Corcoran CM, Smith C, McLaughlin D, Auther A, Malaspina D, Cornblatt B. HPA axis function and symptoms in adolescents at clinical high risk for schizophrenia. Schizophrenia Research. 2012; 135:170–174. [PubMed: 22226904]

Czyrak A, Mackowiak M, Chocyk A, Fijal K, Wedzony K. Role of glucocorticoids in the regulation of dopaminergic neurotransmission. Polish Journal of Pharmacology. 2003; 55:667–674. [PubMed: 14704461]

Granger DA, Blair C, Willoughby M, Kivlighan KT, Hibel LC, Fortunato CK, Wiegand LE. Individual differences in salivary cortisol and alpha-amylase in mothers and their infants: relation to tobacco smoke exposure. Developmental Psychobiology. 2007; 49:692–701. [PubMed: 17943979]

Hill EE, Zack E, Battaglini C, Viru M, Viru A, Hackney AC. Exercise and circulating cortisol levels: the intensity threshold effect. Journal of Endocrinological Investigation. 2008; 31:587–591. [PubMed: 18787373]

Johns LC. Hallucinations in the general population. Current psychiatry reports. 2005; 7:162–167. [PubMed: 15935129]

Kelleher I, Cannon M. Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. Psychological Medecine. 2011; 41:1–6.

Lovatt A, Mason O, Brett C, Peters E. Psychotic-like experiences, appraisals, and trauma. The Journal of Nervous and Mental Disease. 2010; 198:813–819. [PubMed: 21048472]

Mittal VA, Dhruv S, Tessner KD, Walder DJ, Walker EF. The relations among putative biorisk markers in schizotypal adolescents: minor physical anomalies, movement abnormalities, and salivary cortisol. Biological Psychiatry. 2007; 61:1179–1186. [PubMed: 17188254]

Mittal VA, Walker EF. Minor physical anomalies and vulnerability in prodromal youth. Schizophrenia Research. 2011; 129:116–121. [PubMed: 21429715]

Morgan C, Fisher H, Hutchinson G, Kirkbride J, Craig TK, Morgan K, Dazzan P, Boydell J, Doody GA, Jones PB, Murray RM, Leff J, Fearon P. Ethnicity, social disadvantage and psychotic-like experiences in a healthy population based sample. Acta Psychiatrica Scandinavica. 2009; 119:226–235. [PubMed: 19053965]

Overall, JE.; Gorham, DR. The Brief Psychiatric Rating Scale. In: WG, editor. ECDEU Assessment Manual Psychopharmacology. U.S. Department of Health Education and Welfare; Rockville: 1976. p. 156-169.

Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology. 2003; 28:916–31. [PubMed: 12892658]

Saxbe D, Repetti RL. For better or worse? Coregulation of couples' cortisol levels and mood states. Journal of Personality and Social Psychology. 2010; 98:92–103. [PubMed: 20053034]

Soliman A, O'Driscoll GA, Pruessner J, Holahan AL, Boileau I, Gagnon D, Dagher A. Stress-induced dopamine release in humans at risk of psychosis: a [11C]raclopride PET study. Neuropsychopharmacol. 2008; 33(8):2033–41.

Stefanis NC, Hanssen M, Smirnis NK, Avramopoulos DA, Evdokimidis IK, Stefanis CN, Verdoux H, Van Os J. Evidence that three dimensions of psychosis have a distribution in the general population. Psychological Medecine. 2002; 32:347–358.

Sugranyes G, Thompson JL, Corcoran CM. HPA-axis function, symptoms, and medication exposure in youths at clinical high risk for psychosis. Journal of Psychiatric Research. 2012; 46:1389–1393. [PubMed: 22892058]

Thompson KN, Berger G, Phillips LJ, Komesaroff P, Purcell R, McGorry PD. HPA axis functioning associated with transition to psychosis: combined DEX/CRH test. Journal of Psychiatric Research. 2007; 41(5):446–50. [PubMed: 16403528]

van't Wout M, Aleman A, Kessels RP, Laroi F, Kahn RS. Emotional processing in a non-clinical psychosis-prone sample. Schizophrenia Research. 2004; 68:271–281. [PubMed: 15099609]

Vellante M, Laroi F, Cella M, Raballo A, Petretto DR, Preti A. Hallucination-Like Experiences in the Nonclinical Population. The Journal of Nervous and Mental Disease. 2012; 200:310–315. [PubMed: 22456584]

Walker E, Mittal VA, Tessner K. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annual Review of Clinical Psychology. 2008; 4:189–216.

Walker EF, Brennan PA, Esterberg M, Brasfield J, Pearce B, Compton MT. Longitudinal changes in cortisol secretion and conversion to psychosis in at-risk youth. Journal of Abnormal Psychology. 2010; 119:401–408. [PubMed: 20455612]

Wand GS, Oswald LM, McCaul ME, Wong DF, Johnson E, Zhou Y, Kuwabara H, Kumar A. Association of amphetamine-induced striatal dopamine release and cortisol responses to psychological stress. Neuropsychopharmacology. 2007; 32:2310–2320. [PubMed: 17342167]

Zammit S, Odd D, Horwood J, Thompson A, Thomas K, Menezes P, Gunnell D, Hollis C, Wolke D, Lewis G, Harrison G. Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort. Psychological Medecine. 2009; 39:1457–1467.

Table 1

Participant Demographics, Symptoms, and Resting Cortisol

	High Non-Clinical Psychosis	Low Non-Clinical Psychosis	Grand Total	Group Differences
Gender				
Males	13 (38.2%)	14 (48.3%)	27 (42.9%)	*N.S*
Females	21 (61.8%)	15 (51.7%)	36 (57.1%)	
Total	34	29	63	
Age				
Mean Years (SD)	18.8 (1.0)	19.2 (1.6)	18.9 (1.3)	*N.S.*
Parent Education				
Mean Years (SD)	15.9 (1.4)	15.0 (3.5)	15.5 (2.6)	*N.S.*
Non-Clinical Psychosis				
Mean (SD)	26.6 (3.0)	1.86 (1.0)	15.2 (12.7)	$p \leq 0.01$
Depression	7.75 (4.11)	3.86 (2.31)	5.93 (3.89)	$p \leq 0.01$
Mean (SD)				
Cortisol				
Mean (SD)	0.28 (0.21)	0.25 (0.14)	0.26 (0.26)	$p \leq .01$
AUC_g (SD)	0.54 (0.41)	0.49 (0.29)	0.52 (0.36)	$p \leq 0.01$

Note: not significant (N.S.); Launay-Slade Hallucination Scale (LSHS) ranges from 0–48; Scores on the depressive symptom frequency subscale of the Community Assessment of Psychic Experiences (CAPE) range from 0–24. Analysis of group differences for cortisol was conducted utilizing analyses of covariance (ANCOVA) with sampling time of day as a covariate. The units of cortisol are listed in μg/dl. AUC_g refers to the total area under the curve with respect to ground.