TECHNICAL COMMENTARY

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Hypothalamic-Pituitary-Adrenal axis

Introduction

Stress is defined as a threat to the body's ability to regulate internal processes following exposure to an adverse event. People adapt physiologically and behaviourally in response to stress in order to re-establish internal balance. The biological response to stress is mediated through the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Sympathetic Nervous System (SNS). This is achieved through the release of cortisol and adrenocorticotropin hormone (ACTH). Altered HPA axis activity can result in prolonged exposure to cortisol or ACTH which can be detrimental to physical and psychological health. HPA activity can be measured by basal cortisol and ACTH levels in an unstressed or resting state. HPA activity can also be measured after a stressful stimulus (chemical or psychological). There is evidence that the HPA axis may be dysfunctional in several mental disorders, including schizophrenia.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate to low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

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Hypothalamic-Pituitary-Adrenal axis

Results

We found six systematic reviews that met our inclusion criteria[3-8].

- High quality evidence shows a medium-sized reduction in the cortisol awakening response in people with schizophrenia or first-episode psychosis, but not in people with at-risk mental states.
- Moderate to high quality evidence finds a small increase in morning cortisol levels (≤10am) in people with schizophrenia compared to controls, with no difference when compared to people with bipolar disorder.
- Moderate to high quality evidence suggests a small to medium-sized increase in blood cortisol levels in people with first-episode psychosis.
- Moderate quality evidence finds increased salivary basal cortisol levels in people at ultra-high risk of psychosis compared to controls, with no difference in people in their first episode of psychosis.
- Moderate to low quality evidence suggests increased basal cortisol may be related to increased symptom severity.
- Moderate to low quality evidence finds a blunted cortisol psychological stress response in people with schizophrenia compared to controls.

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Hypothalamic-Pituitary-Adrenal axis

Berger M, Kraeuter AK, Romanik D, Malouf P, Amminger GP, Sarnyai Z

Cortisol awakening response in patients with psychosis: Systematic review and meta-analysis

Neuroscience & Biobehavioral Reviews 2016; 68: 157-66

View review abstract online

Comparison	**Cortisol awakening response in people with schizophrenia, first-episode psychosis, or at-risk mental states vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) shows a medium-sized reduction in the cortisol awakening response in people with schizophrenia or first-episode psychosis, but not in people with at-risk mental states.**

Cortisol awakening response

A significant, medium-sized reduction in the cortisol awakening response in people with schizophrenia, first-episode psychosis, or at-risk mental states;

11 studies, N = 879, g = -0.426, 95%CI -0.585 to -0.267, $p < 0.001$, I^2 = 24%, p = 0.213

The effect was similar for schizophrenia and first-episode psychosis but not for at-risk mental states;

Schizophrenia: 2 studies, N = 114, g = -0.556, 95%CI -1.069 to -0.044, $p < 0.05$, I^2 not reported

First-episode psychosis: 6 studies, N = 505, g = -0.544, 95%CI -0.731 to -0.358, $p < 0.001$, I^2 not reported

At-risk mental states: 3 studies, N = 259, g = -0.17, 95%CI -0.435 to -0.095, p = 0.207, I^2 not reported

Meta-regression modelling found larger effects in more recent publications in the clinical samples and no moderating effects of antipsychotic medication, sample size, or age.

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Chaumettea B, Kebira O, Mam-Lam-Fooka C, Morvand Y, Bourgina J, Godsilc BP, Plazea M, Gaillarda R, Jay TM, Krebsa M

Salivary cortisol in early psychosis: New findings and meta-analysis

Psychoneuroendocrinology 2016; 63: 262-270

View review abstract online

Comparison	**Salivary basal cortisol levels in adolescents (older than 12 years) and adults at ultra-high risk for psychosis (attenuated psychosis symptoms, brief limited intermittent psychotic symptoms, schizotypal personality, and/or a family history of psychosis plus functional decline), or who are in their first-episode of psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests increased salivary basal cortisol levels in people at ultra-high risk of psychosis compared to controls, with no differences between people in their first episode of psychosis and controls.**

Salivary basal cortisol levels

A significant elevation of salivary basal cortisol levels was found in people at ultra-high risk of psychosis compared to controls;

8 studies, N = 1,060, MD = 0.225, 95%CI 0.072 to 0.378, $p < 0.05$, I^2= 78%, $p < 0.001$

There were no increases in people in their first episode of psychosis;

6 studies, N = 441, MD = -0.153, 95%CI -1.405 to 1.100, $p = 0.56$, I^2= 77%, $p < 0.001$

No significant differences were found between people in their first episode of psychosis and people at ultra-high risk of psychosis, nor between high-risk individuals who converted to psychosis and those who did not convert to psychosis.

Consistency in results	Inconsistent
Precision in results	Unable to assess; standardised mean differences were not reported.
Directness of results	Direct

Girshkin L, Matheson SL, Shepherd AM, Green MJ

Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis

Psychoneuroendocrinology 2014; 49: 187-206 View review abstract online	
Comparison 1	**Morning cortisol levels (≤10am) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small increase in morning cortisol levels in people with schizophrenia compared to controls, with variability partly explained by medication free status and HPLC method of assay.**
Morning cortisol levels (measured in plasma, serum or saliva)	
A small-to-medium size increase in morning cortisol levels in people with schizophrenia; 44 studies, N = 2,613, g = 0.387, 95%CI 0.154 to 0.619, p = 0.001, I^2 = 86.9%, p < 0.001 I^2 reduced to 75.6% without 2 outliers, and the effect reduced to small (g = 0.253, p = 0.004) Subgroup analyses showed greatest effect in people with schizophrenia who were free of antipsychotic medication at the time of testing (g = 0.468, p < 0.001, I^2 = 59.19%, p = 0.001), in studies with sampling times before 8 am (g = 0.521, p < 0.001, I^2 = 67.51%, p = 0.001), in people with an established illness (g = 0.355, p < 0.001, I^2 = 63.46%, p < 0.001), and in studies of inpatients (g = 0.304, p = 0.046, I^2 = 81.17%, p < 0.001). No differences were reported between controls and first-episode patients, medication naïve or currently medicated patients, in studies with sampling conducted after 8 am, or in studies of outpatients, although between group differences were not significant for inpatient vs. outpatients. A multivariate regression estimated the effects of significant moderators (method of assay [RIA, HPLC or ELISA], time of sampling [≤ 8 a.m. or > 8 a.m.] illness stage [first episode or established illness] and medication status [medicated, medication free or medication naïve] and explained 42% of between-study variance. The multivariate model showed the most important moderators were medication free status (b = 0.443, p = 0.059), and HPLC method of assay (b = 0.591, p = 0.044) when all other covariates were held constant.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Morning cortisol levels (≤10am) in people with schizophrenia vs. bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (consistent, precise, direct, medium sample size) suggests no differences in morning cortisol levels between people with schizophrenia or bipolar**

	disorder.
Morning cortisol levels (measured in plasma, serum or saliva)	
No differences between people with schizophrenia or bipolar disorder; 7 studies, N = 392, *g* = 0.038, 95%CI -0.185 to 0.261, *p* = 0.738, I^2 = 0%, *p* = 0.464	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Hubbard DB, Miller BJ

Meta-analysis of blood cortisol levels in individuals with first-episode psychosis

Psychoneuroendocrinology 2019; 104: 269-75

View review abstract online

Comparison	**Blood cortisol levels in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small to medium-sized increase in blood cortisol levels in people with first-episode psychosis.**
Blood cortisol levels	
A small to medium-sized effect showed blood cortisol levels were increased in people with first-episode psychosis; 26 studies, N = 2,080, SMD = 0.37, 95%CI 0.16 to 0.57, *p* < 0.001, I^2 = 78% Larger effect sizes were found in studies conducted in Asia than the Middle East.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Murri B, Pariante CM, Dazzan P, Hepgul N, Papadopoulos AS, Zunszain P, Di Forti M, Murray RM, Mondelli V

Hypothalamic-pituitary-adrenal axis and clinical symptoms in first-episode psychosis

Psychoneuroendocrinology 2012; 37: 629-644

View review abstract online

Comparison	**Relationship between cortisol levels (measured at various times of the day) and symptoms in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (direct, unable to assess consistency or precision) suggests increased cortisol levels may be related to increased symptom severity.**

Correlation with between cortisol levels and symptoms (using various measures)

2 studies, (N = 76) reported *increased* morning cortisol levels associated with *increased* total symptom severity rating (*r* = 0.33 to 0.40, BPRS or PANSS).

6 studies, (N = 276) reported *increased* morning or afternoon cortisol levels associated with *increased* negative symptom severity (*r* = 0.28 to 0.50, SANS or PANSS negative).

4 studies, (N = 135) reported *increased* morning or afternoon cortisol levels associated with *increased* positive symptom severity (*r* = 0.34 to 0.61, SAPS, BPRS or PANSS positive).

1 study (N = 19) reported *increased* morning cortisol levels with *increased* disorganised symptoms (*r* = 0.53, SAPS).

1 study (N = 37) reported that *increased* cortisol levels and older age predicted *increased* levels of depression. However, a second study (N = 46) reported no differences between patients with or without comorbid depression.

2 studies (N = 74) reported *increased* cortisol levels was related to *increased* severity of anxiety.

1 study (N = 31) reported *increased* cortisol levels (time not stated) with *decreased* positive symptoms (PANSS positive).

2 studies (N = 86) reported *increased* daytime cortisol levels associated with *decreased* negative symptom severity (morning increase *r* = -0.42 and AUC = -0.45, PANSS negative).

7 studies (N = 182) reported no significant correlations between cortisol levels and symptoms; 2 studies (N = 90) reported no difference in cortisol levels between patients with positive or negative symptoms; and 1 study (N = 31) reported no changes in symptoms over time with changes in cortisol levels.

Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Zorn JV, Schur RR, Boks MP, Kahn RS, Joels M, Vinkers CH

Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis

Psychoneuroendocrinology 2017; 77: 25-36

View review abstract online

Comparison	**Cortisol response to a psychological stressor (the Trier Social Stress Test) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, imprecise, direct) suggests a blunted cortisol psychological stress response in people with schizophrenia.**

Cortisol psychological stress response

Significant, medium-sized reduction in cortisol stress response in people with schizophrenia;

4 studies, N = 180, AUCi (rate of change over time) SMD = -0.594, 95%CI -1.150 to -0.037, p = 0.04; AUCg (total secretion) SMD = -0.543, 95%CI -0.968 to -0.118, p = 0.01

Subgroup analysis of gender showed similar AUCg effects between males and females (SMD = -0.64 vs. -0.75), but only males showed significantly lower AUCi levels (SMD = -0.84 vs. -0.24).

There were no moderating effects of age or medication dose.

Consistency in results	Authors report results were inconsistent.
Precision in results	Imprecise
Directness of results	Direct

Hypothalamic-Pituitary-Adrenal axis

Explanation of acronyms

ACTH = adrenocorticotropin hormone, AUC = area under the curve, *g* = Hedges' *g* = standardised mean difference, ELISA = enzyme-linked immunosorbant assay, HPLC = high-performance liquid chromatography, HPA = hypothalamic-pituitary-adrenal axis, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RIA = radioimmunoassay, SMD = standardised mean difference, vs. = versus

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Hypothalamic-Pituitary-Adrenal axis

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[9].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[9].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[10]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[9];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[11].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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