TECHNICAL COMMENTARY

Hypothalamic-Pituitary-Adrenal axis

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Introduction

Stress is defined as a threat to the body's ability to regulate internal processes following exposure to an adverse event[1]. 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[1]. 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[2].

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. 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, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review 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[3]. 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)[4]. 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).

Results

We found two systematic reviews that met our inclusion criteria[5, 6].

- High quality evidence suggests a small-medium increase in awakening and post-dexamethasone cortisol levels in people with bipolar disorders compared to controls.
- Moderate to high quality evidence suggests morning, nighttime and 12-24hour cortisol levels are also increased.

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- The manic phase of the illness was associated with larger effect sizes, while the use of antipsychotics was associated smaller effect sizes. Radioimmunoassay and older age were associated with trend effects for larger effect sizes.
- Moderate quality evidence suggests adrenocorticotropic hormone, but not corticotropin-releasing hormone, is increased in people with bipolar disorder.
- Moderate quality evidence shows no differences in morning cortisol levels when compared to those in people with schizophrenia.

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Belvederi Murri M, Prestia D, Mondelli V, Pariante C, Patti S, Olivieri B, Arzani C, Masotti M, Respino M, Antonioli M, Vassallo L, Serafini G, Perna G, Pompili M, Amore M

The HPA axis in bipolar disorder: Systematic review and meta-analysis

Psychoneuroendocrinology 2016; 63: 327-42

View review abstract online

Comparison 1	**Cortisol, adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) levels in people with bipolar disorder vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small-medium increase in awakening and post-dexamethasone cortisol levels in people with bipolar disorders compared to controls.** **Moderate to high quality evidence (inconsistent) suggests morning, nighttime and 12-24hour cortisol are also increased in people with bipolar disorders.** **Manic phase was associated with larger effect sizes for cortisol, while the use of antipsychotics was associated smaller effect sizes. Radioimmunoassay and older age were associated with a trend for larger effect sizes.** **Moderate quality evidence (inconsistent, small samples) suggests ACTH, but not CRH is also increased in people with bipolar disorder.**

Cortisol

Small to medium-sized effects of increased cortisol levels in people with bipolar disorder, both basal and after dexamethasone administration;

Awakening: 5 studies, N = 649, g = 0.27, 95%CI 0.09 to 0.44, p = 0.003, I^2 = 0%, p = 0.52

Morning: 23 studies, N = 1,628, g = 0.40, 95%CI 0.23 to 0.58, p < 0.001, I^2 = 48%, p = 0.006

Nighttime: 9 studies, N = 1,326, g = 0.27, 95%CI 0.12 to 0.43, p = 0.001, I^2 = 51%, p = 0.04

12 or 24h: 7 studies, N = 547, g = 0.38, 95%CI 0.19 to 0.57, p < 0.001, I^2 = 64%, p < 0.001

Post-dexamethasone: 5 studies, N = 998, g = 0.24, 95%CI 0.11 to 0.37, p < 0.001, I^2 = 0%, p = 0.82

Trend effect of increased cortisol levels in the afternoon;

Afternoon: 7 studies, N = 856, g = 0.23, 95%CI -0.02 to 0.47, p = 0.07, I^2 = 55%, p = 0.04

Controlling for all potential moderating variables, manic phase was associated with larger effect sizes, while the use of antipsychotics was associated smaller effect sizes. Radioimmunoassay and older age were associated with a trend for larger effect sizes. Authors report that this model explained a high proportion of between-study heterogeneity (R^2 = 97%). Authors report no evidence of publication bias.
ACTH
Medium-sized effect of increased ACTH levels in people with bipolar disorder; 4 studies, N = 153, *g* = 0.42, 95%CI 0.09 to 0.76, *p* < 0.001, I^2 = 72%, *p* = 0.01 3 of 4 studies were conducted in the morning; removing the study conducted at night did not change the results.
CRH
No significant differences between groups; 2 studies, N = 111, *g* = 0.19, 95%CI -0.18 to 0.56, *p* = 0.31, I^2 = 83%, *p* = 0.02

Consistency in results‡	Consistent for cortisol awakening and post-dexamethasone only.
Precision in results§	Precise
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 bipolar disorder vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small increase in morning cortisol levels in people with bipolar disorders compared to controls.**

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Morning cortisol levels (measured in plasma, serum or saliva)	
A small, significant increase in cortisol levels in people with bipolar disorders compared to controls; 19 studies, N = 704, *g* = 0.27, 95%CI 0.08 to 0.45, *p* = 0.004, I^2 = 28%, *p* > 0.05 With one outlier removed; 18 studies, N = 686, *g* = 0.210, 95%CI 0.056 to 0.364, *p* = 0.008, I^2 = 0% There were no significant moderating effects of setting, bipolar phase, sex, age, medication status, or sampling time. Authors report no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Morning cortisol levels (≤ 10am) in people with bipolar disorders vs. schizophrenia.**
Summary of evidence	**Moderate quality evidence (consistent, precise, direct, medium-sized sample) 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

Explanation of acronyms

CI = confidence interval, *g* = Hedges's g, standardised mean difference, I^2 = degree of heterogeneity across study results not explained by chance, N = number of participants, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), vs. = versus

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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[7].

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† 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[7].

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[8]. 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.

Correlation coefficients (eg, r) indicate the strength of association or relationship

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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[7];

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

§ 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[9].

‖ 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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References

1. Kyrou I, Tsigos C (2009): Stress hormones: physiological stress and regulation of metabolism. *Current Opinion in Pharmacology* 9: 787-93.
2. Bradley AJ, Dinan TG (2010): A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. *Journal of Psychopharmacology* 24: 91-118.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
4. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
5. Belvederi Murri M, Prestia D, Mondelli V, Pariante C, Patti S, Olivieri B*, et al.* (2016): The HPA axis in bipolar disorder: Systematic review and meta-analysis. *Psychoneuroendocrinology* 63: 327-42.
6. Girshkin L, Matheson SL, Shepherd AM, Green MJ (2014): Morning cortisol levels in schizophrenia and bipolar disorder: A meta-analysis. *Psychoneuroendocrinology* 49: 187-206.
7. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
8. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
9. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*.