Published in final edited form as:

J Psychiatr Res. 2018 August ; 103: 46–53. doi:10.1016/j.jpsychires.2018.05.007.

Cortisol trajectory, melancholia, and response to electroconvulsive therapy

Brian J. Mickey, MD, PhD^{1,2}, Yarden Ginsburg, MS², Adam F. Sitzmann, BS², Clara Grayhack, BS², Srijan Sen, MD, PhD², Clemens Kirschbaum, PhD³, Daniel F. Maixner, MD, MS², and James L. Abelson, MD, PhD²

¹Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, USA

²Department of Psychiatry, University of Michigan Medical School, Ann Arbor, USA

³Department of Psychology, Technische Universität Dresden, Dresden, Germany

Abstract

While biomarkers have been used to define pathophysiological types and to optimize treatment in many areas of medicine, in psychiatry such biomarkers remain elusive. Based on previously described abnormalities of hypothalamic-pituitary-adrenal (HPA) axis function in severe forms of depression, we hypothesized that the temporal trajectory of basal cortisol levels would vary among individuals with depression due to heterogeneity in pathophysiology, and that cortisol trajectories that reflect elevated or increasing HPA activity would predict better response to electroconvulsive therapy (ECT). To test that hypothesis, we sampled scalp hair from 39 subjects with treatment-resistant depression just before ECT. Cortisol trajectory over the 12 weeks preceding ECT was reconstructed from cortisol concentrations in sequential hair segments. Cortisol trajectories varied widely between individuals, and exploratory analyses of clinical features revealed associations with melancholia and global severity. ECT non-responders showed a decreasing trajectory (mean change -25% , 95%-CI= $[-1\%, -43\%]$) during the 8 weeks preceding ECT (group-by-time interaction, $p=0.004$). The association between cortisol trajectory and subsequent ECT response was independent of clinical features. A classification algorithm showed that cortisol trajectory predicted ECT response with 80% accuracy, suggesting that this biomarker might be developed into a clinically useful test for ECT-responsive depression. In conclusion, cortisol trajectory mapped onto symptoms of melancholia and independently predicted response to ECT in this severely depressed sample. These findings deserve to be replicated in a larger sample. Cortisol trajectory holds promise as a reliable, noninvasive, inexpensive biomarker for psychiatric disorders.

Keywords

depression; cortisol; electroconvulsive therapy; biomarker; melancholia

Correspondence: Brian J. Mickey, 501 Chipeta Way, Salt Lake City, UT, 84108, 801-587-0159, brian.mickey@utah.edu.

Potential conflicts of interest: The authors report no financial or other relationship relevant to the subject of this article.

Introduction

Biomarkers have been used to define disease types and select treatments in many areas of medicine, but such biomarkers remain elusive in psychiatry. For example, clinicians who treat patients with depression strive to match each patient with potential treatments -- including psychosocial interventions, medications, and brain stimulation therapies -- but no objective biomarkers have yet proven useful for clinical decision-making (Strawbridge et al., 2017). For patients with severe depression, a common decision point is whether to proceed with electroconvulsive therapy (ECT). ECT is uniquely effective for medication-resistant depression but also associated with significant side effects. Furthermore, of the estimated 100,000 patients treated annually in the US (Hermann et al., 1995), roughly one-third do not respond to ECT (Haq et al., 2015; Lisanby, 2007). The effectiveness of ECT can vary with factors such as correct diagnosis, depression severity, concurrent medication, and how the ECT is administered, but for many patients the reasons for non-response remain obscure. Accurate prediction of individual response to ECT could therefore reduce exposure of many patients to an ineffective treatment, while encouraging the appropriate use of this intervention for patients with ECT-responsive depression.

These potential benefits have kindled interest in identifying clinical features and biomarkers that predict ECT outcomes. Recent meta-analyses by our group and others showed that clinical features -- including depressive episode duration, recent medication failure, age, and psychotic features -- predicted ECT response, hinting that a patient's recent history might be informative for predicting subsequent outcomes (Haq et al., 2015; van Diermen et al., 2018). Yet, the relatively weak associations of pre-treatment clinical features with subsequent ECT response indicate that clinical features alone have limited predictive power (Haq et al., 2015; van Diermen et al., 2018). Evidence for pre-treatment plasma and genetic biomarkers that predict ECT response has been mixed, as reviewed recently (Pinna et al., 2016). Several studies have reported association of ECT response with pre-treatment neuroimaging features. For example, two recent magnetic resonance imaging studies applied machine learning and demonstrated the capacity to predict ECT response with accuracies of 68–89% (Redlich et al., 2016; Wade et al., 2016). These findings suggest that biomarkers -- perhaps in combination with clinical features -- might aid clinicians in deciding whether to attempt ECT.

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol secretion have long been associated with chronic stress and related psychiatric disorders (Holsboer and Ising, 2010) including the major mood disorders, as recently reviewed (Belvederi Murri et al., 2016; Gold, 2015; Zorn et al., 2017). Furthermore, several studies have associated HPA phenotypes with treatment outcomes, suggesting that such phenotypes might be useful in defining pathophysiological types of depression. For example, excessive HPA activity predicted poorer response to psychotherapy (Fischer et al., 2017); abnormal cortisol response to the combined dexamethasone suppression corticotropin-releasing hormone stimulation test predicted better response to antidepressant medication (Binder et al., 2009); and higher post-dexamethasone salivary cortisol was associated with better response to ECT (Vukadin et al., 2011). While these results are promising, it remains unclear whether HPA measures could predict outcomes in a clinically useful way.

Hair cortisol provides a unique window into the recent history of an individual's HPA function. Recent studies indicate that hair cortisol measurements are reliable across laboratories (Russell et al., 2015) and sensitive to stress (Dettenborn et al., 2012; Stalder et al., 2017; Wester and van Rossum, 2015). Because scalp hair grows at a rate of ~0.25 cm/week (Loussouarn et al., 2005), cortisol concentrations in each 1-cm segment of hair reflect the average cortisol level over a specified 4-week period. Cortisol measured from sequential hair segments can therefore be used to reconstruct an individual's cortisol trajectory over recent weeks. We hypothesized that cortisol trajectory would vary among patients with treatment-resistant depression due to heterogeneity in underlying pathophysiology, and that cortisol trajectories reflecting elevated or increasing HPA activity would predict better response to ECT. To test this hypothesis, we measured hair cortisol concentrations in depressed patients treated with ECT.

Materials and methods

Study design and participants

In this prospective, observational study of treatment-resistant depression, we recruited adult inpatients and outpatients who were referred for ECT at a single academic center. The study was approved by the local institutional review board and carried out in accordance with the Declaration of Helsinki. All subjects provided written informed consent. Eligible participants had medication-resistant, moderate-to-severe depression (DSM-IV/5 major depressive disorder or bipolar disorder) for at least 2 months. As detailed in the Supplemental Methods, medication resistance was defined by failure of at least one medication trial of adequate dose and duration within the current episode; all participants had a lifetime history of multiple medication failures. Forty-two eligible participants consented, provided hair samples, and completed ECT. Three subjects were excluded, leaving 39 available for analysis. See Supplemental Methods for details.

Baseline assessments

Each patient was assessed by two board-certified psychiatrists and a masters-level psychologist. Assessment included the Mini International Neuropsychiatric Interview Plus, version 5.0.0 (Sheehan et al., 1998) and the Structured Interview Guide for the Hamilton Depression Rating Scale (Williams et al., 1988). Based on evidence that classic melancholia is not adequately characterized by DSM-IV/5 criteria (Parker et al., 2010), we also rated each subject on a series of 11 signs and symptoms traditionally associated with melancholia (Gold, 2015; Parker et al., 2010; Taylor and Fink, 2006) and calculated a *melancholia index* (number of signs/symptoms of melancholia divided by 11; range 0–1). See Supplemental Methods for details.

Treatment and post-treatment assessments

During this observational study, ECT treatments were administered as clinically indicated using bitemporal or right-unilateral, brief-pulse stimulation. The primary outcome measure was post-treatment “responder” status, a dichotomous variable. Responders were defined as 1 or 2 (“very much” or “much” improved) and non-responders as 3 on the Clinical Global Impression (CGI) improvement scale. CGI ratings were based on depressive symptom

ratings, patient and caregiver reports, and team consensus, and were performed before cortisol was assayed to prevent bias. Responder status was chosen as the primary outcome over other measures (e.g., change in a depression rating scale) because it represents meaningful benefit that informs dichotomous clinical decision-making. More specifically, ECT would likely not have been attempted with non-responders had the outcome been known, and a non-responder would be unlikely to attempt ECT again in the future. See Supplemental Methods for details.

Hair cortisol quantification

Hair samples were collected just before the ECT series using established procedures (see Supplemental Methods). Each subject's cortisol trajectory was reconstructed from this single hair sample. The most proximal 3-cm portion of each hair sample was cut into three 1-cm segments (5.5 mg per segment), washed, pulverized, and alcohol extracted (Kirschbaum et al., 2009). Cortisol concentrations (picograms of cortisol per mg of hair) were quantified with a commercial chemoluminescence-based immunoassay (Dettenborn et al., 2012). Because the distribution of cortisol concentration values was skewed and wide-ranging, values were $\log_{10}$ transformed, and changes were expressed as fold-change (i.e., the ratio of final over initial concentration).

Statistical analysis

Analyses were performed using R statistical software (version 3.2.4). Hair cortisol concentration was modeled as a repeated measure using a linear mixed model (*lmer* function, *lme4* package, version 1.1–12) with subject as the random effect. To test the primary hypothesis that cortisol trajectory was associated with subsequent response to ECT, response group, time (i.e., hair segment), group-by-time, and age were modeled as fixed effects. Similarly, in exploratory analyses of each clinical feature, the feature, time, feature-by-time, and age terms were included as fixed effects. Wald χ^2 tests and corresponding p-values were calculated from fitted models using the *Anova* function (*car* package, version 2.1–2).

To evaluate the predictive potential of pre-treatment cortisol trajectory, we applied the K-nearest neighbors (KNN) algorithm (*knn* function, *class* package, version 7.3–14), a supervised, non-parametric, statistical learning tool (James et al., 2015). The KNN classifier was chosen over alternative approaches such as logistic regression or linear discriminant analysis because it makes no assumptions about the shape of the decision boundary, and it typically performs better than other methods when the number of features is small (James et al., 2015). Ten-fold cross-validation was applied to prevent overfitting. Confidence intervals were calculated using random permutation (n=1000). The optimal value of *K* was determined algorithmically as the value that produced maximal mean accuracy; for this data set, *K*=3 was optimal, *K*=4 was next best (accuracy 72%), and other values of *K* performed poorly (accuracy <70%).

Results

Participants and clinical outcomes

Socio-demographic, clinical, and concomitant medication data are shown in Tables 1 and 2. Twenty-four participants (62%) were ECT responders. Response status was not associated with ECT lead placement or number of treatments ($p>0.05$, Wilcoxon rank sum tests). This lack of association may have been due to the consistent use of high-dose stimulation ($>5x$ threshold) when using the right unilateral configuration and the strategy of switching to bilateral stimulation when patients experienced no significant improvement after ~6 unilateral treatments.

Hair cortisol and clinical features

We first calculated each subject's time-averaged hair cortisol concentration as the mean over the three hair segments (proximal, middle, and distal). Time-averaged concentrations spanned a wide range from 1.4 to 107 pg/mg (Figure 1A), consistent with previous measurements from healthy and depressed individuals (Dettenborn et al., 2012; Russell et al., 2015). Concentration did not differ by sex ($t=0.1$, $df=32.9$, $p=0.91$, Welch two-sample t test) but it did correlate positively with age ($r=0.49$, $n=39$, $p=0.0015$, Pearson correlation) so age was included as a covariate in all models.

Next we examined change in hair cortisol concentration across segments (i.e., over time) using linear mixed models. Substantial variation was observed in individual cortisol trajectories (Figure 1B-D) but change in concentration across segments was not significant in the sample as a whole (effect of time: $\chi^2=0.15$, $df=1$, $p=0.70$).

To explore whether cortisol trajectory over time was associated with clinical subtypes of depression, we applied linear mixed models to each of the demographic and clinical features shown in Table 1. These analyses showed that just two clinical features were strongly associated with cortisol trajectory: melancholia index (main effect: $\chi^2=5.3$, $df=1$, $p=0.022$; melancholia-by-time interaction: $\chi^2=7.0$, $df=1$, $p=0.0080$) and CGI severity (main effect: $\chi^2=3.2$, $df=1$, $p=0.074$; severity-by-time interaction: $\chi^2=12.3$, $df=1$, $p=0.00046$). These two variables were also correlated with each other ($\rho=0.63$, $n=39$, $p=0.00002$, Spearman correlation). Downward cortisol trajectories were more common among less melancholic and less severe subjects (Figure 2A-C). The findings remained significant when an outlier was excluded from analyses (melancholia main effect: $p=0.013$; time interaction: $p=0.019$; CGI severity main effect: $p=0.041$; time interaction: $p=0.0030$). Weaker effects were found for catatonic features, social phobia, generalized anxiety disorder, and global assessment of functioning (GAF) score (see Supplemental Results). No significant associations were found for the other features in Table 1, including DSM-IV melancholic features ($p>0.05$, all main effects and interactions).

Cortisol trajectory and ECT response

We then tested the hypothesis that cortisol trajectory predicts subsequent clinical response to ECT. An interaction was found between response group and time ($\chi^2=8.5$, $df=1$, $p=0.0036$, linear mixed model), indicating that change in cortisol concentration across hair segments

differed between responders and non-responders (Figure 3A). Main effects of response group and time were not significant (group: $\chi^2=0.36$, $df=1$, $p=0.55$; time: $\chi^2=0.16$, $df=1$, $p=0.69$). As shown in Figure 3B, cortisol concentrations tended to increase slightly among responders (mean change 11%; 95%-CI=[-3%,27%]) and decrease in the non-responder group (mean change -25%; 95%-CI=[-1%, -43%]) in the proximal segment. Although proximal cortisol concentration by itself tended to be lower among non-responders, the difference was not statistically significant ($t=1.62$, $df=37$, $p=0.11$, Welch two-sample t test), indicating that a simple assay of the most proximal segment is less informative than between-segment cortisol trajectory.

Control analyses showed that this group-by-time interaction remained significant when the outlying subject was excluded from the analysis ($p=0.013$), indicating that this subject did not unduly influence the results. When percentage-change in Hamilton or Montgomery-Asberg depression score was used as the outcome instead of response group, the response-by-time interaction persisted ($p=0.03$ and $p=0.005$, respectively), demonstrating that this finding was robust to the particular outcome measure used. A series of analyses of potential confounding factors -- age, sex, body mass index, oral contraceptives, frequency of hair washing, hair treatments, concurrent medications -- indicated that the group-by-time interaction was not explained by these variables (see Supplemental Results).

The finding that cortisol trajectory was associated with melancholia and global severity, and also with subsequent ECT response, suggested that a downward cortisol trajectory may simply index a less severe form of depression that is ECT-nonresponsive. However, further analyses countered that idea. First, ECT response was not associated with either melancholia index ($t=0.33$, $df=28.6$, $p=0.74$, two-sample t -test) or CGI severity ($p=0.35$, Wilcoxon rank sum test). In fact, no demographic or clinical feature was significantly associated with ECT response (all $p>0.05$). Second, in the linear-mixed-model framework, the group-by-time interaction persisted when including melancholia and melancholia-by-time terms ($p=0.0013$) or severity and severity-by-time terms ($p=0.011$). Therefore, we conclude that cortisol trajectory is associated with ECT response and *independently* with melancholia and global severity. In other words, cortisol trajectory provides information about subsequent ECT response that surpasses the information provided by clinical features.

Prognostic classification

To evaluate the potential clinical utility of hair cortisol as a biomarker to predict ECT response, we employed a statistical classification algorithm (K-nearest neighbors, KNN). As shown in Figure 3C, when change in cortisol concentration from middle to proximal hair segment is plotted against middle-segment concentration, subjects segregate to some degree by response group. The KNN algorithm classified each subject as a responder or non-responder based on the actual response of that subject's nearest neighbors on this two-dimensional plane. The optimal model ($K=3$) produced a mean accuracy of 80% (95%-CI=[72%,85%]). When the outlying subject was excluded, the results were essentially unchanged (accuracy 81%; 95%-CI=[74%,84%]). Classifier performance degraded when clinical variables were added as features (data not shown) indicating that these features burdened the classifier without adding information useful for predicting ECT response.

The KNN classifier may be conceptualized as a diagnostic test for ECT-responsive depression with an accuracy of 0.80 (sensitivity 0.86, specificity 0.70). Assuming a pre-test probability of response of 62% (the actual response rate in our sample), the positive and negative predictive values were 0.82 and 0.76, respectively. In other words, a pre-treatment test result of “responder” increases the probability of response to 82%, whereas a test result of “non-responder” decreases the probability of response to 24% (1–0.76). These test characteristics provide “proof-of-concept” evidence that a predictive biomarker like this one could usefully inform clinical decision-making.

Discussion

This study measured hair cortisol trajectories in individuals with treatment-resistant depression and produced three major findings. First, hair cortisol concentrations and trajectories varied substantially between individuals. Second, cortisol trajectories were associated with clinical features, especially classic melancholia and global severity. Third, cortisol trajectory predicted subsequent response to ECT independently from clinical features, with decreasing trajectories being less favorable. Notably, this finding differed somewhat from our *a priori* hypothesis that high levels or increasing trajectories would predict better clinical response. We conclude that cortisol trajectories reveal individual differences in HPA function that are clinically relevant and potentially prognostic.

Hair cortisol concentration is thought to index the body’s average, long-term, basal cortisol level. A question under active investigation is how hair cortisol concentration relates to traditional plasma, salivary, or urinary cortisol measures. Recent work indicates that hair cortisol is weakly correlated ($r < 0.2$) with momentary salivary cortisol (Stalder et al., 2017) but more strongly correlated ($r > 0.4$) with time-averaged salivary or urinary measures (D’Anna-Hernandez et al., 2011; Short et al., 2016; van Ockenburg et al., 2016). In this context, our findings suggest that ECT response and clinical features are associated with long-term alterations in basal cortisol levels that occur over weeks to months. To our knowledge, fluctuations of basal cortisol levels on a time scale of weeks to months have not been described previously. Future long-term longitudinal studies of healthy and depressed individuals would be helpful to determine whether such fluctuations occur in healthy individuals or as part of the natural course of the disease.

An important consideration in measurement of hair cortisol trajectory is systematic bias across hair segments. Because more distal hair segments are older, degradation over time may cause greater loss of cortisol in those segments, causing an *apparent increase* in cortisol concentration over time, even when actual cortisol levels are unchanged. Critically, this bias does not affect *between-subject* statistical comparisons (i.e., ECT response or melancholia) since the bias is expected to influence each subject similarly. A recent study (Stalder et al., 2017) estimated the magnitude of this systematic bias at 29% per 3 cm of hair which corresponds to an apparent increase of 11% per cm, assuming exponential decay. Among ECT responders, we observed an apparent increase from middle to proximal segments of 11%, consistent with the expected bias. In contrast, non-responders showed an apparent *decrease* (mean change -25% ; 95%-CI= $[-1\%, -43\%]$) that was inconsistent with 11% per cm. We therefore favor the interpretation that actual cortisol levels decreased over time in

the ECT non-responder group, reflecting a change in adaptive HPA function during the 2-month period leading up to treatment.

Why cortisol would decrease in some individuals is not clear. There are three principal mechanisms known to alter cortisol secretion -- central HPA drive, sensitivity to glucocorticoid-receptor-mediated negative feedback, and autonomous cortisol secretion at the adrenal gland (Carroll et al., 2012). A decrease in central HPA drive in future ECT non-responders seems unlikely in the weeks preceding ECT, when depression is typically severe and worsening. Development of hypersensitivity to negative feedback among future non-responders is possible, and would implicate changes in cortisol sensitivity of major HPA nodes, or of brain structures that regulate the hypothalamus (Herman et al., 2016; McKlveen et al., 2015). The third mechanism may be the most likely: a decrease in basal adrenal secretion of cortisol, independent of HPA drive or feedback, among future ECT non-responders. Under this scenario, basal cortisol production decreases as depression worsens during the run up to ECT. In other words, non-responders fail to mount the HPA response expected under such challenging conditions. In support of this general mechanism, Carroll and colleagues found evidence of increased autonomous cortisol secretion (independent of changes in HPA drive or negative feedback) among individuals with hypercortisolemic depression (Carroll et al., 2012). The idea that ECT works best when cortisol secretion is appropriately elevated parallels previous studies of the hypothalamic-pituitary-thyroid (HPT) and HPA axes that found associations between intact neuroendocrine function and better antidepressant response (Abulseoud et al., 2007; Abulseoud et al., 2013; Cole et al., 2002; Frank et al., 1984; Frye et al., 1999) as well as literature suggesting an association between HPT axis function and response to ECT (Kirkegaard and Faber, 1986). Future work will be needed to distinguish among these mechanisms and to determine whether this phenotype simply marked an ECT-nonresponsive subtype of depression, or perhaps interfered with the therapeutic mechanisms of ECT.

This study has important limitations. First, as highlighted in a recent meta-analysis, several variables can confound hair cortisol measurements -- notably, age, sex, body mass index, oral contraceptives, frequency of hair washing, and hair treatments (Stalder et al., 2017). Our analyses indicated that the association of ECT response with cortisol trajectory was not explained by these variables or by concurrent medications, increasing confidence in the results. Nonetheless, with a relatively small analyzable sample size of 39 subjects, our ability to statistically control for confounding factors was limited, as was our capacity to detect small-to-moderate-sized effects. Furthermore, sample heterogeneity increases the likelihood of unknown confounders (e.g., medications). Although severe treatment-resistant depression represents a subset of patients with depression, substantial heterogeneity still exists in our sample. For example, 26% of our sample had bipolar disorder; we found no significant association of cortisol trajectory with bipolar disorder but differences might be evident in larger samples. Second, the generalizability of our findings remains uncertain. Our sample was drawn from a single academic medical center and, furthermore, we were unable to include some of the most severe patients seen in clinical practice (i.e., severely catatonic, psychotic, or agitated patients). Similarly, our sample may not be representative of outpatients with mild-to-moderate depression or those with prominent personality or substance-abuse comorbidities. Replication and extension of these findings with a larger

multi-site study will be necessary to develop greater confidence in our findings. Finally, although we extensively phenotyped our participants, we did not systematically collect reports of childhood adversity, which has previously been linked with adult HPA function (Bunea et al., 2017; Danese and McEwen, 2012). Future studies are warranted to investigate the relationship between early-life stress and cortisol trajectory during adulthood.

Hair cortisol trajectory holds promise as a clinically-useful predictive biomarker for depression, and potentially for other conditions. Measurement of hair cortisol concentration is noninvasive, inexpensive, and reproducible across laboratories (Russell et al., 2015), providing an advantage over more complex biomarkers such as neuroimaging measures. Furthermore, our analyses indicated that cortisol trajectory distinguished two groups of patients who had a 24% versus 82% chance of response to ECT. We believe patients and clinicians would find this information useful when deciding whether to pursue ECT. If these findings can be replicated, a predictive test like this one has the potential to help many patients avoid a burdensome and ineffective treatment, while encouraging use of this unique intervention for patients with ECT-responsive illness. Beyond the specific application to ECT, cortisol trajectory might also prove useful for personalized targeting of novel therapeutics like the anti-glucocorticoid agent mifepristone (Flores et al., 2006) or other established pharmacologic and psychosocial interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We thank the patients, nurses, technicians, administrators, and physicians of the University of Michigan ECT Program for their enthusiastic support of this study.

Funding: This research was supported by the National Institute of Mental Health (K23 MH 092648), Michigan Institute for Clinical & Health Research (National Center for Advancing Translational Sciences, 2UL1 TR 000433), Taubman Medical Research Institute, and University of Michigan Depression Center. The sponsors had no role in the design, analysis, interpretation, or publication of this study.

References

- Abulseoud O, Sane N, Cozzolino A, Kiriakos L, Mehra V, Gitlin M, Masseling S, Whybrow P, Altshuler LL, Mintz J, Frye MA, 2007 Free T4 index and clinical outcome in patients with depression. *J Affect Disord* 100(1–3), 271–277. [PubMed: 17123630]
- Abulseoud OA, Gitlin M, Altshuler L, Frye MA, 2013 Baseline thyroid indices and the subsequent response to citalopram treatment, a pilot study. *Brain Behav* 3(2), 89–94. [PubMed: 23533025]
- Belvederi Murri M, Prestia D, Mondelli V, Pariante C, Patti S, Olivieri B, Arzani C, Masotti M, Respingo M, Antonioli M, Vassallo L, Serafini G, Perna G, Pompili M, Amore M, 2016 The HPA axis in bipolar disorder: Systematic review and meta-analysis. *Psychoneuroendocrinology* 63, 327–342. [PubMed: 26547798]
- Binder EB, Kunzel HE, Nickel T, Kern N, Pfennig A, Majer M, Uhr M, Ising M, Holsboer F, 2009 HPA-axis regulation at in-patient admission is associated with antidepressant therapy outcome in male but not in female depressed patients. *Psychoneuroendocrinology* 34(1), 99–109. [PubMed: 18829172]
- Bunea IM, Szentagotai-Tatar A, Miu AC, 2017 Early-life adversity and cortisol response to social stress: a meta-analysis. *Transl Psychiatry* 7(12), 1274. [PubMed: 29225338]

- Carroll BJ, Iranmanesh A, Keenan DM, Cassidy F, Wilson WH, Veldhuis JD, 2012 Pathophysiology of hypercortisolism in depression: pituitary and adrenal responses to low glucocorticoid feedback. *Acta Psychiatr Scand* 125(6), 478–491. [PubMed: 22211368]
- Cole DP, Thase ME, Mallinger AG, Soares JC, Luther JF, Kupfer DJ, Frank E, 2002 Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. *Am J Psychiatry* 159(1), 116–121. [PubMed: 11772699]
- D'Anna-Hernandez KL, Ross RG, Natvig CL, Laudenslager ML, 2011 Hair cortisol levels as a retrospective marker of hypothalamic-pituitary axis activity throughout pregnancy: comparison to salivary cortisol. *Physiol Behav* 104(2), 348–353. [PubMed: 21397617]
- Danese A, McEwen BS, 2012 Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol Behav* 106(1), 29–39. [PubMed: 21888923]
- Dettenborn L, Muhtz C, Skoluda N, Stalder T, Steudte S, Hinkelmann K, Kirschbaum C, Otte C, 2012 Introducing a novel method to assess cumulative steroid concentrations: increased hair cortisol concentrations over 6 months in medicated patients with depression. *Stress* 15(3), 348–353. [PubMed: 22043813]
- Fischer S, Strawbridge R, Vives AH, Cleare AJ, 2017 Cortisol as a predictor of psychological therapy response in depressive disorders: systematic review and meta-analysis. *Br J Psychiatry* 210(2), 105–109. [PubMed: 27908897]
- Flores BH, Kenna H, Keller J, Solvason HB, Schatzberg AF, 2006 Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* 31(3), 628–636. [PubMed: 16160710]
- Frank E, Jarrett DB, Kupfer DJ, Grochocinski VJ, 1984 Biological and clinical predictors of response in recurrent depression: a preliminary report. *Psychiatry Res* 13(4), 315–324. [PubMed: 6441181]
- Frye MA, Denicoff KD, Bryan AL, Smith-Jackson EE, Ali SO, Luckenbaugh D, Leverich GS, Post RM, 1999 Association between lower serum free T4 and greater mood instability and depression in lithium-maintained bipolar patients. *Am J Psychiatry* 156(12), 1909–1914. [PubMed: 10588404]
- Gold PW, 2015 The organization of the stress system and its dysregulation in depressive illness. *Mol Psychiatry* 20(1), 32–47. [PubMed: 25486982]
- Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ, 2015 Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. *J Clin Psychiatry* 76(10), 1374–1384. [PubMed: 26528644]
- Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, Scheimann J, Myers B, 2016 Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Compr Physiol* 6(2), 603–621. [PubMed: 27065163]
- Hermann RC, Dorwart RA, Hoover CW, Brody J, 1995 Variation in ECT use in the United States. *Am J Psychiatry* 152(6), 869–875. [PubMed: 7755116]
- Holsboer F, Ising M, 2010 Stress hormone regulation: biological role and translation into therapy. *Annu Rev Psychol* 61, 81–109, C101–111. [PubMed: 19575614]
- James G, Witten D, Hastie T, Tibshirani R, 2015 *An Introduction to Statistical Learning with Applications in R* Springer, New York.
- Kirkegaard C, Faber J, 1986 Influence of free thyroid hormone levels on the TSH response to TRH in endogenous depression. *Psychoneuroendocrinology* 11(4), 491–497. [PubMed: 3104947]
- Kirschbaum C, Tietze A, Skoluda N, Dettenborn L, 2009 Hair as a retrospective calendar of cortisol production-Increased cortisol incorporation into hair in the third trimester of pregnancy. *Psychoneuroendocrinology* 34(1), 32–37. [PubMed: 18947933]
- Lisanby SH, 2007 Electroconvulsive therapy for depression. *N Engl J Med* 357(19), 1939–1945. [PubMed: 17989386]
- Loussouarn G, El Rawadi C, Genain G, 2005 Diversity of hair growth profiles. *Int J Dermatol* 44 Suppl 1, 6–9. [PubMed: 16187948]
- McKlveen JM, Myers B, Herman JP, 2015 The medial prefrontal cortex: coordinator of autonomic, neuroendocrine and behavioural responses to stress. *J Neuroendocrinol* 27(6), 446–456. [PubMed: 25737097]

- Parker G, Fink M, Shorter E, Taylor MA, Akiskal H, Berrios G, Bolwig T, Brown WA, Carroll B, Healy D, Klein DF, Koukopoulos A, Michels R, Paris J, Rubin RT, Spitzer R, Swartz C, 2010 Issues for DSM-5: whither melancholia? The case for its classification as a distinct mood disorder. *Am J Psychiatry* 167(7), 745–747. [PubMed: 20595426]
- Pinna M, Manchia M, Oppo R, Scano F, Pillai G, Loche AP, Salis P, Minnai GP, 2016 Clinical and biological predictors of response to electroconvulsive therapy (ECT): a review. *Neurosci Lett* S0304-3940(16), 30801.
- Redlich R, Opel N, Grotegerd D, Dohm K, Zaremba D, Burger C, Munker S, Muhlmann L, Wahl P, Heindel W, Arolt V, Alferink J, Zwanzger P, Zavorotnyy M, Kugel H, Dannlowski U, 2016 Prediction of Individual Response to Electroconvulsive Therapy via Machine Learning on Structural Magnetic Resonance Imaging Data. *JAMA Psychiatry* 73(6), 557–564. [PubMed: 27145449]
- Russell E, Kirschbaum C, Laudenslager ML, Stalder T, de Rijke Y, van Rossum EF, Van Uum S, Koren G, 2015 Toward standardization of hair cortisol measurement: results of the first international interlaboratory round robin. *Ther Drug Monit* 37(1), 71–75. [PubMed: 25387254]
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC, 1998 The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20, 22–33;quiz 34–57.
- Short SJ, Stalder T, Marceau K, Entringer S, Moog NK, Shirtcliff EA, Wadhwa PD, Buss C, 2016 Correspondence between hair cortisol concentrations and 30-day integrated daily salivary and weekly urinary cortisol measures. *Psychoneuroendocrinology* 71, 12–18. [PubMed: 27235635]
- Stalder T, Steudte-Schmiedgen S, Alexander N, Klucken T, Vater A, Wichmann S, Kirschbaum C, Miller R, 2017 Stress-related and basic determinants of hair cortisol in humans: A meta-analysis. *Psychoneuroendocrinology* 77, 261–274. [PubMed: 28135674]
- Strawbridge R, Young AH, Cleare AJ, 2017 Biomarkers for depression: recent insights, current challenges and future prospects. *Neuropsychiatr Dis Treat* 13, 1245–1262. [PubMed: 28546750]
- Taylor MA, Fink M, 2006 *Melancholia* Cambridge University Press, New York.
- van Diermen L, van den Ameel S, Kamperman AM, Sabbe BCG, Vermeulen T, Schrijvers D, Birkenhager TK, 2018 Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. *Br J Psychiatry* 212(2), 71–80. [PubMed: 29436330]
- van Ockenburg SL, Schenk HM, van der Veen A, van Rossum EF, Kema IP, Rosmalen JG, 2016 The relationship between 63days of 24-h urinary free cortisol and hair cortisol levels in 10 healthy individuals. *Psychoneuroendocrinology* 73, 142–147. [PubMed: 27497154]
- Vukadin M, Birkenhager TK, Wierdsma AI, Groenland TH, van den Broek WW, 2011 Post-dexamethasone cortisol as a predictor for the efficacy of electroconvulsive therapy in depressed inpatients. *J Psychiatr Res* 45(9), 1165–1169. [PubMed: 21481419]
- Wade BS, Joshi SH, Njau S, Leaver AM, Vasavada M, Woods RP, Gutman BA, Thompson PM, Espinoza R, Narr KL, 2016 Effect of Electroconvulsive Therapy on Striatal Morphometry in Major Depressive Disorder. *Neuropsychopharmacology* 41(10), 2481–2491. [PubMed: 27067127]
- Wester VL, van Rossum EF, 2015 Clinical applications of cortisol measurements in hair. *Eur J Endocrinol* 173(4), M1–10. [PubMed: 25924811]
- Williams JBW, Link MJ, Rosenthal NE, Terman M, 1988 *Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD)* New York State Psychiatric Institute, New York.
- Zorn JV, Schur RR, Boks MP, Kahn RS, Joels M, Vinkers CH, 2017 Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology* 77, 25–36. [PubMed: 28012291]

Figure 1.

Variation in cortisol trajectory in treatment-resistant depression. **(A)** Time-averaged hair cortisol concentration is plotted versus age for females (circles) and males (squares). Concentrations are plotted on a logarithmic scale. Median concentration, 7.2 pg/mg; mean concentration, 13.8 pg/mg; mean (SD) cortisol concentration in $\log_{10}$ transformed units, 0.93 (0.41). **(B)** Hair cortisol concentration is shown for each hair segment. The distal, middle, and proximal hair segments represent time periods approximately 8–12, 4–8, and 0–4 weeks prior to ECT, respectively. **(C)** The data in (B) are re-plotted to show cortisol trajectories of individual subjects. **(D)** Change in hair cortisol concentration between segments is shown. Fold change is defined as the ratio of final over initial concentrations.

Figure 2.

Cortisol trajectory and melancholia. **(A)** Mean hair cortisol concentration is plotted versus hair segment for patients grouped by melancholia index: low (1st tertile, $n=13$, black), moderate (2nd tertile, $n=15$, blue), and high (3rd tertile, $n=11$, cyan). Error bars are 95%-confidence intervals. **(B)** Mean change in hair cortisol concentration between segments is plotted shown for patients grouped by melancholia index. Error bars are 95%-confidence intervals. **(C)** Change in hair cortisol concentration between distal and proximal segments is plotted versus melancholia index. Cortisol trajectories varied in a similar way as a function of global severity, which correlated with melancholia index (data not shown).

Figure 3.

Cortisol trajectory and response to electroconvulsive therapy (ECT). **(A)** Mean hair cortisol concentration is plotted versus hair segment for ECT responders ($n=24$, black) and non-responders ($n=15$, red). Error bars are 95%-confidence intervals. **(B)** Mean change in hair cortisol concentration between segments is shown for ECT responders and non-responders. Error bars are 95%-confidence intervals. **(C)** Change in hair cortisol concentration between middle and proximal segments is plotted versus cortisol concentration in the middle segment. The segregation apparent between non-responders (red) and responders (black) was quantified using the K-nearest-neighbors classifier (see text). For clarity, the outlier evident in Figures 1 and 2 is not shown; the results were essentially unchanged when the outlier was excluded from analyses.

Table 1.Sociodemographic and clinical features of the sample¹

Sociodemographic characteristics	
Age, years, mean (SD), range	49.4 (17.0), 19–80
Female	24 (62%)
Race, white or Caucasian	34 (87%)
Marital status, married	19 (49%)
single	11 (28%)
other	9 (23%)
Education, years, mean (SD), range	15.7 (2.5), 12–23
Employment status, on disability	11 (28%)
retired	9 (23%)
student, homemaker, part-time	9 (23%)
full-time	6 (15%)
unemployed	4 (10%)
Annual household income (n=35), < \$25,000	13 (37%)
\$25,000 - \$49,999	7 (20%)
\$50,000 - \$74,999	5 (14%)
\$75,000	10 (29%)
Diagnostic features	
Primary mood disorder: major depressive disorder, recurrent	24 (62%)
major depressive disorder, single-episode	5 (13%)
bipolar 1 disorder	7 (18%)
bipolar 2 disorder	3 (8%)
Psychotic features	6 (15%)
Melancholic features (DSM-IV)	30 (77%)
Atypical features	2 (5%)
Catatonic features	3 (8%)
Melancholia index, mean (SD)	0.57 (0.20)
Current anxiety disorder, n=35	29 (83%)
generalized anxiety disorder	21 (60%)
agoraphobia	19 (54%)
social anxiety disorder	9 (26%)
panic disorder	7 (20%)
specific phobia	0 (0%)
post-traumatic stress disorder	0 (0%)
obsessive-compulsive disorder	0 (0%)
Current substance use disorder, n=35	6 (17%)
alcohol use disorder	4 (11%)
tobacco use disorder	3 (9%)
other substance use disorder	2 (6%)

Sociodemographic characteristics

Severity scales

Clinical Global Impression severity scale, mean (SD)	5.92 (0.62)
Global Assessment of Functioning scale, mean (SD)	28.0 (9.7)
Montgomery Asberg Depression Rating Scale, mean (SD), n=35	35.9 (5.4)
17-item Hamilton Depression Rating Scale, mean (SD), n=35	23.2 (4.5)

Chronicity and resistance

Current episode duration, months, mean (SD)	36.5 (45.7)
median (IQR), range	18 (26), 3–180
duration 6 months	34 (87%)
duration 1 year	26 (67%)
duration 2 years	17 (44%)
duration 5 years	7 (18%)
Onset age, years, mean (SD)	21.6 (12.9)
median (IQR), range	17 (15.5), 7–54
Lifetime number of depressive episodes (n=38): single	5 (13%)
2	7 (18%)
3	6 (16%)
4–5	4 (11%)
> 5	16 (42%)
Massachusetts General Hospital staging score, mean (SD)	7.2 (4.6)
Maudsley staging score, mean (SD)	9.2 (2.0)
Past improvement with ECT	9 (23%)

Other clinical features

Parental history of mood disorder (n=35)	14 (40%)
maternal	10 (29%)
paternal	8 (23%)
Left-handed or ambidextrous	2 (5%)
Body mass index, mean (SD)	29.0 (6.3)

Post-treatment scales

Montgomery Asberg Depression Rating Scale, mean (SD), n=36	16.7 (9.6)
17-item Hamilton Depression Rating Scale, mean (SD), n=35	11.4 (6.5)
Montreal Cognitive Assessment, mean (SD), n=34	26.9 (3.1)

Values represent number of subjects (% of subjects), except where indicated

¹ Total number of subjects is 39; for variables with missing values, the number of subjects with available data (n) is shown

Table 2.**Concomitant medications¹**

Antidepressants (33)	Hormones (16)
trazodone (14)	levothyroxine or liothyronine (10)
venlafaxine (8)	estrogen or progesterone (3)
bupropion (7)	melatonin (3)
mirtazapine (5)	dexamethasone or hydrocortisone, topical (2)
duloxetine (4)	
escitalopram (3)	Other psychoactive medications
fluoxetine (3)	lithium (4)
sertraline (3)	diphenhydramine (3)
nortriptyline (2)	hydroxyzine (2)
selegiline (1)	hydrocodone (2)
vilazodone (1)	buspirone (2)
vortioxetine (1)	nicotine (2)
doxepin (1)	propranolol (1)
imipramine (1)	sumatriptan (1)
	clonidine (1)
Anticonvulsants (12)	benztropine (1)
gabapentin (7)	levodopa (1)
topiramate (4)	L-methylfolate (1)
lamotrigine (3)	cyclobenzaprine (1)
	cyclobenzaprine (1)
Antipsychotics (17)	dextroamphetamine (1)
olanzapine (6)	olanzapine (6)
quetiapine (6)	
aripiprazole (4)	Other medications that may affect hair growth or
risperidone (2)	cortisol levels²
lurasidone (1)	fluconazole (1)
ziprasidone (1)	warfarin (1)
	warfarin (1)
Sedative-hypnotics (21)	
clonazepam (12)	
lorazepam (9)	
alprazolam (4)	
zolpidem (2)	
diazepam (1)	

Values in parentheses represent the number of subjects taking each medication or class

¹Total number of subjects is 39. Only psychotropic medications and medications with known effects on hair growth or cortisol are shown.

²No subjects were taking amantadine, aminoglutethimide, amiodarone, bromocriptine, cabergoline, captopril, cimetidine, colchicine, cyproheptadine, ketanserin, ketoconazole, lanreotide, metergoline, metyrapone, mifepristone, mitotane, octreotide, pasireotide, penicillamine, pioglitazone, reserpine, ritanserin, rosiglitazone, trilostane, or valproate.