Hair cortisol and psychotherapy response

Hair cortisol and childhood trauma predict psychological therapy response in depression and anxiety disorders

Susanne Fischer, PhD\textsuperscript{1,2}, Sinéad King, MSc\textsuperscript{1}, Andrew Papadopoulos, PhD\textsuperscript{1}, Matthew Hotopf, FMedSci, PhD\textsuperscript{1,3}, Allan H. Young, MB ChB, PhD\textsuperscript{1,3} & Anthony J. Cleare, MBBS, PhD\textsuperscript{1,3}

1 King’s College London, Institute of Psychiatry, Psychology & Neuroscience, Psychological Medicine, Denmark Hill, London SE5 8AF, United Kingdom

2 University of Zurich, Institute of Psychology, Clinical Psychology and Psychotherapy, Binzmuehlestrasse 14 / Box 26, 8050 Zurich, Switzerland

3 South London and Maudsley NHS Foundation Trust, Maudsley Hospital, Denmark Hill, London SE5 8AF, United Kingdom

\textbf{Corresponding author:}

Dr. Susanne Fischer, University of Zurich, Institute of Psychology, Clinical Psychology and Psychotherapy, Binzmuehlestrasse 14 / Box 26, 8050 Zurich, Telephone: +41 44 635 74 60, \texttt{s.fischer@psychologie.uzh.ch}
Abstract

Objective
Around 30%-50% of patients with depression and anxiety disorders fail to respond to standard psychological therapy. Given that cortisol affects cognition, patients with altered hypothalamic-pituitary-adrenal (HPA) axis functioning may benefit less from such treatments. To investigate this, reliable pre-treatment cortisol measures are needed.

Method
N=89 outpatients with depression and anxiety disorders were recruited before undergoing therapy within an Improving Access to Psychological Therapies (IAPT) service. Three-months hair cortisol was determined and the Childhood Trauma Questionnaire was administered. Patients were classified as responders if they showed significant decreases in depression (>= 6 points on the Patient Health Questionnaire) or anxiety (>= 5 points on the Generalised Anxiety Disorder Scale).

Results
Non-responders in terms of depression (57%) had lower pre-treatment hair cortisol concentrations ($p=.041$) and reported more physical abuse ($p=.024$), sexual abuse ($p=.010$), and total trauma ($p=.039$) when compared to responders. Non-responders in terms of anxiety (48%) had lower pre-treatment hair cortisol ($p=.027$), as well as higher levels of emotional abuse ($p=.034$), physical abuse ($p=.042$), and total trauma ($p=.048$).

Conclusion
If future research confirms hair cortisol and childhood trauma to be predictors of psychological therapy response, this may prove a useful clinical biomarker which identifies a subgroup requiring more intensive treatments.

Keywords: anxiety disorders; childhood trauma; depression; hair cortisol; psychological therapy

Significant outcomes:
This is the first study to show that pre-treatment hair cortisol can predict psychological therapy outcomes in patients with depression and anxiety disorders.
Limitations:

Half of the initial sample was lost due to patients’ inability to provide hair samples.
Introduction

Psychological therapy is one of the most effective treatments for depression and anxiety disorders (1, 2). In terms of depression, the most important interventions are behavioural activation and cognitive restructuring, while relaxation training and exposure to threat cues are key modules of standard first-line therapies for anxiety disorders. Given the high comorbidity between depression and anxiety (e.g., 3), these elements are often combined to provide treatments that are tailored to the needs of the individual patient. However, despite the general efficacy of such approaches, around 30% of patients with anxiety disorders (4) and 50% of patients with depression (1) do not respond sufficiently to psychological therapy. This raises the question of which factors may predict non-responses.

A number of studies have identified illness chronicity, severity, and comorbidity with other mental disorders as the most promising candidates to predict non-responses (4, 5). More recently, biological markers reflecting specific pathophysiological alterations have attracted researchers’ attention (e.g., 6). The glucocorticoid cortisol, the main end product of the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis, was among the first biomarkers to be tested as a predictor of treatment outcomes. As evident from recent systematic reviews and meta-analyses, depressed patients retaining relatively high levels of cortisol when probed with dexamethasone (a synthetic glucocorticoid) seem less likely to respond to psychological therapy when compared to those with relatively low levels (7). In patients with anxiety disorders, the majority of studies find lower levels during exposure sessions predictive of non-responsiveness (8). These findings are intriguing in light of the evidence linking cortisol with cognition (9, 10), and may implicate that patients with alterations in pre-treatment HPA axis functioning are less likely to profit from treatments relying on cognitive processes, such as psychological therapy.

Interestingly, while both of the above syntheses of the literature found evidence for post-challenge cortisol concentrations to predict responses to psychological therapy, the evidence in terms of resting cortisol was far less consistent. One explanation for this discrepancy is that post-challenge values require repeated sampling schedules, and as such provide more reliable estimates of pre-treatment HPA axis functioning than single time point measures, which are often used for resting cortisol. Indeed, only studies using cumulative measures of resting cortisol, such as 24h urine samples (11, 12) or repeated saliva sampling over the course of at least one day (13, 14) seem to be able to demonstrate a link with treatment outcomes. By contrast, studies using one-off morning blood samples (15) or saliva samples immediately before a therapy session (16) were unable to yield positive findings, which may
have also been also due to anticipatory stress linked with venepuncture or treatment. Clearly, studies employing reliable and valid measures of resting cortisol are warranted to further disentangle the role of cortisol in the non-response to psychological therapy phenomenon.

The main aim of the present study was to investigate for the first time whether hair cortisol concentrations representing the three months preceding psychological therapy could predict outcomes in a mixed sample of patients with depression and anxiety disorders. Hair bears several advantages over traditional specimens to determine cortisol: it is economical in that repeated sampling can be avoided, non-invasive, and - in covering a period of several weeks - is less susceptible to the influence of state-like confounders (e.g., anticipatory stress; 17, 18). Based on prior evidence of attenuated hair cortisol in patients with comorbid major depressive disorder (MDD) and generalised anxiety disorder (GAD; 19, 20), it was expected that non-responders to psychological therapy would be characterised by lower hair cortisol concentrations when compared to responders. In addition, the study aimed to explore the role of childhood trauma, which not only has been found an important predictor of non-response in depression (see 21 for a meta-analysis), but appears to have direct links with hair cortisol in patients with MDD (22, 23).

Methods

Sample and protocol

This study was part of a larger project on predictors of outcomes following psychological therapy (PROMPT). Details on the general procedures can be found in the published study protocol (24). The project used a naturalistic observational design. All patients referred to the Improving Access to Psychological Therapies (IAPT) service in the London borough of Southwark from 30th January, 2014 to 30th July 2016 were contacted. The service represents a national initiative that aims at reducing both mild to severe depression and anxiety by widespread deliverance of evidence-based psychological therapy (25). Individuals interested in participating in the study were scheduled for an appointment at the NIHR/Wellcome Trust King’s Clinical Research Facility. For the present study, inclusionary criteria were fluency in English, hair length of at least 3cm, and having any of the following depressive or anxiety disorders: MDD, dysthymia, bipolar disorder, panic disorder, agoraphobia, specific phobia, social anxiety disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), or GAD. In addition, patients had to complete at least one session of IAPT therapy. Exclusionary criteria were intake of corticosteroids, alcohol and substance abuse or dependence, psychotic disorders, and
anorexia nervosa. After obtaining written informed consent, a standardised clinical assessment was conducted to establish diagnoses of mental disorders, and questionnaires assessing sociodemographic variables, current medication, and childhood trauma were administered (see below). Hair samples were collected at the end of the appointment. Treatment at the IAPT service included all therapeutic approaches for mild to moderate depressive and anxiety disorders as recommended by NICE guidelines (see also 26). Patients received Step 2 versus Step 3 treatment according to the severity of their symptoms. Step 2 therapies are low intensity treatments usually of up to six sessions, and include guided self-help, computerised cognitive behavioural therapy (CBT) and various group therapies such as psychoeducation, behavioural activation, and mindfulness. Step 3 therapies are high intensity treatments usually of longer duration, and predominantly consist of CBT, but also include counselling and interpersonal psychotherapy. Measures of depressive symptoms and anxiety are taken routinely in the IAPT service; for the present study we extracted from the IPAT database the scores obtained at the pre-treatment initial assessment and during the final IAPT therapy session. The final sample size of this study was N=89. This study was approved by the Bromley NHS Research Ethics Committee (Ref.: 13/LO/1347).

Psychological measures

*Depression and anxiety disorders* were diagnosed by means of the Mini-International Neuropsychiatric Interview (MINI; 27). The MINI captures (recurrent) MDD, dysthymia, manic and hypomanic episodes, panic disorder, agoraphobia, social phobia, OCD, PTSD, alcohol abuse and dependence, substance use and dependence, psychotic disorders, anorexia nervosa, bulimia nervosa, GAD, and antisocial personality disorder in accordance with DSM-IV-TR criteria (28). Borderline personality disorder was diagnosed via the Structured Clinical Interview for DSM Personality Disorders (SCID-II; 29). All interviewers had a degree in psychology and were extensively trained in conducting clinical interviews by a psychiatrist (AJC) with regular standardisation sessions during the study.

The Childhood Trauma Questionnaire (CTQ; 30) was administered to measure *childhood abuse and neglect*. The CTQ distinguishes five trauma domains: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, each measured by five items. For the present study, subscale sum scores and a total score were calculated and individuals were categorised as with vs. without trauma based on validated moderate to severe cut-off scores (31).
Depression severity was measured by the depression module of the Patient Health Questionnaire (PHQ-9; 32). Nine items based on DSM-IV-TR criteria are rated on a four-point Likert scale from 0 (“not at all”) to 3 (“nearly every day”). Scores above five (out of 27) indicate mild levels of depression, scores above ten moderate levels, and scores from 15 onwards severe levels of depression. The PHQ-9 was administered twice: at the beginning of IAPT therapy and at the end. The validity of the PHQ-9 as a measure of symptom severity has been demonstrated in numerous studies (e.g., 32). A Reliable Change Index (RCI) was calculated, according to which patients were considered treatment responders in terms of depression if they displayed a decrease of at least six points on the PHQ-9 (33).

Anxiety severity was measured by means of the Generalised Anxiety Disorder Scale (GAD-7; 34). The GAD-7 consists of seven items based on the DSM-IV-TR criteria for GAD, but the scale is commonly used as a general measure of anxiety. The answering scale ranges from 0 (“not at all”) to 3 (“nearly every day”). Scores above five correspond to mild levels of anxiety, scores above ten represent moderate levels, and scores from 15 onwards indicate severe anxiety. Evidence for the validity of the GAD-7 as a means to assess symptom severity has been provided by numerous studies (e.g., 34). Patients were categorised as treatment responders in terms of anxiety if their GAD-7 scores had decreased by at least five points at the end of their IAPT treatment (33).

Biological measures
Two to three clusters of hair were collected from as close to the scalp as possible and cut into 3cm segments, reflecting a three-month retrospective period. All samples were washed twice with 2mL isopropanol and dried at room temperature for 24h. The hair was then pulverised with a ball mill and 10-15mg were incubated with 1.5mL of methanol for 1 hour in order to extract cortisol. The methanol was removed at 60°C under a gentle stream of nitrogen and the residue was reconstituted in 1mL of phosphate buffer. Cortisol concentrations were determined using the Immulite Immunoassay analyser (www.diagnostics.siemens.com) as described previously (35). The inter- and intra-assay variance of this assay is below 10%.

Statistical analysis
Data were checked for normal distribution and hair cortisol concentrations were log-transformed as a result of this. First, non-responders and responders were compared in terms of pre-treatment symptom severity, pre-treatment degree of comorbidity, and variables related to treatment. Mann-Whitney U tests
and Chi-squared tests were used to test this. Pre-treatment symptom severity, type of treatment, and number of treatment sessions were accounted for in all statistical models comparing non-responders and responders. Previously identified confounders of hair cortisol, namely age, BMI, the season reflected in the hair sample, heat-based treatments (e.g., curling irons), intake of hormonal contraceptives, antidepressants, and painkillers (36) were included in all models with hair cortisol as the dependent variable. Second, univariate ANOVAs were conducted to compare non-responders and responders regarding a) pre-treatment hair cortisol concentrations, and b) childhood trauma. This was to answer the main research question of this study, namely whether hair cortisol and childhood trauma predict treatment outcomes. Third, patients with vs. without childhood trauma were compared in terms of hair cortisol, again using univariate ANOVAs. The purpose of this was to investigate whether hair cortisol concentrations were related to experiences of childhood trauma. Finally, explorative analyses were undertaken to examine whether hair cortisol moderated any potential effect of childhood trauma on treatment outcomes. Binary logistic regression analyses were used for this. All analyses were performed in SPSS 22 and the alpha error was set at 5%.

Results

Patient characteristics

Patient characteristics are presented in Table 1. Nearly the entire sample was female, which most likely was due to a combination of the general female preponderance of depression and anxiety disorders and their increased ability to provide hair samples (47% of the total sample had been unable and 3% had been unwilling to give hair). Patients were in their mid-thirties and slightly overweight on average. The most frequent diagnosis was GAD, followed by MDD and agoraphobia. Comorbidity was high, with 52% of patients fulfilling criteria for both a depressive and an anxiety disorder. A little less than half of the patients were on antidepressants, while almost no other psychotropic medication was used. The median pre-treatment depression score was 14 (9.5), corresponding to a moderate level of depression. The median anxiety score was 12 (8.5), which meant that the sample presented with moderate anxiety before treatment. The median number of treatment sessions was 11 (9) and the median time between the first and the final treatment sessions was 6 (7) months. Low intensity group therapies (46%), and high intensity CBT (17%) and counselling (17%) were the most frequent types of IAPT therapies patients received. The overall response rates were 43% regarding depression (overall median post-treatment score: 8 (8)) and 52% regarding anxiety (overall median post-treatment score: 7 (7)).
Non-responders and responders did not differ in the number of pre-treatment diagnoses of mental disorders, nor in their intake of antidepressants, IAPT treatment duration, number of treatment sessions, and type of therapy received (all $p>.147$). Non-responders did, however, have lower pre-treatment levels of depression ($U=-4.67$, $p<.001$) and anxiety ($U=-3.94$, $p<.001$) when compared to responders. Symptom severity, type of treatment, and number of treatment sessions, and confounders of hair cortisol were included as predictors in all subsequent statistical models.

**Hair cortisol as predictor of treatment response**

Median hair cortisol concentrations were 153 (321.2) pg/mg. Controlling for pre-treatment levels of depression, type of treatment, number of treatment sessions, and confounders of hair cortisol, non-responders in terms of depression had significantly lower pre-treatment hair cortisol when compared to responders (131.9 (214.1) pg/mg vs. 153 (409) pg/mg, $F(1, 60)=4.371$, $p=.041$, $\eta^2=.068$). Likewise, non-responders in terms of anxiety had lower pre-treatment cortisol concentrations when compared to responders (131.9 (214.1) pg/mg vs. 150.6 (245) pg/mg, $F(1, 60)=4.965$, $p=.027$, $\eta^2=.079$).

**Childhood trauma as predictor of treatment response**

The prevalence of childhood trauma was 24% for emotional abuse, 21% for emotional neglect, 19% for sexual abuse, 17% for physical neglect, 6% for physical abuse, and 24% for any type of childhood trauma. Controlling for pre-treatment levels of depression, type of treatment, and number of treatment sessions, non-responders in terms of depression had higher levels of physical abuse ($F(1, 67)=5.306$, $p=.024$, $\eta^2=.073$), sexual abuse ($F(1, 67)=6.971$, $p=.010$, $\eta^2=.094$), and childhood trauma in general ($F(1, 67)=4.412$, $p=.039$; $\eta^2=.062$; see also Figures 1A and 1B). Similarly, controlling for pre-treatment levels of anxiety, type of treatment, and number of treatment sessions, non-responders in terms of anxiety reported more emotional abuse ($F(1, 67)=4.711$, $p=.034$, $\eta^2=.066$), physical abuse ($F(1, 67)=4.281$, $p=.042$, $\eta^2=.060$), and childhood trauma in general ($F(1, 67)=4.061$, $p=.048$, $\eta^2=.057$; see also Figures 2A and 2B).

-Hair cortisol in relation to childhood trauma-
Controlling for confounders of hair cortisol, there were no differences in hair cortisol concentrations when comparing patients without vs. with childhood abuse and neglect (emotional abuse: 152.5 (396.5) pg/mg vs. 150.9 (156.2) pg/mg, F(1, 72)=1.073, \( p=0.304 \), \( \eta^2=0.015 \); physical abuse: 153 (289.8) pg/mg vs. 152.1 (338.2) pg/mg, F(1, 72)=0.303, \( p=0.584 \), \( \eta^2=0.004 \); sexual abuse: 152.1 (338.2) pg/mg vs. 146.8 (179.4) pg/mg, F(1, 72)=0.004, \( p=0.950 \), \( \eta^2=0.000 \); emotional neglect: 149 (257) pg/mg vs. 152.1 (237.2) pg/mg, F(1, 72)=1.646, \( p=0.204 \), \( \eta^2=0.022 \); physical neglect: 160.6 (305.7) pg/mg vs. 132.4 (130.7) pg/mg, F(1, 72)=1.263, \( p=0.265 \), \( \eta^2=0.017 \); total score: 152.5 (396.5) pg/mg vs. 150.9 (156.2) pg/mg, F(1, 72)=1.073, \( p=0.304 \), \( \eta^2=0.015 \)).

Exploratory analyses revealed that hair cortisol neither moderated the observed effects of childhood trauma on treatment response in terms of depression (interaction term emotional abuse: OR=0.987 (0.881-1.106), \( p=0.820 \); physical abuse: OR=1.056 (0.635-1.756), \( p=0.843 \); sexual abuse: OR=1.094 (0.750-1.596), \( p=0.640 \); emotional neglect: OR=1.069 (0.956-1.194), \( p=0.242 \); physical neglect: OR=1.062 (0.851-1.326), \( p=0.596 \); total score: OR=1.012 (0.970-1.055), \( p=0.581 \)), nor in terms of anxiety (interaction term emotional abuse: OR=1.067 (0.933-1.221), \( p=0.344 \); physical abuse: OR=1.019 (0.607-1.709), \( p=0.944 \); sexual abuse: OR=1.140 (0.829-1.569), \( p=0.421 \); emotional neglect: OR=1.134 (0.999-1.288), \( p=0.052 \); physical neglect: OR=1.131 (0.886-1.443), \( p=0.323 \); total score: OR=1.039 (0.987-1.093), \( p=0.143 \)).

**Discussion**

The present study yielded two findings. First, in this mixed sample of patients with depression and anxiety disorders, those who were later classified as non-responders to psychological therapy had lower hair cortisol concentrations when compared to responders. Second, patients reporting childhood trauma were more likely to be non-responders. However, childhood trauma was found unrelated to hair cortisol suggesting that these are independent predictors of non-responses.

This is the first study using hair cortisol as a predictor of response to standard first-line treatments (i.e., psychological therapy, antidepressants). In addition, only a handful of studies have investigated cortisol as a predictor of response to psychological therapy. In depression, a recent meta-analysis yielded a trend for higher resting cortisol to predict more depressive symptoms upon completion of psychological therapy (7), while no such associations were found in anxiety disorders (8). However, all studies employing cumulative (i.e., 24h urine) or repeated measures of cortisol (i.e., saliva sampling
over the course of the day) were able to demonstrate a link between higher pre-treatment cortisol levels and outcomes, while those using one-off measures (most of which were confounded by venepuncture or anticipation of therapy sessions on the same day) yielded null-findings. Supporting this notion, another meta-analysis large enough to also allow meta-regression showed that only studies determining cortisol in urine and saliva were able to find links with antidepressant treatment response (37). When taken together, the current state of the literature suggests that resting cortisol is able to predict responses to psychological therapy, albeit only when measured in a reliable and valid way (i.e., using hair, 24 h urine, or repeated saliva sampling).

The studies employing such measures found higher rather than lower cortisol concentrations predicted non-responses to psychological therapy (11-14). This appears to stand in contrast to the findings of the present study. One explanation for this discrepancy is that hair cortisol reflects long-term (e.g., three months) rather than short-term (12h or 24h) cortisol secretion (17, 18). Indeed, hair, saliva, and urinary cortisol are significantly correlated only when the latter two measures are repeatedly measured and integrated to cover the same period that is reflected in the hair sample (e.g., one month; 38). This means that while all three measures are valid indicators of HPA axis activity, they differ in the time frame covered. Further studies in patient populations are warranted to determine which specimen/time frames are best chosen to distinguish patients from healthy controls (e.g., 39), characterise subtypes of a particular disorder (e.g., depression; 40), or predict treatment responses. A second explanation lies in sample characteristics: while previous studies were confined to either depressed or anxious patients, ours was a mixed sample of patients with depression and anxiety disorders (52% comorbidity), as typically encountered in clinical and population studies as well as in IAPT services (26). Considering the high degree of comorbidity, our finding is consistent with previous evidence of attenuated hair cortisol in patients fulfilling diagnostic criteria for both MDD and GAD (19, 20) and could be interpreted as showing that patients with more severe pre-treatment alterations of the HPA axis are less likely to respond to standard psychological therapy. The finding is also interesting in light of evidence linking cortisol with fear extinction, a pivotal cognitive process in the psychological treatment of anxiety disorders, such as GAD (10). More specifically, there is evidence to suggest that increases in cortisol during exposure therapy sessions are beneficial in impeding the retrieval of the fear memory while at the same time facilitating the consolidation of the extinction memory. In line with this, a recent systematic review showed that lower cortisol concentrations during exposure therapy sessions was linked with worse treatment responses (8). It is thus possible that the lowered HCC in non-
responders in the present study is paralleled by a failure to mount sufficient cortisol responses over the course of treatment. Mechanistic studies are now warranted to examine to what extent pre-treatment alterations of the HPA axis interfere with specific psychological interventions, such as exposure to threat cues.

Our second finding of childhood trauma predicting non-responses is in agreement with a meta-analysis showing that depressed patients with childhood trauma are more likely to be non-responders to standard first-line treatments (21). Our study shows that this appears to extend to mixed samples of patients with both depression and anxiety disorders undergoing treatment via IAPT services (26). In the above meta-analysis, childhood trauma was not only found a predictor of non-response to treatment, but also of protracted illness trajectories (i.e., recurrent or persistent forms of depression; 21). From a clinical perspective, both findings fit in well with the notion of a particular subgroup of depressed patients characterised by severe interpersonal difficulties, which are rooted in early maladaptive caregiving and may require specific psychological therapy that goes beyond what is offered by standard IPT or CBT (e.g., 41).

Not only may childhood trauma result in interpersonal difficulties, but traumatised patients have repeatedly been shown to exhibit distinct biological signatures (e.g., 42). An extensive literature has documented the effects of childhood trauma on HPA axis functioning (e.g., 43, 44-46). In terms of hair cortisol, both Hinkelmann et al. (23) and Duncko, Fischer (22) found attenuated levels in depressed patients with versus without childhood trauma. It is noteworthy that childhood trauma was found unrelated to hair cortisol concentrations in the current sample, but again, the diagnostic heterogeneity of the present sample renders a comparison with the two previous studies difficult and further studies are required to investigate this issue in greater detail. Ideally, such studies would be large enough to also allow for a stratification of the sample according to the severity of childhood trauma, which may be followed by different alterations of the HPA axis. For instance, while Heim, Newport (47) found increased cortisol responses to acute stress in depressed women with severe childhood abuse, Carpenter, Carvalho (48) found an opposite pattern in healthy women exposed to less severe maltreatment during childhood. A crucial mechanism by which such alterations occurs is via DNA methylation within genes encoding different HPA axis components (e.g., NR3C1; 49). More specifically, it is assumed that parental behaviour towards offspring shapes phenotypes to match the early life environment, such as that both increased and decreased HPA axis reactivity may be considered adaptive, depending on the
amount of early life stress present. Boyce and Ellis (50) have argued that both low and high levels of early life stress favour the development higher biological sensitivity to context. Following from this, it is intriguing to speculate that highly reactive or sensitive individuals may also be more responsive to the effects of psychological therapy (see also 51). Large trials integrating measures of a patients’ genetic and epigenetic make-up with in-depth accounts of their early life environment are necessary to test these hypotheses systematically.

This study offers a number of strengths, such as it being the first to use hair cortisol as a predictor of psychological therapy outcomes. Hair cortisol is a reliable and valid indicator of long-term HPA axis activity and bears several advantages when compared to conventional methodologies, including its non-invasiveness and the possibility to avoid repeated sampling. This also renders hair cortisol an interesting candidate when conceiving of ways to translate the findings of this research into clinical practice. Another strength of our study is its high ecological validity, which results from recruiting patients via an IAPT service rather than within a clinical trial. Finally, this was the first study to use both cortisol and childhood trauma as predictors of psychological therapy response, and we believe that the combination of biological and psychological markers has greater potential in characterising a subgroup of patients who are non-responsive to standard first-line treatments. A number of limitations equally deserve mentioning. First, hair sampling requires that participants are both willing and able to give hair, and 50% of patients had to be excluded from our study for this reason. This not only reduced our sample size, but also affected the composition of the present sample, which was largely women, hence limiting the generalisability of our findings. Second, for economic reasons, we relied on short, self-reported outcome measures, while it would have been preferable to use more in-depth questionnaires or interviews. Third, the downside of high ecological validity is low internal validity. Recruiting from an IAPT service, we were unable to determine which intervention modules in particular may have been affected by patients’ HPA functioning. Finally, no post-treatment measures of cortisol were obtained, which arguably would have been informative in terms of the mechanisms underlying successful therapies.

In sum, the present study demonstrates that both pre-treatment hair cortisol and the degree of childhood trauma are able to predict whether depressed and/or anxious patients go on to respond to standard psychological therapy. Further research is required to replicate this finding and determine why HPA axis functioning might be instrumental to successful psychological therapy. More specifically, it should be tested to what extent particular interventions inherent in evidence-based treatments for
depression and anxiety are affected by pre-treatment alterations in the HPA axis (e.g., cognitive restructuring). In addition, large-scale studies allowing to stratify patients according to the presence of childhood trauma and diagnostic (sub-)categories are warranted to examine whether HPA alterations are indicative of a particular subgroup of patients. It is our hope that this research will ultimately result in more effective application of current standard first-line therapies and the development of additional or alternative options for those in need of more specific treatment.
Acknowledgments

Dr. Fischer was supported by the Swiss National Science Foundation. Prof. Young has received honoraria for lectures/consulting from Astra Zeneca, Eli Lilly, Janssen, Livanova, Lundbeck, Servier, and Sunovion, and grant funding from Janssen, the BMA, the CCS Depression Research Fund, the CIHR, MSFHR, MRC, NARSAD, NIHR, NIMH, the Royal College of Physicians, Stanley Medical Research Institute, UBC-VGH Foundation, WEDC, the Wellcome Trust. Prof. Cleare has in the last three years received honoraria for lectures/consulting from Astra Zeneca, Lundbeck, Livanova and Allergan, and a research grant from Lundbeck, as well as grant funding from the National Institutes of Health Research, Medical Research Council, Wellcome Trust and Royal Society. This paper represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The funding sources had no role in the study design, data collection, analysis, and interpretation, or in the drafting of the manuscript and the decision to submit it for publication. The authors gratefully acknowledge the support of Irene Papadopoulos in conducting the hair cortisol analyses.
Declaration of interest

The authors declare no biomedical financial interests or conflicts of interest.
References


42. HEIM C, NEWPORT DJ, MLETZKO T, MILLER AH, NEMEROFF CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 2008;33:693-710.


Table legends

**Table 1** Pre-treatment patient characteristics of patients with depression and anxiety disorders (N=89).

Descriptives are given as median and interquartile range or frequencies.
Figure legends

Figures 1A and 1B Childhood trauma scores (total score and subscales) in non-responders vs. responders to psychological therapy. Results are shown for responses in terms of depression (PHQ-9). Bars represent means and standard errors.

Figures 2A and 2B Childhood trauma scores (total score and subscales) in non-responders vs. responders to psychological therapy. Results are shown for responses in terms of anxiety (GAD-7). Bars represent means and standard errors.
**Table 1** Pre-treatment patient characteristics of patients with depression and anxiety disorders (N=89).

Descriptives are given as median and interquartile range or frequencies.

<table>
<thead>
<tr>
<th>Descriptive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>34 (20.5)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>83 (93%)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (7%)</td>
</tr>
<tr>
<td><strong>Body Mass Index (BMI; kg/m²)</strong></td>
<td>24.4 (10.1)</td>
</tr>
<tr>
<td><strong>Diagnoses (MINI and SCID-II)</strong></td>
<td></td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>33 (38%)</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Borderline personality disorder</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>54 (61%)</td>
</tr>
<tr>
<td>Hypomanic episode</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Past</td>
<td>16 (18%)</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>37 (42%)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>31 (36%)</td>
</tr>
<tr>
<td>Manic episode</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Past</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>17 (19%)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>18 (21%)</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Social anxiety disorder</td>
<td>29 (33%)</td>
</tr>
</tbody>
</table>

**Medication**
<table>
<thead>
<tr>
<th>Medication</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>38 (43%)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Mood stabilisers</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

MINI = Mini-International Neuropsychiatric Interview  
SCID-II = Structured Clinical Interview for DSM-IV Personality Disorders
Figures 1A and 1B  Childhood trauma scores (total score and subscales) in non-responders vs. responders to psychological therapy. Results are shown for responses in terms of depression (PHQ-9). Bars represent means and standard errors.

*p<.05
CTQ = Childhood trauma questionnaire
EA = Emotional abuse
EN = Emotional neglect
PA = Physical abuse
PHQ-9 = Depression module of the Patient Health Questionnaire
PN = Physical neglect
SA = Sexual abuse
Figures 2A and 2B Childhood trauma scores (total score and subscales) in non-responders vs. responders to psychological therapy. Results are shown for responses in terms of anxiety (GAD-7). Bars represent means and standard errors.

*p<.05
CTQ = Childhood trauma questionnaire
EA = Emotional abuse
EN = Emotional neglect
GAD-7 = Generalised Anxiety Disorder Scale
PA = Physical abuse
PN = Physical neglect
SA = Sexual abuse