University of Wollongong
Research Online

Illawarra Health and Medical Research Institute | Faculty of Science, Medicine and Health

2019

Cortisol, oxytocin, and quality of life in major depressive disorder

Ai Ling Tang
University of Wollongong, alcat204@uowmail.edu.au

Susan J. Thomas
University of Wollongong, sthomas@uow.edu.au

Theresa A. Larkin
University of Wollongong, tlarkin@uow.edu.au

Follow this and additional works at: https://ro.uow.edu.au/ihmri

 Part of the Medicine and Health Sciences Commons

Recommended Citation

Tang, Ai Ling; Thomas, Susan J.; and Larkin, Theresa A., "Cortisol, oxytocin, and quality of life in major depressive disorder" (2019). *Illawarra Health and Medical Research Institute*. 1435.
https://ro.uow.edu.au/ihmri/1435

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library: research-pubs@uow.edu.au

Cortisol, oxytocin, and quality of life in major depressive disorder

Abstract

Purpose: Quality of life (QoL) is greatly impaired in major depressive disorder (MDD). These impairments are not fully accounted for by symptom severity, may persist beyond depressive episodes, and are a risk factor for poor outcomes. MDD is often associated with prominent neuroendocrine changes and increased risk of chronic disease. However, there is a lack of research examining whether biological factors are related to QoL in MDD. This research examined relationships between cortisol, oxytocin, symptom severity, and QoL in MDD.

Methods: Sixty adults meeting DSM-5 criteria for MDD and 60 healthy controls provided morning plasma samples which were analysed for cortisol and oxytocin levels, and completed measures of QoL and psychopathology.

Results: Participants with MDD had lower QoL than controls. Cortisol correlated negatively with overall QoL and all QoL domains. Oxytocin correlated positively with overall QoL, and Psychological and Social-Relationships domains. Additionally, cortisol levels were inversely related to psychological QoL, and oxytocin was positively related to social QoL, after controlling for symptom severity and demographic variables.

Conclusions: This study provides novel evidence linking neuroendocrine pathways to particular domains of QoL in MDD. The results indicate that activity of the hypothalamic-pituitary-adrenal axis is linked to poor psychological QoL, and that oxytocin is important to social QoL, independently of severity of psychopathology. Biopsychosocial approaches to QoL associated with mental health conditions may lead to greater understanding of the underlying mechanisms and to improved, tailored interventions.

Disciplines

Medicine and Health Sciences

Publication Details

Tang, A., Thomas, S. J. & Larkin, T. (2019). Cortisol, oxytocin, and quality of life in major depressive disorder. Quality of Life Research, 28 (11), 2919-2928.

This journal article is available at Research Online: https://ro.uow.edu.au/ihmri/1435

Title page

Cortisol, Oxytocin, and Quality of Life in Major Depressive Disorder

Ai Ling Tang
School of Psychology,
Faculty of Social Sciences,
University of Wollongong,
Northfields Avenue,
Wollongong,
NSW,
Australia 2522
alcat204@uowmail.edu.au

Susan J Thomas (corresponding author)
Graduate Medicine,
Faculty of Science, Medicine and Health
& Illawarra Health and Medical Research Institute,
University of Wollongong
NSW
Australia 2522
sthomas@uow.edu.au
Telephone: +61242215928
https://orcid.org/0000-0003-3609-4443

Theresa Larkin
Graduate Medicine,
Faculty of Science, Medicine and Health
& Illawarra Health and Medical Research Institute,
University of Wollongong
NSW
Australia 2522

Abstract

Purpose:

Quality of life (QoL) is greatly impaired in major depressive disorder (MDD). These impairments are not fully accounted for by symptom severity, may persist beyond depressive episodes and are a risk factor for poor outcomes. MDD is often associated with prominent neuroendocrine changes and increased risk of chronic disease. However, there is a lack of research examining whether biological factors are related to QoL in MDD. This research examined relationships between cortisol, oxytocin, symptom severity, and QoL in MDD.

Methods:

Sixty adults meeting DSM-5 criteria for MDD and 60 healthy controls provided morning plasma samples which were analysed for cortisol and oxytocin levels, and completed measures of QoL and psychopathology.

Results:

Participants with MDD had lower QoL than controls. Cortisol correlated negatively with overall QoL and all QoL domains. Oxytocin correlated positively with overall QoL, and *Psychological* and *Social-Relationships* domains. Additionally, cortisol levels were inversely related to psychological QoL, and oxytocin was positively related to social QoL, after controlling for symptom severity and demographic variables.

Conclusions:

This study provides novel evidence linking neuroendocrine pathways to particular domains of QoL in MDD. The results indicate that activity of the hypothalamic-pituitary-adrenal axis is linked to poor psychological QoL, and that oxytocin is important to social QoL, independently of severity of psychopathology. Biopsychosocial approaches to QoL associated with mental health conditions may lead to greater understanding of the underlying mechanisms and to improved, tailored interventions.

Key words: Oxytocin, Cortisol, Hormones, Major Depressive Disorder, Quality of Life, Depression

Introduction

Quality-of-life (QoL) is increasingly recognised as an important consideration in mental health care and research. While the complex determinants are still unclear, the interaction of distress factors such as psychopathology and protection factors including physical health and social relationships contribute to QoL [1]. The WHO definition of QoL incorporates the individual's cultural, social and environmental context and addresses specific domains including health, work, family, social relationships and leisure activities [2].

People with major depressive disorder (MDD) report much lower QoL relative to non-depressed people and also those with chronic medical conditions including cancer, hypertension, diabetes and chronic pain [3]. Additionally, individuals with MDD suffer from poor QoL even after reduction of symptom severity during treatment, and poor QoL may predict further depressive episodes [4]. QoL is therefore considered important in the assessment and treatment of MDD, and is viewed as the ultimate outcome measure of treatment success [4]. The relationship of QoL to MDD has received little attention relative to other mental disorders [1, 4].

Clinically-depressed individuals may report poorer QoL due to distress associated with negative thinking and low mood which are core depressive symptoms. Depressive symptoms and poor QoL, however, are not synonymous [4]. Previous research indicates that QoL is not the opposite of depression; there are only weak-moderate correlations between depressive symptoms and QoL [5] and depressive symptoms only explain around a quarter to a third of variance in QoL [4]. QoL is therefore multi-dimensional and only partly attributable to depressive symptoms [4]. Further research is needed to understand which factors in addition to clinical symptom severity, particularly biological factors, are associated with poor QoL in MDD [3, 4, 6], with a view to improving interventions [3, 7].

The burden of MDD extends beyond psychosocial functioning to somatic health, with MDD being associated with increased risk of cardiovascular and diabetic morbidity and mortality. Prominent neuroendocrine changes are reported in MDD, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol secretion [8], which is hypothesised to underpin the links with these chronic health comorbidities [9]. There is also evidence from several studies that the oxytocin system is altered in MDD [10, 11]. The neuropeptide oxytocin is involved in regulating complex social behaviour, anxiety, and HPA axis physiology in mammals [12, 13], all of which are related to MDD. These biological correlates may be associated with the variance of QoL measures in MDD that are not explained by depressive symptoms alone.

Cortisol is a glucocorticoid hormone which plays a vital role in stress responses and the progression of MDD [14]. Cortisol synthesis and release from the adrenal cortex is primarily controlled by the HPA axis [15]. Cortisol regulates stress responses through the inhibition of the HPA axis via negative feedback mechanisms in the hippocampus [16], and additionally regulates functions such as neurogenesis, metabolism, immune responses, memory formation, and diurnal sleep patterns [17].

Disturbances in HPA axis function are reliably found in psychiatric disorders [18] and may partially mediate the relationship between stress and psychiatric disorders [19]. Cortisol is often correlated with psychopathology, stress and negative affect [20], and epidemiological studies have found that cortisol output in healthy populations is inversely correlated with positive wellbeing [21]. Additionally, a substantial literature has identified elevated cortisol levels [22] or dysregulated cortisol release [23] in MDD.

Few studies have examined relationships between cortisol and QoL, particularly in MDD. Knuth, Cocco [24] reported that, among health professionals, salivary cortisol was inversely related to Environmental-QoL; but not to depression. Carlson, Speca [25] found

that improvement in QoL was associated with reduced afternoon cortisol levels in cancer outpatients; but no relationship between depressive symptoms and cortisol. In patients with functional somatic syndromes, Mutsuura, Kanbara [26] found inverse correlations between morning salivary cortisol and depressive scores, and positive correlations between cortisol and psychological-QoL, however controls showed the reverse pattern. Further examination of these relationships, including interactions with other hormones, such as oxytocin, which attenuates HPA activity, is needed to understand relationships between neuroendocrine markers and QoL.

Oxytocin is synthesised in the hypothalamus, projected into other brain regions and released into the bloodstream where it has peripheral effects. Oxytocin is increasingly recognised as a key regulator in many complex social behaviours, and is implicated in mental disorders that involve impaired social interactions including schizophrenia, autism, and MDD [27]. Blunted oxytocin functioning has been associated with reduced attachment, trust and social support-seeking behaviours [e.g. 20]. It may therefore be associated with impaired social QoL seen in MDD. Oxytocin also regulates neuroendocrine stress responses [28] and promotes social approach behaviour [20]; which may improve QoL. To our knowledge, no study has examined relationships between oxytocin and QoL in MDD. Given that oxytocin is important to emotionality, stress coping and complex social interactions, which shape our personality and mental health [29], it is reasonable to predict that it will be related to QoL in MDD.

Aims and Hypotheses

Understanding relationships between biological factors and QoL is necessary to understand how to improve function and wellbeing in MDD. There is a scarcity of research in this area, and to the best of the authors' knowledge, no previous research has examined whether these neuroendocrine measures predict QoL in MDD. This

study therefore addressed the following research questions, which have yet to be answered by the existing body of research.

1. Are markers of neuroendocrine activity, specifically plasma cortisol and oxytocin concentrations, related to QoL in MDD?
2. Do the different domains of QOL show differential relationships with cortisol and oxytocin?
3. Are cortisol and oxytocin associated with decrements in QoL in MDD beyond that explained by demographics and severity of psychopathology symptoms including those of depression and other disorders?

It was hypothesised that:

1. Cortisol levels will be negatively related to overall QoL and oxytocin levels will be positively related to overall QoL.
2. Cortisol will be inversely related to psychological and physical domains of QoL and oxytocin will be positively related to the social relationships domain of QoL.
3. Cortisol and oxytocin will account for unique variance in QoL in MDD, after controlling for age, sex and severity of psychopathology symptoms including depression.

Method

Participants

We recruited 120 participants (60 adults meeting DSM-5 diagnostic criteria for MDD and 60 healthy controls, 67 females, 53 males) aged between 18 and 69 years of age (M = 32.14, SD = 12.92). The sample size was selected on an a-priori basis based on power calculations and previous research. Using the G*Power statistical tool, version 3.1.9.4 [30], to achieve a statistical power of 80% with significance at p <.05, for two-tailed correlations with a medium effect size (.03), a total of 84 participants is required. For linear multiple regression examining R^2 increase, with a medium effect size (.15) and five predictor variables, a sample size of 92 participants is required [30]. Participants were recruited through local advertisements which were placed online and around the university campus. Details of the study requirements and inclusion and exclusion criteria were given to people making contact, and those who were interested were thoroughly screened prior to participation to ensure they were suitable. The MDD group consisted of 32 females and 28 males, aged between 18 and 69 years of age (M = 31.90, SD = 14.55). The control group consisted of 35 females and 25 males, aged between 20 and 60 years of age (M = 31.83, SD = 10.98).

Inclusion criteria required that participants with MDD were not receiving any pharmacological or psychological treatment for depression. Controls did not have any history of significant mental health problems or diagnosed mental disorders. Further, exclusion criteria across both groups included neurological illness, substance use disorders, and use of corticosteroid medications. Participants received a store voucher to compensate them for their time and inconvenience. The study was part of a larger study into health in MDD and the protocol has been previously reported [31]. The cortisol and oxytocin levels have also been

previously reported in relation to different psychometrics and research questions; participants with MDD had higher plasma cortisol and lower plasma oxytocin levels than controls [31].

Materials

The WHOQOL-BREF was chosen as a valid and brief measure of QoL which is suitable for use in healthy and clinical populations [2]. It is a 26-item self-report scale that measures perceived QoL across four domains: *Physical-Health*, *Psychological-Health*, *Social-Relationships*, and *Environment* [32], with higher scores connoting higher QoL. The *Physical-Health* domain comprises facets such as energy and fatigue. The *Psychological-Health* domain comprises facets such as feelings and thoughts. The *Social-Relationships* domain comprises facets such as personal relationships and social support. The *Environmental* domain comprises facets such as physical safety and security. The mean score of items within each domain is used to calculate a domain score. Each domain score is then multiplied by 4 in order to make domain scores comparable with the scores used in the WHOQOL-100 on a 0-100 scale. Additionally, an individual's *Overall* QoL life is assessed through the first question of the WHOQOL-BREF, which asks them to rate their global QOL, with a possible range of scores from 1-5. The four domain scores yielded by the WHOQOL-BREF correlated highly from .89 (*Social-Relationships*) to .95 (*Physical-Health*) with that of its longer form, WHOQOL-100, demonstrating good validity, consistency, and test-retest reliability [2].

The Brief Symptom Inventory (BSI) is a 53-item self-report inventory that measures psychological symptoms of most mental disorders including depressive symptoms [33]. The BSI was chosen as it measures severity of and distress associated with depression and other psychopathology more broadly, which may be related to QoL. Respondents indicate the degree to which they were distressed by various psychological symptoms over the past week, with responses ranging from 0 (not at all) to 4 (extremely). Higher scores connote higher

levels of distress. The BSI profile produces three global indices of distress and nine symptom dimensions [33]. The three global indices of distress, designed to capture the range and intensity of past and present psychopathology, include: *Global Severity Index* (GSI), that provides a composite score of psychopathology; *Positive Symptoms Total Index* (PSTI), that reflects the number of symptoms experienced; and *Positive Symptoms Distress Index* (PSDI), measures the intensity of psychopathology symptoms. The different symptom dimensions on the BSI are highly correlated within the range of .92 to .99 with that of its longer parent instrument, Symptom Checklist-90-Revised (SCL-90-R) [34].

Procedure

The University of Wollongong ethics committee approved the protocol in accordance with the Australian National Statement for the Ethical Conduct of Research, and all participants provided informed written consent. Participants were screened prior to attending to ensure they met inclusion and exclusion criteria. Participants attended a single visit at the university clinical trials unit. Those in the MDD group were interviewed using the Mini International Neuropsychiatric Interview [35], a semi-structured interview (version 7.0.2) based on DSM-5 diagnostic criteria, to confirm that they met diagnostic criteria for MDD. All participants completed psychometric measures. A phlebotomist drew 8ml of blood from the antecubital vein into an EDTA (ethylenediaminetetraacetic acid) tube with aprotinin (enzyme inhibitor). All blood samples were taken between 9am and 11am. Further measures that are not included here were taken as part of the larger program of research into physical health in MDD. The whole procedure took approximately one hour.

Biological sample collection and analysis. Blood samples were stored on ice until centrifuged for 10 mins at 2800rpm and 4^{o}C, and then plasma stored at -80 ^{o}C until analysis. Plasma concentrations of oxytocin and cortisol were analysed using an ELISA kit (Abcam), with absorbance detection at 450nm. For oxytocin analysis, samples were initially extracted

with acetonitrile and then measured in duplicate, with a limit of detection of 2 ng/ml for cortisol and 15 pg/ml for oxytocin.

Statistical analyses. Data were analysed using the Statistical Package for Social Sciences (SPSS), Version 21, with an alpha level of $p < .05$. Raw cortisol and oxytocin values were log transformed prior to analyses, to better approximate normal distributions. Chi square was used to compare sex distributions, and one-way analysis of variance (ANOVA) was used to compare ages, between groups.

A multivariate analysis of covariance (MANCOVA) was conducted to examine the effects of Depression status (MDD, healthy controls) on QoL domains (Physical-Health, Psychological-Health, Social-Relationships, and Environment; measured by WHOQOL-BREF). Age and sex were included as covariates.

As the assumption of univariate normality was violated for all variables, except for *Overall-QoL*, *Physical-Health* and *Environment* domains in WHOQOL-BREF, non-parametric Spearman's rho two-tailed correlations were conducted to investigate relationships between QoL and hormones. The seven variables were oxytocin, cortisol, *Overall-QoL* and the four domains of QoL.

To investigate whether cortisol and oxytocin levels explained unique variance in *Overall-QoL* and domain-specific QoL (measured by WHOQOL-BREF), beyond that accounted for by demographic variables and severity of psychopathology including depression, five hierarchical multiple regression analyses (HMRAs) were performed. The dependent variables (DVs) were *Overall-QoL* and the four individual QoL domains. We included cortisol and oxytocin as the independent variables (IVs) of interest, to investigate their contribution to variability in overall QoL and each domain of QoL. Because symptom severity, sex and age may affect QoL, we included these in step 1 of each hierarchical regression to separately account for their contribution to QoL. The five predictors (IVs) were

Age, Sex, *GSI* (symptom severity including depressive symptoms), cortisol and oxytocin levels. Because this analysis was exploratory in nature, we did not correct for multiple comparisons in the HMRAs.

Prior to interpretation of results, all variables were evaluated for accuracy of input, missing data, and violation of assumptions. The assumptions of multicollinearity, and assumption of linearity and homoscedasticity of residuals were all met. However, the assumption of multivariate outliers and homogeneity of variance-covariance matrices were violated. Additionally, examination of the Shapiro-Wilk statistics and histograms indicated some violations of normality in some of the BSI and QoL subscales. Additionally, the assumptions of normality, univariate and multivariate outliers for cortisol and oxytocin were violated. The presence of genuine outliers and non-normal distributions is commonly noted in hormonal research and may reflect natural variability in endogenous hormone levels [36, 37]. Further, MANOVA [38, 39] and linear regressions [40] have been shown to be robust to most violations, particularly in sample sizes over 30, and studies have shown that only severe violations would affect statistical inferences. Nevertheless, Log10 transformation was conducted on variables which were skewed. The pattern of results was equivalent between the non-transformed and transformed data for each part of the study. Thereafter, analyses were performed by removing the outliers in the non-transformed data. As the significant effects were equivalent to the analysis prior to their removal, the outliers were retained and analyses with the outliers are reported.

Results

Descriptive statistics and reliability values are presented in Table 1. The Cronbach's alpha values for all measures and subscales exceeded .70, indicating acceptable internal consistency. The MDD and control groups did not differ significantly on age, F (1, 118) = .036, p = .850. or sex distribution, X^2 (2, N = 120) = 0.22, p = 0.72.

The MANCOVA indicated that after controlling for age and sex, the main effect of Depression group (MDD, Control) on QoL was significant, $\Lambda = .47$, F (5, 114) = 25.65, $p < .001$, partial $\eta^2 = .53$. Age was a significant covariate, $\Lambda = .77$, F (5, 114) = 6.89, $p < .001$, partial $\eta^2 = .23$. The main effect of sex was not significant, $\Lambda = .97$, F (5, 114) = .66, $p = .65$, partial $\eta^2 = .03$. There were no significant interaction effects. Table 2 presents the between-subject effects. Depressed individuals reported significantly lower QoL in all domains than controls (Table 1).

Correlational results for all participants in both MDD and control groups are presented in Table 3. Cortisol correlated negatively with *Overall-QoL* and all four domains. Oxytocin correlated positively with *Overall-QoL, Psychological-Health QoL,* and *Social-Relationships QoL*. Correlational analyses were also conducted separately for the MDD and control groups. These showed similar patterns to the combined group correlations, however there were fewer significant correlations due to the reduced power. For correlations, to detect medium effect sizes with .05 alpha, 84 participants are needed to achieve 80% power [30], hence the analysis by single group was underpowered. We have therefore reported the results for the combined groups.

Results of the hierarchical multiple regression analyses (HMRAs) and regression statistics are presented in Tables 4 and 5. The first HMRA investigated the relative contribution of cortisol and oxytocin to variance in *Overall-QoL,* controlling for Age, Sex, and *Global Severity Index (GSI),* a measure of the severity of psychopathology symptoms, including depression. At step 1, Age, Sex, and *GSI* were entered, accounting for a significant 44% of the variance in *Overall-QoL*, $p < .001$. At step 2, cortisol and oxytocin were added to the regression equation, and explained a non-significant additional 2% of the variance in *Overall-QoL*, $p = .22$. Collectively, the five independent variables (IVs) explained 46% of the variance in *Overall-QoL*, $p < .001$. Table 4 indicates that, at step 2, Age and *GSI* were

significantly associated with *Overall-QoL,* with *GSI* being the strongest predictor, β = -.60, $p < .001$. B indicated that a one unit increase in psychopathology was associated with a .7 unit decrease in overall QoL, and β indicated that a one SD increase in psychopathology (GSI) was associated with a .6 SD decrease in overall QoL, other variables being held constant.

The second HMRA indicated that at step 1, Age, Sex, and *GSI* accounted for a significant 33% of the variance in *Physical-Health QoL*, $p < .001$. At step 2, cortisol and oxytocin were added, explaining an additional non-significant 3% of the variance in *Physical-Health QoL*, $p = .114$. Collectively, the five IVs explained 35% of the variance in *Physical-Health QoL*, $p < .001$. At step 2, only *GSI* was significantly related to *Physical-Health QoL*, β = -.55, $p < .001$, with each SD increase in GSI yielding a .55 SD decrease in *Physical QoL,* with other variables being held constant (Table 5).

In the next HRMA, Age, Sex, and *GSI* together accounted for a significant 54% of the variance in *Psychological-Health QoL*, $p < .001$. At step 2, cortisol and oxytocin were added, significantly improving the model and explaining an additional 2.4% of the variance in *Psychological-Health QoL, p* = .047. Collectively, the five IVs explained 57% of the variance in *Psychological-Health QoL, p* < .001. At step 2, *GSI,* β = -.64, $p < .001$, and cortisol, β = -.16, $p = .029$, were significant predictors of *Psychological-Health QoL,* with one SD of increase in the predictors being associated with a .64 and .16 SD decrease in *Psychological QoL,* respectively, other variables being held constant (Table 5).

For *Social-Relationships QoL*, Age, Sex, and *GSI* initially accounted for a significant 34% of variance, $p < .001$. The addition of cortisol and oxytocin significantly improved the model, explaining an additional 3.5% of the variance in *Social-Relationships QoL, p* = .048. Collectively, the five IVs explained 37% of the variance in *Social-Relationships QoL, p* < .001. At step 2, *GSI,* β = -.49, $p < .001$, and oxytocin, β = .17, $p = .031$, were significantly associated with *Social-Relationships QoL* (Table 5). Each SD increase in GSI was associated

with a .49 SD decrease in Social QoL, and each SD increase in oxytocin yielded a .17 SD increase in Social QoL, holding other variables constant.

For *Environmental-QoL,* Age, Sex, and *GSI* initially accounted for a significant 41% of the variance, $p < .001$. Adding cortisol and oxytocin explained a non-significant additional 1% of the variance in *Environmental-QoL*, $p = .35$. Collectively, the five IVs explained 42% of the variance in *Environmental-QoL*, $p < .001$. At step 2, only *GSI* was significantly associated with *Environmental-QoL*, $\beta = -.58$, $p < .001$, with each SD increase in GSI yielding a .58 SD decrease in *Environmental-QoL* (Table 5).

Discussion

As hypothesised, clinically depressed individuals reported lower QoL in all domains than non-depressed individuals, after controlling for demographic variables, and QoL was inversely correlated to intensity of psychopathology symptoms. These findings are consistent with past studies [41-43]. MDD is a highly debilitating condition which involves a complex interaction of psychological, biological, social, and environmental factors, thus it is unsurprising that individuals with MDD show broad impairments in QoL. Additionally, the participants with MDD had significantly higher levels of psychopathology severity than the healthy controls, which were comparable to outpatient norms [44].

To the authors' knowledge, our study is the first to show that neuroendocrine markers are related to QoL in MDD. We predicted that cortisol levels would be inversely related to psychological and physical domains of QoL. Firstly, in bivariate analyses which did not adjust for other variables, cortisol levels were broadly and inversely correlated with overall QoL and all domains of QoL. Although there is a lack of comparable research focussed on MDD, the current finding is consistent with some past research that reported an inverse relationship between salivary cortisol and environmental QoL in health professionals [24], and afternoon cortisol levels and QoL in cancer outpatients [25].

Cortisol regulates a wide variety of functions in the body related to physical and mental health, such as immune responses, memory formation, and diurnal sleep patterns [17], and can influence individuals' physical and psychosocial responses through stress-related pathologies [45]. It is therefore not surprising that cortisol levels correlated broadly with all domains of QoL. The current findings of inverse relationships between cortisol and QoL provide new information about links between neuroendocrine functioning and QoL in MDD. Hyperactivity of the HPA axis, indexed by elevated cortisol levels, is often reported in MDD [46], and may be a factor accounting for QoL impairments in depression.

It was predicted that oxytocin would be positively related to the social relationships QoL domain. In the bivariate analyses, oxytocin was correlated with overall, social and psychological QoL. Although there is a lack of prior research examining oxytocin and QoL in MDD, the present findings are consistent with studies reporting lower plasma oxytocin levels in patients with fibromyalgia with depressive symptoms [47], and in adults facing psychological distress [48]. Oxytocin has been linked to aspects of social functioning in mental disorders including MDD [27, 49]. The current findings, combined with previous research, are consistent with the possibility that oxytocin plays a two-fold role in QoL: social approach behaviour, and anti-stress function [48]. Oxytocin may enhance prosocial behaviour by reducing negative mood and stress, establishing a calmer state [50], thus facilitating social proximity and support [20], which are protective against MDD [48]. The role of oxytocin in regulating HPA axis activation and anxiety [12] is consistent with its positive correlation with psychological QoL in the current study.

We also investigated the extent to which cortisol and oxytocin accounted for unique variance in QoL in MDD, after controlling for demographic factors and severity of psychopathology including depressive symptoms. In the regression analyses, we found that severity of psychological symptoms accounted for a significant amount of variance in all types QoL, congruent with prior research [6]. Additionally, cortisol accounted for unique variance in psychological QoL, beyond that accounted for by demographics and psychopathology including depressive symptoms. Although significant, the amount of variance explained by cortisol was small, once the strong relationship between QoL and psychopathology had been accounted for. Glucocorticoids are known to be neurotoxic in some circumstances [51] and prolonged HPA hyperactivity is associated with cognitive impairment [52], social withdrawal behaviour and mood changes [51]. Additionally, QoL and functional impairments in MDD often persist beyond depressive symptoms [53]. Further

research may help to understand whether direct links between cortisol and QoL may help to explain why QoL impairments may persist after recovery from depressive symptoms.

Cortisol did not significantly account for unique variance in physical QoL, after accounting for psychopathology. A possible explanation could be due to the the range of different items that are included in WHOQOL-BREF *Physical-Health subscale,* such as *dependence on medical aid*, which may not be directly related to cortisol levels. As this is one of the first studies examining biomarkers and QoL, future research looking at mechanisms and associations between cortisol and QoL is needed. Nevertheless, cortisol uniquely accounted for variance in psychological QoL beyond that accounted for by psychopathology, suggesting its importance to QoL in MDD.

Oxytocin levels accounted for unique variance in social relationships QoL beyond that accounted for by demographics and symptom severity. This was consistent with our predictions, as oxytocin mediates complex social behaviours including trust, proximity and social support [e.g. 20]. The results suggest that higher levels of oxytocin are directly associated with higher perceived quality of life in terms of social relationships.

Taken together, these findings suggest that, in bivariate analyses, cortisol is negatively related to all domains of QoL and oxytocin is positively related to social and psychological QoL. When controlling for other variables, cortisol accounts for unique variance in psychological QoL, and oxytocin accounts for unique variance in social QoL above that accounted for by intensity of psychopathology symptoms. The results provide new indications that individual domains of QoL are differentially associated with markers of neuroendocrine functioning. Additionally, they provide new information about physiological mechanisms associated with individuals' subjective experience in terms of their self-rated satisfaction with life. Further research is needed to understand if physiological mechanisms

may help to explain relationships between residual poor QoL and increased risks of relapse in MDD.

Implications

The findings about the biological correlates of QoL may help to guide tailored approaches to assessment and interventions for MDD. In particular, poor QoL in MDD is related to neuroendocrine changes associated with HPA axis activity and cortisol release. Additional associations with activity of the oxytocin system are also of interest. It is important to note that the findings from this study cannot be used to determine cause-and-effect relationships. Rather, the results suggest that there are some associations between cortisol, oxytocin, and QoL which persist when controlling for symptom severity. Future research should consider the implementation of longitudinal methods, to examine possible causal pathways. Nevertheless, these biological factors may show potential as modifiable variables which could be targeted in adjunctive interventions. For example, there is some evidence that cortisol levels are modifiable by diet [54] relaxation training [55] and mindfulness-based interventions [56]. Intra-nasal oxytocin can improve symptoms in psychiatric conditions involving social withdrawal including depression and is considered a promising adjunctive psychiatric treatment [29], however there is still a lack of adequate trials of oxytocin in MDD [11].

Limitations and Future Directions

Some limitations of the current research warrant attention. Firstly, the cross-sectional and correlational nature of this research precludes interpretations of causal relationships between QoL, hormones and psychopathology. Cortisol and oxytocin measures were taken at a single time point and thus provide only a cross-sectional indication of activity associated with activity of the HPA and oxytocin axes. Cortisol shows complex diurnal variations which

may be further affected in MDD, and future studies using more complex, longitudinal collection protocols may further elucidate cortisol-QoL relationships in MDD.

Cortisol and oxytocin levels uniquely accounted for a significant but small variance in QoL above symptom severity, and much variance remains unaccounted for. Future research is needed into other biological and psychosocial factors, for example personality traits, which could act as perpetuating or protective factors in relation to QoL in MDD.

Additionally, there may be a self-selection-bias for people who participate in research. Because of the heterogeneity of MDD, further research with larger sample sizes is necessary to confirm the findings. Therefore, the findings from this research should be considered in light of these limitations. Nonetheless, these are common limitations in similar research [57].

Conclusion

We conducted a novel study of relationships between biomarkers and QoL in MDD. Major findings were that cortisol levels inversely correlated with all aspects of QoL, whereas oxytocin levels correlated with overall, social and psychological QOL. Additionally, cortisol explained unique variance in psychological QoL, and oxytocin in social QoL, above that accounted for by psychopathology, suggesting that each hormone is linked to specific domains of QoL. Further research examining biopsychosocial factors related to QoL in MDD may help to better understand and address the burden of this debilitating condition.

Acknowledgments

We thank Jessica Mills for assistance with data collection and processing.

References

1. Ritsner, M.S., *The Distress/Protection Vulnerability Model of Quality of Life Impairment Syndrome*, in *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders: New Perspectives on Research and Treatment*, M.S. Ritsner and A.G. Awad, Editors. 2007, Springer Netherlands: Dordrecht. p. 3-19.
2. The World Health Organization Group, *The World Health Organization quality of life assessment (WHOQOL): Development and general psychometric properties.* Social Science & Medicine, 1998. **46**(12): p. 1569-1585.
3. Bonicatto, S.C., et al., *Adult outpatients with depression: worse quality of life than in other chronic medical diseases in Argentina.* Social Science & Medicine, 2001. **52**(6): p. 911-919.
4. IsHak, W.W., et al., *Quality of life: the ultimate outcome measure of interventions in major depressive disorder.* Harvard review of psychiatry, 2011. **19**(5): p. 229-239.
5. da Rocha, N.S., et al., *Is there a measurement overlap between depressive symptoms and quality of life?* Comprehensive Psychiatry, 2009. **50**(6): p. 549-555.
6. Papakostas, G.I., et al., *Quality of life assessments in major depressive disorder: a review of the literature.* General Hospital Psychiatry, 2004. **26**(1): p. 13-17.
7. Meltzer-Brody, S. and J.R. Davidson, *Completeness of response and quality of life in mood and anxiety disorders.* Depression and anxiety, 2000. **12**(S1): p. 95-101.
8. Keating, C., et al., *Effects of selective serotonin reuptake inhibitor treatment on plasma oxytocin and cortisol in major depressive disorder.* BMC Psychiatry, 2013. **13**: p. 124-124.
9. Penninx, B.W.J.H., *Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms.* Neuroscience & Biobehavioral Reviews, 2017. **74**: p. 277-286.
10. Neumann, I.D., *Brain oxytocin: a key regulator of emotional and social behaviours in both females and males.* Journal of Neuroendocrinology, 2008. **20**(6): p. 858-865.
11. Cochran, D., et al., *"The role of oxytocin in psychiatric disorders: A review of biological and therapeutic research findings".* Harvard review of psychiatry, 2013. **21**(5): p. 219-247.
12. Parker, K.J., et al., *Preliminary evidence that plasma oxytocin levels are elevated in major depression.* Psychiatry research, 2010. **178**(2): p. 359-362.
13. Slattery, D.A. and I.D. Neumann, *Oxytocin and Major Depressive Disorder: Experimental and Clinical Evidence for Links to Aetiology and Possible Treatment.* Pharmaceuticals (Basel, Switzerland), 2010. **3**(3): p. 702-724.
14. Holsboer, F. and M. Ising, *Stress Hormone Regulation: Biological Role and Translation into Therapy.* Annual Review of Psychology, 2010. **61**(1): p. 81-109.
15. Pariante, C.M. and S.L. Lightman, *The HPA axis in major depression: classical theories and new developments.* Trends in Neurosciences, 2008. **31**(9): p. 464-468.
16. Burke, H.M., et al., *Depression and cortisol responses to psychological stress: A meta-analysis.* Psychoneuroendocrinology, 2005. **30**(9): p. 846-856.
17. Zunszain, P.A., et al., *Glucocorticoids, cytokines and brain abnormalities in depression.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2011. **35**(3): p. 722-729.
18. Raison, C.L. and A.H. Miller, *When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders.* American Journal of Psychiatry, 2003. **160**(9): p. 1554-1565.
19. Kessler, R.C., et al., *Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys.* The British Journal of Psychiatry, 2010. **197**(5): p. 378-385.
20. Booij, S.H., et al., *The temporal dynamics of cortisol and affective states in depressed and non-depressed individuals.* Psychoneuroendocrinology, 2016. **69**: p. 16-25.
21. Steptoe, A., et al., *Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women: the Whitehall II study.* American Journal of Epidemiology, 2007. **167**(1): p. 96-102.

22. Hardeveld, F., et al., *Increased cortisol awakening response was associated with time to recurrence of major depressive disorder.* Psychoneuroendocrinology, 2014. **50**: p. 62-71.
23. Peeters, F., N.A. Nicolson, and J. Berkhof, *Levels and variability of daily life cortisol secretion in major depression.* Psychiatry Research, 2004. **126**(1): p. 1-13.
24. Knuth, B.S., et al., *Stress, depression, quality of life and salivary cortisol levels in community health agents.* Acta Neuropsychiatrica, 2016. **28**(3): p. 165-172.
25. Carlson, L.E., et al., *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients.* Psychoneuroendocrinology, 2004. **29**(4): p. 448-474.
26. Mutsuura, H., et al., *Depression and anxiety correlate differently with salivary free cortisol in the morning in patients with functional somatic syndrome.* Applied Psychophysiology and Biofeedback, 2009. **34**(4): p. 291-298.
27. Cochran, D.M., et al., *The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings.* Harvard Review Of Psychiatry, 2013. **21**(5): p. 219-247.
28. Windle, R.J., et al., *Gonadal steroid modulation of stress-induced hypothalamo-pituitary-adrenal activity and anxiety behavior: role of central oxytocin.* Endocrinology, 2006. **147**(5): p. 2423-2431.
29. Slattery, D.A. and I.D. Neumann, *Oxytocin and major depressive disorder: experimental and clinical evidence for links to aetiology and possible treatment.* Pharmaceuticals, 2010. **3**(3): p. 702-724.
30. Faul, F., et al., *G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences.* Behavior research methods, 2007. **39**(2): p. 175-191.
31. Thomas, S. and T. Larkin, *Plasma cortisol and oxytocin levels predict help-seeking intentions for depressive symptoms.* Psychoneuroendocrinology, 2018. **87**: p. 159-165.
32. World Health Organization, *WHOQOL: Measuring quality of life.* 1997.
33. Derogatis, L. and N. Melisaratos, *The brief symptom inventory: An introductory report.* Psychological Medicine, 1983. **13**(3): p. 595-605.
34. Mohammadkhani, P., et al., *Psychometric properties of the Brief Symptom Inventory in a sample of recovered Iranian depressed patients.* International Journal of Clinical and Health Psychology, 2010. **10**(3): p. 541-551.
35. Lecrubier, Y., et al., *The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI.* European Psychiatry, 1997. **12**(5): p. 224-231.
36. Pollet, T. and L. Meij, *To Remove or not to Remove: the Impact of Outlier Handling on Significance Testing in Testosterone Data.* Adaptive Human Behavior & Physiology, 2017. **3**(1): p. 43.
37. Wilcox, R.R., et al., *Cortisol diurnal patterns, associations with depressive symptoms, and the impact of intervention in older adults: Results using modern robust methods aimed at dealing with low power due to violations of standard assumptions.* Hormones & Behavior, 2014. **65**(3): p. 219-225.
38. Field, A., *Discovering statistics using SPSS*. 3rd ed. 2009, London, England: Sage.
39. Tabachnick, B.G. and L.S. Fidell, *Using multivariate statistics*. 5th ed. 2007, Boston: Allyn & Bacon.
40. Howell, D.C., *Statistical methods for psychology*. 8th ed. 2013, Canada: Wadsworth.
41. Holubova, M., et al., *Self-stigma and quality of life in patients with depressive disorder: A cross-sectional study.* Neuropsychiatric Disease and Treatment, 2016. **12**.
42. IsHak, W.W., et al., *Quality of life in major depressive disorder before/after multiple steps of treatment and one-year follow-up.* Acta Psychiatrica Scandinavica, 2015. **131**(1): p. 51-60.
43. Trivedi, M.H., et al., *Factors associated with health-related quality of life among outpatients with major depressive disorder: a STAR*D report.* The Journal Of Clinical Psychiatry, 2006. **67**(2): p. 185-195.
44. Ryan, C., *British outpatient norms for the Brief Symptom Inventory.* Psychology and Psychotherapy: Theory, Research and Practice, 2007. **80**(2): p. 183-191.

45. Myers, B., J.M. McKlveen, and J.P. Herman, *Glucocorticoid actions on synapses, circuits, and behavior: Implications for the energetics of stress.* Frontiers in Neuroendocrinology, 2014. **35**(2): p. 180-196.
46. Pariante, C.M. and A.H. Miller, *Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment.* Biological psychiatry, 2001. **49**(5): p. 391-404.
47. Anderberg, U.M. and K. Uvnäs-Moberg, *Plasma oxytocin levels in female fibromyalgia syndrome patients.* Zeitschrift Fur Rheumatologie, 2000. **59**(6): p. 373-379.
48. Gordon, I., et al., *Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress.* Psychophysiology, 2008. **45**(3): p. 349-352.
49. McQuaid, R.J., et al., *Making room for oxytocin in understanding depression.* Neuroscience & Biobehavioral Reviews, 2014. **45**: p. 305-322.
50. Zhong, S., et al., *U-Shaped Relation between Plasma Oxytocin Levels and Behavior in the Trust Game.* PLoS ONE, 2012. **7**(12): p. 1-9.
51. Sapolsky, R.M., *Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders.* Archives of general psychiatry, 2000. **57**(10): p. 925-935.
52. Lupien, S.J., et al., *Effects of stress throughout the lifespan on the brain, behaviour and cognition.* Nature Reviews. Neuroscience, 2009. **10**(6): p. 434-45.
53. Angermeyer, M., et al., *Depression and quality of life: results of a follow-up study.* International Journal of Social Psychiatry, 2002. **48**(3): p. 189-199.
54. Baudrand, R. and A. Vaidya, *Cortisol dysregulation in obesity-related metabolic disorders.* Current Opinion in Endocrinology, Diabetes and Obesity, 2015. **22**(3): p. 143-149.
55. Chellew, K., et al., *The effect of progressive muscle relaxation on daily cortisol secretion.* Stress, 2015: p. 1-7.
56. Matousek, R.H., P.L. Dobkin, and J. Pruessner, *Cortisol as a marker for improvement in mindfulness-based stress reduction.* Complementary therapies in clinical practice, 2010. **16**(1): p. 13-19.
57. Hanley, J.A., *Correction of Selection Bias in Survey Data: Is the Statistical Cure Worse Than the Bias?* American Journal of Public Health, 2017. **107**(4): p. 503-505.

Table 1

Psychometric Properties of the Study Variables by Groups

Variable	*n*	Both Groups	Clinically Depressed	Healthy Controls	Cronbach α
			M (*SD*)		
Biomarker					
Cortisol	120	180.07 (112.52)	252.29 (102.63)	106.65 (65.08)	
Oxytocin	120	209.39 (157.92)	157.94 (140.00)	263.71 (159.57)	
BSI					
Global Severity Index	120	1.13 (.89)	1.68 (.80)	.50 (.46)	.98
Positive Symptoms Total Index	120	27.79 (15.12)	37.23 (10.69)	17.22 (11.92)	
Positive Symptoms Distress Index	120	1.83 (.72)	2.26 (.62)	1.35 (.46)	
WHOQOL-BREF					
Physical Health	120	48.84 (10.08)	45.44 (11.6)	52.48 (6.48)	.82
Psychological Health	120	48.08 (10.8)	40.8 (8.56)	55.88 (6.84)	.89
Social Relationships	120	51.44 (15.72)	43.08 (14.04)	60.4 (12.2)	.78
Environment	120	57 (11.52)	51.56 (8.01)	62.76 (8.6)	.84
Overall QoL	120	3.59 (1.03)	3 (.93)	4.2 (.74)	.95

Note. *n* = number of responses; *M* = mean; *SD* = standard deviation. BSI = Brief Symptom Inventory; WHOQOL = World Health Organisation Quality of Life.

Table 2

Summary of MANCOVA Results for Quality of Life Between Groups (Clinically Depressed vs. Healthy Controls), with Age and Sex as covariates.

WHOQOL-BREF	*F*	*p* value	Partial Eta^2
Physical Health	17.86	<.001**	.13
Psychological Health	123.19	<.001**	.51
Social Relationships	52.25	<.001**	.31
Environment	38.47	<.001**	.25

Note. WHOQOL = World Health Organisation Quality of Life.
**$p < .001$.

Table 3

Spearman's Rho Correlations for Study Variables for Both Groups (n = 120)

	WHOQOL-BREF				
	Overall QoL	Physical Health	Psychological Health	Social Relationship	Environment
Biomarkers					
Cortisol	-.42**	-.35**	-.52**	-.38**	-.44**
Oxytocin	.25*	.00	.27*	.29*	.15
BSI					
Global Severity Index	-.61**	-.58**	-.75**	-.55**	-.66**
Positive Symptoms Total	-.59**	-.54**	-.71**	-.58**	-.65**
Positive Symptoms Distress	-.53**	-.53**	-.68**	-.44**	-.56**

Note. WHOQOL = World Health Organisation Quality of Life.
*$p < .01$, **$p < .001$.

Table 4

Summary of Hierarchical Multiple Regression Analysis Predicting Overall Quality of Life as Measured by WHOQOL-BREF (n = 120)

Predictor	*B*	β	sr^2	*p*
Step 1	$R^2 = .44$, $F\ (3, 116) = 30.75$, $p < .001$			
Age	-.023	-.29	.07	< .001
Sex	-.280	-.14	.02	.055
GSI	-.793	-.68	.42	< .001
Step 2	$\Delta R^2 = .02$, $\Delta F\ (2, 114) = 1.54$, $p = .218$			
Age	-.021	-.26	.06	.001
Sex	-.236	-.11	.01	.111
GSI	-.705	-.60	.23	< .001
Cortisol	-.001	-.11	.01	.167
Oxytocin	.001	.1	.01	.178
Total	$R^2 = .46$, adjusted $R^2 = .43$, $F\ (5, 114) = 19.24$, $p < .001$			

Note. WHOQOL = World Health Organisation Quality of Life; GSI = Global Severity Index.

Table 5

Summary of Hierarchical Multiple Regression Analyses Predicting the Four Domains of Quality of Life as Measured by WHOQOL-BREF (n = 120)

	WHOQOL-BREF							
	Physical Health				Psychological Health			
	B	β	sr^2	*p*	*B*	β	sr^2	*p*
Step 1	$R^2 = .33$, F (3, 116) = 18.73, $p < .001$				$R^2 = .54$, F (3, 116) = 46.08, $p < .001$			
Age	0.014	0.075	0.005	0.355	-0.002	-0.008	.000	0.901
Sex	-0.093	-0.019	0.000	0.810	-0.466	-0.086	.007	0.177
GSI	-1.544	-0.545	0.270	< 0.001	-2.266	-0.739	.497	< 0.001
Step 2	$\Delta R^2 = .03$, ΔF (2, 114) = 2.21, $p = .114$				$\Delta R^2 = .024$, ΔF (2, 114) = 3.15, $p = .047$			
Age	0.013	0.068	0.004	0.400	0.005	0.023	.000	0.733
Sex	-0.236	-0.047	0.002	0.545	-0.336	-0.062	.004	0.331
GSI	-1.559	-0.550	0.193	< 0.001	-1.953	-0.637	.259	< 0.001
Cortisol	-0.001	-0.033	0.001	0.715	-0.004	-0.162	.018	0.029
Oxytocin	-0.002	-0.154	0.021	0.055	0.002	0.107	.010	0.103
Total	$R^2 = .35$, adjusted $R^2 = .32$, F (5, 114) = 12.36, $p < .001$				$R^2 = .57$, adjusted $R^2 = .55$, F (5, 114) = 29.93, $p < .001$			
	Social Relationships				Environment			
	B	β	sr^2	*p*	*B*	β	sr^2	*p*
Step 1	$R^2 = .34$, F (3, 116) = 19.52, $p < .001$				$R^2 = .41$, F (3, 116) = 27.26, $p < .001$			
Age	-0.035	-0.114	0.012	0.155	-0.002	-0.007	0.000	0.927
Sex	-1.027	-0.130	0.017	0.090	-0.420	-0.072	0.005	0.316
GSI	-2.635	-0.592	0.318	< 0.001	-2.120	-0.645	0.378	< 0.001
Step 2	$\Delta R^2 = .035$, ΔF (2, 114) = 3.12, $p = .048$				$\Delta R^2 = .01$, ΔF (2, 114) = 1.05, $p = .35$			
Age	-0.025	-0.081	0.006	0.313	0.003	0.011	0.000	0.882
Sex	-0.744	-0.094	0.008	0.220	-0.391	-0.067	0.004	0.360
GSI	-2.174	-0.488	0.152	< 0.001	-1.901	-0.578	0.213	< 0.001
Cortisol	-0.005	-0.147	0.015	0.099	-0.003	-0.122	0.010	0.153
Oxytocin	0.004	0.172	0.026	0.031	0.000	0.011	0.000	0.879
Total	$R^2 = .37$, adjusted $R^2 = .34$, F (5, 114) = 13.39, $p < .001$				$R^2 = .42$, adjusted $R^2 = .40$, F (5, 114) = 16.79, $p < .001$			

Note. WHOQOL = World Health Organisation Quality of Life; GSI = Global Severity Index.