



Plasma cortisol and oxytocin levels predict help-seeking intentions for depressive symptoms

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ARTICLE INFO

Keywords:

Depression
Help-seeking
Cortisol
Oxytocin

ABSTRACT

Background: Depressed individuals often refuse or withdraw from help, a phenomenon termed help-negation, which is a risk factor for poor outcomes. Most previous research has investigated psychosocial factors including stigma as causes of low help-seeking intentions for depression, however these do not adequately explain the problem. We hypothesised that because help-negation worsens with symptom severity, it might be linked to important biological changes associated with depression itself. We investigated the relative contributions of cortisol, a stress hormone linked to depression, and oxytocin, a hormone which mediates social behaviours, alongside psychosocial factors, to help-seeking intentions among depressed and non-depressed individuals.

Methods: Morning plasma cortisol and oxytocin levels, psychopathology, suicidal ideation, help-seeking intentions from informal sources including family and friends, and formal sources including health professionals, and perceived social support were quantified in 63 adults meeting DSM-5 criteria for major depressive disorder (MDD) who were not receiving any treatment, and 60 healthy controls. Between-group analyses of variance, correlations, and hierarchical multiple regressions were employed.

Results: Help-seeking intentions were lower in depressed than healthy participants, negatively correlated to cortisol and positively correlated to oxytocin. Cortisol negatively, and oxytocin positively, predicted help-seeking intentions from informal but not formal sources, after controlling for psychopathology and psychosocial factors.

Conclusions: Neuroendocrine changes associated with depression may contribute to low help-seeking from friends and family, which may have implications for interpersonal support and outcomes. Research and clinical approaches which incorporate biological as well as psychosocial factors may allow for more targeted and effective early interventions to address lack of help-seeking and depression progression.

1. Introduction

Depressive disorders and suicide are leading causes of morbidity worldwide, and their magnitude is increasing (Whiteford et al., 2013). Early treatment reduces long term impairment and is cost effective (Chisholm et al., 2004), however, large scale research spanning numerous countries and including thousands of participants shows that most people with major depressive disorder (MDD) do not receive treatment, even where effective treatments are available (Kocsis et al., 2008; Thornicroft et al., 2017). Reasons for the under-treatment of depression are multi-factorial, however a major contributing factor is a widespread reluctance of affected people to seek help (Kocsis et al., 2008; Thornicroft et al., 2017). This refusal of, or withdrawal from, help has been termed *help-negation* (Clark and Fawcett, 1992; Rudd et al., 1995) and is considered the most difficult barrier to the treatment

of depression (Han et al., 2006).

Previous research differentiates between help-seeking from informal sources including friends and family, and formal sources including health care professionals and helplines. Most previous studies of help-seeking for mental health problems have involved sub-clinical student populations, who prefer seeking informal rather than formal help (Thomas et al., 2014). A large-scale epidemiological study also found a general preference for informal sources of help, and that the presence of depressive symptoms was associated with lower intentions to seek help from family and friends, but no differences in formal help-seeking intentions (Chin et al., 2015). It is important to consider informal supports, because friends and family often facilitate treatment uptake and adherence in those with depressive symptoms (Chin et al., 2015; Lindsey et al., 2010), and are important points of intervention in suicidal behaviour (Barnes et al., 2002).

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It has traditionally been assumed that psychosocial factors underlie the widespread reluctance of people to seek help for depression, and much research has examined the contributions of factors such as stigma or embarrassment, however these seem to be only weakly negatively associated with help-seeking (Clement et al., 2015). There is no clear evidence to demonstrate that campaigns to increase treatment uptake through targeting stigma are successful (Dumesnil and Verger, 2009; Henderson et al., 2013). Additionally, somewhat counterintuitively, avoidance of treatment for depressive symptoms and psychological distress is greater in individuals with greater psychopathology, stress levels, and suicidal ideation (e.g. Carlton and Deane, 2000; Rudd et al., 1995; Sawyer et al., 2012). These factors lead us to propose that help-negation might be related to biological, particularly neuroendocrine, changes associated with the onset or progress of depression itself, which may be linked to interpersonal difficulties and social withdrawal. To date there has been little examination of relationships between help-seeking intentions, psychopathology and biological factors. Overlooking the contribution of biological factors to help-negation may account for the sub-optimal success of treatment uptake campaigns targeting psychosocial factors, and further research is needed.

Cortisol, an output of the hypothalamus-pituitary-adrenal (HPA) axis, is a consistent neurobiological indicator of stress, anxiety and depression (Levine et al., 2007). Prolonged HPA hyperactivity through chronic stress is related to cognitive impairment (Lupien et al., 2009), social withdrawal behaviour (Tops et al., 2005) and mood changes (Sapolsky, 2000). Excess cortisol is a risk factor for developing MDD, and those with MDD often have disturbances in diurnal cortisol rhythms, increased resistance to the feedback action of glucocorticoids, higher basal levels and cortisol awakening response (Herbert, 2013). There are indications that individuals with higher basal cortisol display both reduced closeness and that others desire to be less close to them (Ketay et al., 2017). Individuals with severe MDD often show increased HPA-axis activity, which normalises during successful antidepressant pharmacotherapy (Barden et al., 1995). Anti-depressants might elevate mood in MDD through their long-term effects on HPA regulation (Barden et al., 1995). Depression-like withdrawal and immobility can be induced in laboratory animals (Kulkarni and Dhir, 2007), indicating that they can occur without language-based cognition, which implies a role for physiological processes. Vegetative symptoms in depression may stem from processes that evolved to preserve energy during insurmountable stress (Gilbert, 2001; Hart, 1988; Tsiouris, 2005). When placed in stressful situations from which escape is not possible, animals will initially struggle and try to escape, but eventually develop immobility, a failure to persist in active forms of coping with stressful stimuli. This passive behaviour is termed behavioural despair, which is believed to be equivalent to depression (Porsolt et al., 1977), and it is reversed with selective-serotonin reuptake inhibitors and with tricyclic antidepressants (Kulkarni and Dhir, 2007). Cortisol levels may therefore be related to help-negation and to depressive symptoms including vegetative symptoms, social withdrawal and cognitive impairment. Relationships between cortisol levels, help-negation and symptom severity are not yet known.

Oxytocin is a hormone which mediates a range of complex social behaviours relevant to group-living mammals, including attachment, trust, and social support-seeking and in some circumstances aggression (Heinrichs et al., 2009; Smith et al., 2017). Oxytocin is also implicated in depression (Viero et al., 2010). It may therefore help to explain help-negation as symptoms worsen in MDD. Oxytocin is a nonapeptide hormone which is synthesised in hypothalamic nuclei and released directly into the bloodstream from axon terminals in the posterior pituitary (MacDonald and MacDonald, 2010). Oxytocin is also transported from the hypothalamus to key brain areas, where it acts as a neurotransmitter (MacDonald and MacDonald, 2010). Central effects of oxytocin include inhibition of stress-induced hypothalamus-pituitary-adrenal (HPA) axis responsiveness, promotion of social behaviours, and anti-depressant effects (Scantamburlo et al., 2007). Oxytocin is

implicated in numerous psychopathologies characterised by social discomfort, including depression, anxiety and psychoses (Viero et al., 2010). Some symptoms of depression (social withdrawal, reduced eye contact and low libido) may reflect blunted oxytocin function (Neumann, 2008). Help-seeking, particularly informally, usually involves interpersonal exchanges. Because oxytocin is often inversely related to depressive symptoms, anxiety and stress (Scantamburlo et al., 2007), and modulates social withdrawal and stress coping (Pompili et al., 2010), oxytocin abnormalities may be related to help-negation in MDD. This possibility has yet to be examined.

Given the clear involvement of biological processes in depression and withdrawal behaviour, it is of interest to investigate their role in help-seeking intentions. Both cortisol and oxytocin may represent modifiable risk factors for help-negation which potentially could be targeted in novel interventions. The current study examined biological processes in connection with symptom severity and help-seeking intentions in depressed and healthy individuals.

Based on previous research, it was predicted that:

- 1 Help-seeking intentions, particularly from informal sources, would be lower in participants with MDD than healthy controls.
- 2 Cortisol will be negatively related to help-seeking intentions and perceived social support and positively related to psychopathology, and the opposite patterns would be observed for oxytocin.
- 3 Cortisol and oxytocin levels would be more closely related to informal than formal help-seeking intentions, as these involve more socially based interpersonal interactions.
- 4 Cortisol and oxytocin would both uniquely predict variance in help-seeking intentions, after accounting for levels of psychopathology and perceived social support.

2. Methods

2.1. Participants

The protocol was approved by the local ethics committee, and all participants gave informed written consent. Sixty-three adults were recruited who met the DSM-5 diagnostic criteria for MDD, were not currently receiving treatment and had not recently had any treatment, along with 60 healthy controls. Participants were recruited through advertisements in local media and notices at the university. Exclusion criteria across groups included neurological disorders, substance use disorders, and use of corticosteroid medication. Participants were screened prior to the study with regard to exclusion criteria, and to ensure that depressed participants likely met DSM-5 criteria for MDD and healthy controls had no significant mental health problems. Depressed participants were also interviewed by a clinical psychologist on arrival at the clinical trials unit to confirm that they met DSM-5 diagnostic criteria for major depressive disorder, using the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997), and to ascertain treatment history and reasons for not being in treatment. Participants received a store voucher of small value as a reimbursement for their time and inconvenience.

2.2. Measures

All participants completed the following measures: The Depression, Anxiety and Stress Scales-21 (Lovibond and Lovibond, 1995), an overall measure of psychological distress incorporating *Depression*, *Anxiety* and *Stress* subscales. The General Help-Seeking Questionnaire-Vignette version (Wilson et al., 2005), a measure of intentions to seek help in the event of mental health problems. Participants indicate on a 7-point Likert scale how likely they would be to seek help for depressive symptoms from specific informal (e.g. friends, family, partner) and formal (e.g. doctor, psychologist, helpline) sources if they were experiencing the same problems as the person in the vignette

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