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LINKING THE PSYCHOSOCIAL AETIOLOGY AND NEUROBIOLOGY OF UNIPOLAR DEPRESSION

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SUMMARY

Psychosocial factors are an important contributor to the aetiology of unipolar depression. This paper reviews the evidence for the contribution of different psychosocial factors, and provides an overview of the proposed neurobiological mechanisms underlying the link between psychosocial factors and depression.

Implicated psychosocial factors fall into three interrelated groups: life events, socioeconomic status, and social support. The life events most strongly linked with depression are bereavement, disability or medical illness, and childhood maltreatment. Others include refugee status, workplace stressors, and obesity. Studies linking low socioeconomic status with depression are conflicting. There is strong evidence for the association between lack of social support and depression.

Multiple neurobiological mechanisms linking psychosocial factors to depression have been suggested, though evidence remains limited. The key foci of evidence point to increased activity in the hypothalamic-pituitary-adrenal axis, epigenetic modifications of key genes, and inflammatory processes. Other mechanisms being explored include structural changes to the limbic system, prefrontal cortex, cingulate cortex, and hippocampus, and the role of other molecules such as cholecystokinin, tachykinins, spinophillin, synaptophysin and myelin basic protein. There is overlap between these mechanisms.

Key words: *depressive disorder – psychosocial - risk factors - neurobiology*

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INTRODUCTION

Unipolar depression has a significant psychosocial aetiology, with the heritability estimated to account for only 37% of disease occurrence (Sullivan et al. 2000). The psychosocial factors which have been implicated in the aetiology of unipolar depression fall into three interrelated groups: life events, socioeconomic status, and social support. The neurobiological mechanisms by which these factors lead to depression are poorly understood, but are the subject of ongoing research.

PSYCHOSOCIAL FACTORS

Life events

Negative life events, or life stressors, are one of the most studied risk factors for unipolar depression. The relevance of a life event to the risk of depression may depend on a number of characteristics, including its perceived undesirability, the extent to which the individual has control over it, its magnitude, the degree to which it is life threatening, and its duration (Bruce 2002). The strength of association of many life events or stressors with depression varies according to age, with stronger associations found in the age groups in which occurrence is lowest and least expected (Schaakxs 2017).

Strongest evidence exists for the roll of bereavement (Florence 2015, Bruce 1990), disability or medical illness (Geerlings 2000), and childhood maltreatment (Li 2016), in the aetiology of depression. A meta-analysis of 20 prospective cohort studies on risk factors for depression in the elderly found an odds ratio of 3.3 for bereavement, 2.5 for disability, and 1.8-2.1 for medical illness (Cole 2003). A meta-analysis of eight cohort studies investigating the relationship between maltreatment in childhood and depression reported an odds ratio of 2.03 (Li 2016).

The relationship between bereavement and depression appears to be one of the most significant. In part, this may be attributable to the overlapping presentations of normal grief and depression. Factors associated with depression, rather than normal grief, include the individual's coping mechanisms, traumatic or unexpected nature of the death, and the extent to which it results social isolation (Aziz 2013).

Another implicated life stressor is refugee status. A meta-analysis of 35 population based cross-sectional studies found a depression prevalence of 44% among refugees (Lindert 2009). A more recent cross-sectional study of depression among Syrian refugees in a Turkish refugee camp reported the prevalence as 37% (Acarturk 2017).

Workplace stressors may also play a role in the aetiology of depression. A systematic review of 16 prospective cohort studies investigating the relationship between job-related psychosocial factors and depression indicated that exposure to perceived adverse psychosocial factors at work is related to an increased risk of depression (Bonde 2008). The factor for which the relationship was strongest was job strain, which was defined as a combination of high demand and low decision latitude. A cross-sectional study of 1169 people in three European countries suggested that an effort-reward imbalance at work is associated with depression (Pikhart 2004).

Obesity is another proposed factor in the aetiology of depression, particularly among the young (Schaakxs 2017). A meta-analysis of 15 longitudinal cohort studies found an association between obesity and depression, whereby obesity increased the risk of depression with an odds ratio of 1.55, while depression was predictive of the development of obesity (Luppino 2010).

Socioeconomic status

Low socioeconomic status has been associated with depression, and may be related to poorer access to health and mental health services, increased exposure to negative life events, and social support factors (Arean 2005).

A prospective cohort study of 9193 individuals indicated that low socioeconomic position was associated with increased rates of depressive symptoms in all age periods. Indicators of low standards of living showed the strongest associations, with odds ratios reported for depression at age 18 ranging from 1.20 for manual social class to 1.74 for material hardship (Joinson 2017). In another prospective cohort study investigating the risk factors for first-onset unipolar depression in 3170 individuals, the effects of poverty were reduced when controlling for the degree of social isolation, suggesting that the effect of socioeconomic status on depression may be mediated through social support factors (Bruce 1994). However, a systematic review of 25 primarily cross-sectional studies investigating the risk factors for chronic depression concluded that the influence of socioeconomic status was inconsistent (Hölzel 2011). Another systematic review of 71 cross-sectional and longitudinal studies on risk factors for depression in the elderly similarly found that the relationship between low education level or low income and depression was inconsistent (Vink 2008). In short, the evidence for the role of socioeconomic status remains inconclusive.

Social support

A lack of social support, and in particular, a lack of relationships that provide emotional support, has been implicated in the aetiology of depression. This may be because social support both directly enhances psychological well-being, and reduces or buffers the negative impact of the life stressors described above (Bruce 2002).

A systematic review of 25 primarily cross-sectional studies investigating risk factors for chronic depression found that low social support, negative social interaction, and low social integration were all linked to chronic depression (Hölzel 2011). A systematic review of 71 cross-sectional and longitudinal studies on risk factors for depression in the elderly found associations with both quantitative and qualitative aspects of social network, including low contact frequency, smaller network size, being unmarried, and having a lack of social support (Vink 2008).

MECHANISMS

Identifying the neurobiological processes that underlie the association between psychosocial factors and depression may reveal pathways through which the risk for depression can be mitigated. The proposed mechanisms include increased hypothalamic-pituitary-adrenal (HPA) axis activity, epigenetic modification of key genes, and inflammatory processes. Other mechanisms suggested include structural changes in key areas of the brain, such as the limbic system, prefrontal cortex, cingulate cortex and hippocampus, and the role of other molecules such as cholecystokinin (CCK), tachykinins, spinophillin, synaptophysin (SVP) and myelin basic protein (MBP). These proposed mechanisms are summarised in Table 1.

Table 1. Neurobiological mechanisms that may mediate the association between psychosocial stress and depression

Key mechanisms
Increased hypothalamic-pituitary-adrenal axis activity
Epigenetic modification of key genes ▪ SLC6A4 (serotonin transporter gene) ▪ Hypothalamic-pituitary-adrenal axis genes ▪ Brain derived neurotrophic factor
Inflammatory processes
Proposed mechanisms with less well established psychosocial driving evidence
Structural changes in the limbic system, prefrontal cortex, cingulate cortex and hippocampus
Other mechanisms: ▪ Cholecystokinin ▪ Tachykinins ▪ Spinophillin, synaptophysin, and myelin basic protein

Increased HPA axis activity

Increased HPA axis activity has been implicated as a link between psychosocial factors and depression. Hypercortisolaemia occurring as a result of stress has been reported in severe depression (MacKenzie 2007). Early life stress such as prolonged maternal separation has been shown to be associated with an increased risk of depression in mice (Anisman 1998). In another study, mice exposed to maternal deprivation had marked increases in stress induced corticosteroid secretion with increased depressive symptoms and memory deficits (Murgatroyd 2009). Increased HPA axis activity has also been reported at times of prenatal stress in mothers (Owen 2005) and has been associated with higher rates of depression (Markham 2011).

It is hypothesised that early stress may cause hypersensitivity to glucocorticosteroids, an effect that persists into adulthood (Mirescu 2004). This effect of sensitisation has been described in the literature, whereby individuals require less stress to set off certain behaviours with time, making them more prone to

depressive symptoms. This effect was observed in a study (female twin pairs n=292, non-twin sisters n=46) which found that childhood adversity and adult negative life events increased negative affect to daily stressors (Wichers 2009). Another study reported that patients with depression and a history of childhood abuse had enhanced HPA axis activity in response to psychosocial stress compared to controls (Heim 2000), which would further support this hypothesis.

Epigenetic modification of key genes

Recent studies have proposed a role for the epigenetic modification of certain gene regulatory regions in the neurobiology of depression. One review of 25 papers (6 animal studies, 19 human studies) examined the relationship between DNA methylation and stress in the context of depression. The effect of chronic stress was predominantly investigated through animal studies focussing on the HPA axis genes. These studies drew conclusions that stress-related DNA methylation resulted in increased production of corticotrophin releasing factor (CRF), adrenocorticotrophic hormone and glucocorticoids. Thus, epigenetic changes could help explain the link described in the previous section, between HPA axis activity axis and depression. Potential epigenetic targets included the CRF gene, the glucocorticoid receptor NR3C1 and FKBP5 (FK506 binding protein 5 gene). Those studies focussing on the association between depression and DNA methylation were mainly human studies concentrating on neurotransmission. Important genes included those involved in serotonergic transmission (SLC6A4), brain-derived neurotrophic factor (BDNF), dopaminergic/noradrenergic transmission (SLC6A2 – noradrenaline transporter gene) and genes encoding for neural adhesion molecules (Bakusic 2017).

SLC6A4 - serotonin transporter gene:

The role of decreased serotonergic neurotransmission in the aetiology of depression is well recognised. The serotonin transporter gene (SLC6A4) has been a gene of interest for the study of psychosocially driven epigenetic modification. One systematic review of 19 studies looking at the relationship between SLC6A4 methylation and psychosocial events in those aged under 18 years, associated SLC6A4 methylation with exposure to various negative life events, including childhood trauma, environmental stress, prenatal adverse outcomes, pain-related stress, and peer-related trauma (Provenzi 2016).

A prospective cohort study of 132 adolescents (Swartz 2017) demonstrated that adolescents with a lower socioeconomic status displayed increased methylation of the SLC6A4 promoter gene (p=0.02). This methylation was able to predict increased threat related amygdala activity in all groups, and in those with a positive family history of depression, predicted the manifestation of depression in later life (p=0.02). It may be that a positive family history exposes adolescents to a higher degree of life adversity, accounting for the significance in this subset. A second prospective cohort study of 338 African American adolescents had similar findings, showing that poorer socioeconomic status was significantly correlated with increased methylation of the SLC6A4 promoter. The strength of the correlation varied between sexes, between multiple CpG methylation sites, and between short and long serotonin transporter gene alleles (Beach 2014). This may suggest that the association is complex and affected by gene-environment interactions.

Another study (Beach 2010) found that individuals with a history of child abuse had significantly higher methylation of multiple CpG sites within the SLC6A4 promoter gene (n=192, p=0.004). One study (Zhao 2013) analysing 84 monozygotic twin pairs found that differences in methylation of SLC6A4 significantly correlated with intrapair differences in Beck Depressive Inventory (BDI) scores (p=0.01).

Further studies would allow better characterisation of how epigenetic regulation is altered as a result of life adversity and poor socio-environmental exposure.

Hypothalamic-pituitary-adrenal axis genes

Cortisol, the stress hormone, exerts its function through binding to mineralocorticoid receptors and to NR3C1, the glucocorticoid receptor. Decreased expression of NR3C1 results in reduced negative feedback on the HPA axis and hence increased activity.

Animal studies have shown increased methylation of the promoter of NR3C1 in the adrenal and pituitary glands in rats exposed to stress (Witzmann 2012) and demethylation of the CRF promoter in the paraventricular nucleus in mice exposed to stress (Elliott 2010). The mice with demethylation of the CRF promoter also exhibited depression-like behaviours. Increased methylation of NR3C1 decreased its expression in the hypothalamus, resulting in reduced negative feedback on the HPA axis. This may explain the reported hypercortisolaemia in severe depression (MacKenzie 2007).

Conversely, high maternal care in rats has been associated with increased NR3C1 expression in the hippocampus. This was associated with methylation at a specific site in the NR3C1 promoter, thought to be mediated through altered binding of transcription factor NGFI-A to the promoter. The effect of this was greater inhibition of the HPA-axis (Weaver 2004). A second study found supporting results in humans where individuals with a history of child maltreatment were found to have increased methylation at a specific site in the NR3C1 promoter region which limited binding of NGFI-A. The result was decreased NR3C1 expression in the hippocampus (McGowan 2009).

Brain derived neurotrophic factor

Brain derived neurotrophic factor (BDNF) is a neurotrophin involved in neuronal growth and plasticity. A study of 41 patients with major depressive disorder found that the overall methylation in the BDNF promoter gene was higher in depressed patients than controls (D'Addario 2013). Stress has been shown to

cause histone methylation of promoters of the BDNF gene, reducing BDNF protein expression. Early life stress in rats has been associated with reduced BDNF expression in the prefrontal cortex and striatum (Roceri 2004) whilst high levels of maternal care in rats has been associated with increased hippocampal BDNF mRNA (Liu 2000). Another study using a rat model found that early life adversity resulted in persistent changes in levels of methylation of BDNF DNA that affected expression of BDNF in the prefrontal cortex (Roth 2009). This effect was also found to be trans-generationally transmitted to offspring of early life adversity exposed females. These animal studies highlight the BDNF gene promoter as an important region that may be altered as a result of psychosocial exposure and further work will help characterise how this relates to the pathophysiology of depressive disorder.

Inflammatory processes:

There is a body of evidence supporting the role of inflammatory mechanisms in the aetiology of depression (Miller 2016). Further, the role of inflammation has been implicated as a mediator between psychosocial factors and depression (Cattaneo 2015).

A prospective cohort study of 1000 patients demonstrated co-occurrence of depression and elevated C-reactive protein (CRP) in those with a history of childhood maltreatment (Danese 2008). In another prospective cohort study of 147 adolescent females, in those subjects exposed to childhood adversity, the development of depression was accompanied by increases in CRP and interleukin-6 (Miller 2012).

Structural changes

A number of studies have described structural brain changes that occur in association with stress and depression. Women with depression who also suffered from childhood maltreatment were found to have significantly reduced hippocampal volumes when compared to those with depression and no history of childhood maltreatment, as well as compared to healthy controls (Vythilingam 2002). Another study investigating the effect of childhood maltreatment in individuals with major psychiatric disorders including depression, demonstrated that maltreatment in childhood is associated with amygdala reactivity and hippocampal atrophy (Teicher 2013). A study in rats showed that chronic stress reduced hippocampal glycogen levels and induced hippocampal astrocyte atrophy and depression-like behaviour (Zhao 2017).

Other mechanisms

There is a small body of evidence for the role of several other systems in the association between poor psychosocial exposure and depression. The next paragraphs will discuss results from single studies that provide some evidence for these mechanisms. Further studies in these fields would be necessary before any conclusions can be drawn.

Cholecystokinin: Cholecystokinin is a peptide hormone involved in regulation of digestion and hunger. It is found in high concentrations in the brain. In one study, rats exposed to social defeat over four weeks displayed behavioural and biological markers of depression, which included HPA hyperactivity and hypercortisolaemia. The rats also demonstrated chronic cortical cholecystokinin (CCK) release. Use of a specific CCK antagonist prevented the development of behavioural and biological markers of depression. This suggests the potential involvement of CCK in the induction of depression-like behaviours following adverse social exposure (Becker 2007).

Tachykinins: Tachykinins are a family of neuropeptides that serve many diverse functions. Evidence from a study in rats proposed a role for the tachykinin substance P (SP) and neurokinin A (NKA) in the neurobiology of depression. Maternal deprivation in the rats predisposed to developing depression resulted in marked increases in levels of SP ($p<0.001$) in the periaqueductal grey (PAG), and NKA ($p<0.05$) in the PAG and the entorhinal complex (Husum 2008).

Spinophillin, synaptophysin and myelin basic protein: Spinophillin, synaptophysin (SVP) and myelin basic protein (MBP) are synaptic plasticity proteins. In a rodent model, rats exposed to social stress appeared to have significantly decreased levels of spinophilin in the prefrontal cortex ($p<0.05$) and amygdala ($p<0.02$), MBP in the prefrontal cortex (males only) and SVP in the prefronal cortex ($p=0.035$) compared to controls (Leussis 2008). The rats exposed to stress displayed altered behaviour similar to learned helplessness. This was more significant in female rats.

CONCLUSION

Numerous psychosocial factors are implicated in the aetiology of depression. The mechanisms by which these contribute to the disease process are being elucidated, and they overlap, such that more than one mechanism may be involved in the action of each of the psychosocial factors. This being the case, it can be surmised that the manipulation of each of these factors could be of benefit in the overall prevention and treatment of depression.

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Lucia Coulter, and Mina Ibrahimi are joint first authors, they and Ravi Patel carried out the evaluation of the papers.

Mark Agius suggested and supervised the project.

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