**Stress, Cortisol and Suicide Risk**

Daryl B. O’Connor1\*, Nicola Gartland1,

 & Rory C. O’Connor2

2020

**International Review of Neurobiology**

 1School of Psychology, University of Leeds, Leeds UK

4Suicidal Behavior Research Laboratory, Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK

Running head: Stress and suicide

Correspondence to:

Daryl B. O’Connor

School of Psychology

University of Leeds,

Leeds, UK

e: d.b.oconnor@leeds.ac.uk

t: ++44 113 3435727

**ABSTRACT**

Suicide is a global health issue accounting for at least 800,000 deaths per annum. Numerous models have been proposed that differ in their emphasis on the role of psychological, social, psychiatric and neurobiological factors in explaining suicide risk. Central to many models is a stress-diathesis component which states that suicidal behavior is the result of an interaction between acutely stressful events and a susceptibility to suicidal behavior (a diathesis). This article presents an overview of studies that demonstrate that stress and dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity, as measured by cortisol levels, are important additional risk factors for suicide. Evidence for other putative stress-related suicide risk factors including childhood trauma, impaired executive function, impulsivity and disrupted sleep are considered together with the impact of family history of suicide, perinatal and epigenetic influences on suicide risk.

**Introduction**

Every 40 seconds a person dies by suicide somewhere in the world (WHO, 2014). Suicide is a leading cause of mortality and is a major global health issue. It is estimated that 800,000 people die by suicide each year and there are 25 million nonfatal suicide attempts annually. As a result, for many decades, researchers have been exploring the causes of suicidal behavior with an aim to identify targets for suicide prevention. Numerous models have been proposed that differ in their emphasis on the role of psychological, social, psychiatric and neurobiological factors in predicting risk of suicide. (Mann et al., 1999; O’Connor, 2011; O’Connor & Kirtley, 2018; O’Connor & Nock, 2014; van Heeringen and Mann, 2014; van Orden et al., 2010). However, central to many models is a stress-diathesis component which states that suicidal behavior is a result of an interaction between acutely stressful events and a susceptibility to suicidal behavior (a diathesis). Research findings are accruing from post-mortem, neuroimaging and in-vivo studies that a trait diathesis is manifested in dysregulation of hypothalamic-pituitary-adrenal (HPA) axis stress response activity as well as in impairments of the serotonergic and noradrenergic neurotransmitter systems, in structural brain abnormalities and via epigenetic pathways (Mann, 2013; Turecki et al., 2012; van Heeringen et al., 2011; van Heeringen and Mann, 2014). Indeed, evidence is emerging to suggest that biomarkers of a trait diathesis following serious stressful and traumatic psychosocial events, independent of psychiatric co-morbidities, may be useful predictors of suicide risk (van Heeringen and Mann, 2014). However, surprisingly, a relatively small body of work has explored the role of stress and its concomitant biomarker, cortisol, in the context of suicide and suicide vulnerability. The aim of the current chapter is to provide an overview of studies that have investigated the role of stress and cortisol in the context of suicide risk together with studies that have examined other putative stress-related risk factors including childhood trauma, impaired executive function, impulsivity, disrupted sleep and perinatal and epigenetic influences on suicide risk.

The study of stress has a long history. Scientific interest dates back to the First World War, when soldiers were found to exhibit “shellshock”, an extreme reaction to the trauma of battle that was subsequently acknowledged to be a manifestation of post-traumatic stress disorder (Lazarus, 1999). Since this time, stress has become part of everyday vernacular, and there has been a marked increase in media coverage of stress, and as a result, this has led to increased research and public awareness. In terms of research, over many decades we have learned that when we experience stress, the HPA axis is activated and releases cortisol from the adrenal glands. Once released, cortisol has several important functions such as increasing access to energy stores, increasing protein and fat mobilisation, as well as regulating the magnitude and duration of inflammatory responses (Sapolsky et al., 2000). As such, cortisol is the primary effector hormone of the HPA axis stress response system. The HPA axis is regulated by a negative feedback system, whereby the hypothalamus and the pituitary gland have receptors that detect changes in cortisol levels. For example, cortisol secretion will be inhibited when circulating levels rise or it will be stimulated when levels fall. However, if the HPA axis is repeatedly activated, this will trigger increased cortisol output, thereby exposing bodily tissues to excessive concentrations of the hormone (McEwen, 1998; McEwen, 2000; Miller et al., 2007). Over time, such repetitive activation may contribute to tissue damage and future ill health by placing excessive pressure on various bodily systems including the HPA axis (known as allostatic load; McEwen, 1998). In addition, in the longer-term repeated activation may lead to dysregulation of the HPA axis as evidenced by flattened patterns of cortisol secretion across the day (including in the morning as well as in response to stressors). Indeed, in the context of suicide, evidence is accumulating to suggest a link between dysregulation of the HPA axis following chronic exposure to stress and vulnerability to suicide. An important issue this chapter will return to soon, but first a brief overview of the role of stress in the leading models of suicide.

*Stress–Diathesis Models of Suicidal Behavior*

Stress-diathesis models have a long history in the field of suicide research (see O’Connor et al., 2016). More than thirty years ago, Schotte and Clum (1987) put forward their distress-stress-hopelessness model of suicidal behavior. Therein, they posited and found evidence that impaired social problem-solving, a specific cognitive vulnerability factor acted as a diathesis; it was associated with suicide risk in the presence of stress. Since then, there has been an exponential growth in studies which have investigated how a range of different diatheses are associated with suicide risk under particular circumstances. Some of these diatheses are biological, others are cognitive in nature, and others still are personality factors. For example, there is a considerable body of research illustrating how distinct components of perfectionism increase one’s risk of suicidal thinking and behaviour in the presence of stress (O’Connor, 2007).

Another diathesis-stress model, developed by Mann and colleagues, was the clinical model of suicidal behaviour (Mann et al., 1999) where risk is posited to vary as a function of the interaction between psychiatric disorder (stressor) and a trait-like diathesis (e.g., impulsivity). This clinical model has been especially influential within psychiatry and clinical medicine. Whereas psychiatric disorder was a key element within the Mann et al. model, in 2008 Wenzel and Beck (2008) put forward a cognitive model of suicidal behavior which focuses on psychological treatment for suicidal behavior. Similar to the clinical model, it has adopted a distress-stress framework; however on this occasion, the model is psychological in orientation and is characterised by three main constructs: (i) dispositional vulnerability factors, (ii) cognitive processes associated with psychiatric problems and (iii) cognitive processes associated with suicidal behavior. When it was published, this latter model was noteworthy as it systematically identified theoretical components which could be targeted in the delivery of cognitive therapy for suicidal patients. More recently still there has been greater recognition of the heterogeneity of suicide risk and the identification of suicidal sub-types (Bernanke, Stanley, & Oquendo, 2017) in the context of the relationship between stress and suicide risk. To this end, Bernanke et al. (2017) have proposed two distinct phenotypes of suicidal behavior, with one being stress-responsive (governed by the cortisol system) and the other being non-stress responsive (associated with the serotonin system). As these two phenotypes have been suggested as only two of potentially numerous suicidal subtypes, more research is required to better describe the complexity of suicide risk in terms of diathesis-stress responses.

*The Integrated Motivational–Volitional Model of Suicidal Behavior*

Building upon the work of Mann et al. (1999) and Williams (1997), O’Connor (2011) published the integrated motivational-volitional (IMV) model of suicidal behavior in 2011 and refined in 2018 (O’Connor & Kirtley, 2018). The aim of this model was to bring together the disparate constructs from existing models of suicide and integrate them into a single overarching theoretical framework. At its core, the IMV model is a diathesis-stress model which tracks the development of suicide risk across three phases (See Figure 1). The first phase, the pre-motivational phase, outlines the context in which suicidal thinking and suicidal behavior emerge. In this phase, it is posited that vulnerabilities interact with life stress and environmental influences to increase the likelihood that suicidal thinking may occur. However, the presence of vulnerabilities and stress are not sufficient to explain the increase in suicide risk on their own. According to the model, in phase 2 (the motivational phase) suicidal thinking is more likely to emerge if an individual is trapped by feelings of defeat, humiliation and loss. Needless to say, a stressful life event is often a key driver to feelings of defeat or humiliation from which the individual is endeavoring to escape. Defeat and entrapment are part of the final common pathway to the emergence of suicidal thinking. The final phase of the IMV model, the volitional phase, is concerned with the transition from thinking about suicide to acting upon one’s thoughts of suicide, i.e., attempting suicide/dying by suicide. In this behavioural enaction phase, an individual is more likely to attempt suicide if volitional phase factors are also present. These volitional phase factors include having access to the means of suicide, being impulsive, being exposed to the suicidal behavior of others and having higher levels of fearlessness about death (O’Connor & Kirtley, 2018). In addition, although stress is not a key driver to the emergence of suicidal thoughts (beyond defeat and entrapment), it may be important in behavioural enaction (O’Connor et al., 2012). Across a series of studies, as predicted by the IMV model, we have shown that the presence of such factors differentiate individuals who think about suicide or self-harm from those who engage in suicidal behaviour or self-harm (Branley-Bell et al., 2019; Mars et al., 2018; Wetherall et al., 2018). In short, the IMV model is a useful model to consider the role of stress in the context of suicide risk.

[ Insert Figure 1 about here ]

 **Cortisol and suicide risk**

Broadly speaking previous research on HPA axis, cortisol and suicidal behavior has focused in three main areas: 1) assessing HPA axis functioning through pharmacological manipulation of the stress system (Mann and Currier, 2007; Pompili et al., 2010) using the Dexamethasone Suppression Test (DST; Carroll et al., 1968), 2) exploring naturally fluctuating cortisol levels and suicidal behavior and, 3) investigating HPA axis functioning following acute laboratory stressors in vulnerable and non-vulnerable groups.

*The Dexamethasone Suppression Test (DST) and suicide risk*

For many decades researchers have been concentrating scientific effort in identifying clinical and biological predictors of suicide. In particular, during the early 1980s, studies were emerging to suggest that death by suicide may be associated with HPA axis hyperactivity and that a useful clinical tool to detect HPA axis hyperactivity was the dexamethasone suppression test (DST). The DST usually involves participants receiving oral administration of the synthetic glucocorticoid dexamethasone (e.g., 1 mg) on one morning (say at 11am) and then plasma cortisol levels being assessed the following day in the morning (8am) and afternoon (4pm). Failure to suppress cortisol is evidence for HPA axis hyperactivity (due to glucocorticoid receptor insensivity) and has been found, in a number of studies, to predict completed suicide in different groups vulnerable to suicide (Coryell and Schlesser, 1981; Coryell et al., 2006; Jokinen and Nordstrom, 2008; Jokinen and Nordstrom, 2009; Norman et al., 1990). An early example comes from a study by Coryell and Schlesser (1981) in patients with major depressive disorder. These authors showed that the risk estimate of suicide was around 27% in a group of patients who failed to suppress cortisol levels following DST compared to only 3% in patients who exhibited cortisol suppression. Similarly, Jokinen and Nordstrom (2008), in a 17 year follow-up study of elderly hospitalised mood disorder patients, found that DST non-suppression doubled the suicide risk and that patients who had completed suicide had higher post-dexamethasone serum cortisol levels compared to survivors.

Other existing evidence from prospective DST studies suggests that HPA hyperactivity is more consistently associated with completed suicide compared to suicide attempt (Mann & Currier, 2007). For example, in a sample of patients who met the criteria for major depressive disorder, mania, or schizoaffective disorder, Coryell and Schlesser (2001) reported that there was a 14 fold higher risk of suicide in individuals who failed to exhibit suppression of their cortisol levels in the DST compared to individuals who did exhibit suppression. However, the evidence for a clear relationship between HPA hyperactivity, as assessed using the DST, and suicide attempt is mixed. Some studies have shown that DST suppression status is unable to distinguish between individuals who will attempt suicide and those who will not. Yet, as outlined above, other research findings have demonstrated DST non-suppression is associated with a higher rate of suicide attempts (see Mann & Currier, 2007 for a review). In their review of biological predictors of suicidal behaviour in individuals with mood disorders, Mann and Currier (2007) suggest that an important reason why non-suppression on the DST is predictive of completed suicide may be because it is also associated with “a failure to respond to antidepressant treatment or a tendency for early relapse such as shortly after discharge” (p. 10).

Nevertheless, a recent meta-analysis of biological risk factors for suicidal behaviours was inconclusive with regards to the prediction of future suicide behaviours (Chang et al., 2016). Of the small number of tests included (4 for suicide attempt, 8 for completed suicide), the results showed that DST suppression significantly predicted completed suicide (Odds Ratio = 1.75 [1.05-2.90]), but did not significantly predict suicide attempt (Odds Ratio = 1.49 [0.58-3.82]). Moreover, there was also some evidence of publication bias suggesting that if three missing cases (below the mean) were included, the weighted mean odds ratio would have been non-significant.

Therefore, taken together, whilst DST research has contributed enormously to knowledge regarding HPA axis dysregulation and suicide vulnerability, findings remain inconsistent and contradictory (McGirr et al., 2011; Chang et al., 2016). Pharmacological manipulation has also been criticised as it may not adequately mimic the size of the endogenous HPA response to naturally occurring stressors (Burke et al., 2005). In addition, more recent studies have begun to explore other aspects of the cortisol response, such as the diurnal cortisol rhythm (including morning and afternoon/evening cortisol levels; e.g., O’Connor et al., 2018) and cortisol reactivity to stressors (e.g., McGirr et al., 2010) in order to improve understanding of the role of the stress response system and the HPA axis in the context of suicide behaviours.

*Naturally fluctuating cortisol and suicidal behaviour*

The second broad area of research investigating the HPA axis and suicidal behaviour has focussed on exploring the relationship between naturally fluctuating (or baseline) cortisol levels and suicide behaviours. However, before outlining this research, it is important to note that cortisol has a distinct pattern over any 24 hour period. The diurnal pattern of cortisol production is characterised by two distinct components: the peak levels after awakening (i.e., the cortisol awakening response, CAR) and the diminishing levels throughout the rest of the day (i.e., the diurnal slope). As will be shown later, evidence is beginning to converge to suggest that lower (or blunted) CAR and a flatter cortisol slope across the day are associated with more negative health outcomes (e.g., O’Connor et al., 2009; 2020; Adam et al., 2017).

Similar to the findings from the DST studies, research that has explored the associations between naturally fluctuating cortisol and different aspects of suicide behaviours have yielded inconsistent findings. For example, Westrin et al. (1999) found elevated cortisol levels in patients who had recently attempted suicide compared to healthy controls, and Chatzittofis et al. (2013) found higher cortisol levels in (medication free) individuals who had attempted suicide compared to healthy volunteers. In contrast, Lindqvist and colleagues (2008) found that cortisol levels were significantly lower in individuals who had attempted suicide compared to controls and more recently McGirr et al. (2011) also showed patients with depressive disorders exhibited lower levels of cortisol. A number of methodological factors may account for these mixed findings including the timing of the cortisol sampling (morning vs afternoon/evening), study quality, absence of a control comparison group and age of the sample. Given these disparate findings, O’Connor and colleagues (2016) conducted a meta-analysis of all existing studies that has compared participants with at least one prior suicide *attempt* with a comparison group with no suicide attempt history in order: i) to estimate the strength and variability of the association between naturally fluctuating cortisol levels and suicidal behaviour and ii) to identify moderators of this relationship. The systematic literature identified 27 studies (N = 2226; 779 suicide attempters & 1447 non-attempters) that met the inclusion criteria. Overall, there was no significant effect of suicide group on cortisol. However, significant associations between cortisol and suicide attempts were observed as a function of age (see Figure 2). In studies where the mean age of the sample was below 40 years the association was positive (i.e., higher cortisol was associated with suicide attempts; r = .234, p < .001), and where the mean age was 40 or above the association was negative (i.e., lower cortisol was associated with suicide attempts; r = - .129, p < .001).

[ Insert Figure 2 about here ]

The authors concluded that these meta-analytic findings confirm that HPA axis activity, as indicated by age-dependent variations in naturally occurring cortisol levels, are associated with suicide attempt. Moreover, these findings suggest that a reversal in the association between cortisol and suicide attempt occurs when the average age of the sample is around 40 years (or older). This is not to imply that for any individual the shift would happen at 40 years, this is on average (and was the mean age for the sample of studies that were included in this meta-analysis). Nonetheless, what these analyses do show is that for older people the association is negative and for younger people it is positive and that the relationship between cortisol and suicide attempts is more nuanced and complicated than past research has recognised. Furthermore, these results may have implications for research studies (reviewed earlier) that have assessed HPA axis functioning using pharmacological manipulation of the stress system such as the DST and raises the possibility that age may also moderate cortisol suppression following DST manipulation.

 An important question remains unanswered by the findings of this meta-analysis. How might the reversal in the association be explained? It is likely that some of the variability will be accounted for by differences in study design, participants, suicide attempt measures and cortisol measurement. However, the findings are broadly consistent with McEwen’s notion of allostatic load, whereby if the HPA axis is repeatedly activated (by stress) the immune, cardiovascular and the endocrine systems are potentially exposed to excessive demands that over time can lead to dysregulation of these systems (McEwen, 1998; 2000). Moreover, in the context of suicide vulnerability, naturally fluctuating cortisol levels may provide an index (or proxy) for the amount of stress exposure that vulnerable individuals have encountered (O’Connor et al., 2009). This view is also consistent with Fries and colleagues (2005) account of the development of hypocortisolism, which suggests that the latter phenomenon occurs after a prolonged period of hyperactivity of the HPA axis due to chronic stress. Therefore, it would follow that in individuals who are older (40 years or older) and who have likely been exposed to stressful and traumatic events over a more sustained period, their HPA axis is more likely to have become dysregulated leading to lower secretion of cortisol levels. Such patterns have been observed in older Holocaust survivors with PTSD compared to those without PTSD (Yehuda et al., 1995). In contrast, younger individuals (less than 40 years), who have been exposed to serious stressful and psychosocial events, are likely to continue to exhibit an adaptive HPA axis stress response in the short to medium term (by releasing high levels of naturally fluctuating cortisol in response to their adverse and stressful environment).

 The findings from this meta-analysis are also important because they demonstrate that both types of observations (hypereactivity and hyporeactivity) may be valid and true in terms of the relationship between cortisol levels and suicide attempt, but may be accounted for by age-dependent exposure to stress over time. However, much more work is required to understand how naturally fluctuating cortisol-suicide vulnerability relations change prospectively. Future research ought to improve the quality of their studies in this area by utilising longitudinal designs (over many years) that incorporate assessments of suicidal behavior using clinical interviews or validated scales and ensure cortisol is measured at numerous time points across the day (morning, afternoon, evening) over multiple days (cf., Gartland et al., 2014) to capture the full profile of cortisol, in in doing so, use appropriate measurement (e.g. accuracy of sampling, accounting for variables known to influence cortisol etc).

*Cortisol reactivity to laboratory stress and suicide behaviour*

 The third broad area investigating the HPA axis and suicidal behaviour involves studies that have examined whether cortisol reactivity to a laboratory stress task can differentiate individuals who have a history of suicide attempt or ideation compared to individuals who have no such history (e.g., Giletta et al., 2015; McGirr et al., 2010; O’Connor et al., 2017). A leading study in this area was conducted by McGirr and colleagues (2010). These authors investigated whether dysregulation of the HPA axis to a laboratory stressor was a heritable risk factor for suicidal behavior. A sample of first-degree relatives of individuals who had died by suicide and matched controls were compared on their cortisol reactivity to a well-established psychosocial stressor known as the Trier Social Stress Test, a public speaking task and mental arithmetic task in front of a judgmental/negative audience (TSST; Kirschbaum et al., 1993). The results showed that the first-degree relatives exhibited a blunted (i.e. lower) cortisol response to stress. The authors have argued that their findings indicate that blunted cortisol reactivity to stress may represent a trait marker (or phenotype) of suicide risk.

More recently, two studies have used acute laboratory stressors to examine HPA axis responses to stress in vulnerable, at risk groups (Melhem et al., 2016; O’Connor et al., 2017). Melhem et al. (2016) examined cortisol responses to stress (i.e., the TSST) in a large sample of adult offspring of parents with mood disorder. This study found that an offspring suicide attempter group exhibited the lowest levels of total cortisol output during the stressor compared to an offspring with suicide-related behavior but never attempted suicide group, a non-suicidal offspring group and a healthy control group. Moreover, the suicide attempter group also showed the lowest baseline cortisol levels pre-TSST, but, contrary to expectations, there were no significant differences between groups on their measure of cortisol reactivity to stress.

A second study, conducted by O’Connor et al (2017), aimed to investigate whether cortisol reactivity to the Maastricht Acute Stress Test (MAST, Smeets et al., 2012) differentiated individuals who had previously made a suicide attempt from those who had thought about suicide (a suicide ideation group) and control participants. The MAST stress protocol was designed to be both physiologically and psychologically challenging by combining an uncontrollable physical stressor (i.e., a cold pressor challenge) with a social-evaluative (i.e., mental arithmetic) component (Smeets et al., 2012). The results showed that participants who had made a previous suicide attempt exhibited significantly lower cortisol response to the MAST compared to participants in the ideator and control groups (see Figure 3). Furthermore, participants who made an attempt within the past year exhibited a blunted cortisol response compared to participants with a more distant history of attempt. In addition, lower levels of cortisol in response to the MAST were associated with higher levels of suicidal ideation at 1-month follow-up in the suicide attempters group.

[ insert Figure 3 about here ]

In the O’Connor et al. (2017) study, the finding that participants who attempted suicide within the last 12 months appear to exhibit a blunted cortisol response to the laboratory stressor, compared to those with a lifetime history of suicide attempt, is a noteworthy observation. It is important because it suggests, in this study at least, that the cortisol response to stress may have returned to close to normal in the lifetime history group, although, these levels remain lower than in the control and ideator groups. This latter finding is promising as it is consistent with the notion that psychological and pharmacological intervention may yield benefits over time and help facilitate (partial) recovery of the HPA axis stress response system reflecting the higher cortisol levels in the lifetime history group. Therefore, an obvious next step would be for researchers to utilise longitudinal designs to explore

whether dysregulation of cortisol reactivity to stress is restored over time and to investigate if the HPA axis has the potential to return to normal following psychological (e.g., stress management interventions) and/or pharmacological intervention.

Taken together, the results from recent laboratory based cortisol reactivity studies suggest that blunted or lower HPA axis activity may increase risk for suicide attempt among vulnerable individuals. The findings also indicate that the HPA axis stress response system may have become dysregulated in individuals who have tried to take their own lives and as such may increase future suicide risk by impairing their ability to cope and adapt to acute and non-acute stressors.

**Childhood trauma – cortisol – suicide risk**

Childhood trauma has been identified as an important variable in the aetiology of suicide risk. For example, Marshall et al. (2013) found high levels of moderate and severe childhood trauma being associated with suicide attempt in a prospective cohort study of illicit drug users. In particular, they showed that severe sexual, physical and emotional childhood abuse conferred a substantial increased repeated suicide risk in adulthood. In another study, Sachiapone et al. (2007) found that high levels of childhood trauma were associated with suicide attempt in patients with unipolar depression. Similarly, a large longitudinal population-based study in the Netherlands (Enns et al., 2006) found that childhood neglect, psychological abuse and physical abuse were strongly associated with new onset suicide ideation and suicide attempt over a 3-year follow-up. More recently, O’Connor et al. (2018) found that 78.7% of participants with a history of suicide attempt reported exposure to at least one type of childhood trauma that was classified as moderate or severe compared to 37.7% and 17.8% in an ideation and control group, respectively.

Research has begun to focus on the links between childhood trauma and altered dynamics of the HPA axis. In the context of depression, Heim and colleagues (2000; 2008) have shown associations between childhood trauma and dysregulated HPA axis and to persistent sensitization of the stress response system. Childhood trauma effects on depression have also been explained by changes in glucocorticoid resistance, increased central corticotropin-releasing factor (CRF) activity, immune activation, and reduced hippocampal volume. In contrast, the results are less clear relating childhood trauma to cortisol activity (e.g., cortisol reactivity to stress). A study by Carpenter et al. (2007) showed decreasedcortisol levels in response to a laboratory stressor in childhood maltreated men who were never depressed. In a later study, the same team also found that women who reported childhood physical abuse displayed a blunted cortisol response to the TSST compared to women without physical abuse (Carpenter et al., 2011). These findings contradict earlier work by Heim et al. (2000) who showed that women who had a history of childhood abuse, with and without major depression, exhibited increasedcortisol to an acute laboratory stressor. However, more broadly, there is also converging evidence to suggest that early life adversity is associated with blunted cortisol reactivity to stress (e.g., Lovallo et al., 2012). For example, Lovallo et al. (2012) using data from the Oklahoma Family Health Patterns Project showed that experience of adversity predicted reduced cortisol response to an acute laboratory stress challenge.

Similarly, two recent studies by O’Connor and colleagues (2018; 2020) provide further support linking childhood trauma with blunted, or lower cortisol levels in response to stress and in naturalistic settings. In a laboratory-based study investigating the effects of childhood trauma on cortisol reactivity to an acute stressor and on resting cortisol levels, O’Connor et al. (2018) found that higher levels of trauma were associated with blunted cortisol reactivity to stress and lower resting cortisol levels. In particular, individuals who reported more than one moderate or severe type of childhood trauma exhibited the lowest cortisol levels in response to stress (see Figure 4) and at rest. In a second study, O’Connor et al. (2020), investigated for the first time, whether childhood trauma and daily stressors and emotions were associated with diurnal cortisol levels (i.e., cortisol levels following waking and the decline in cortisol levels across the rest of the day) over a 7-day study in individuals vulnerable to suicide. The results showed that participants with a history of suicide attempt (a suicide attempt group) or previously had thoughts of ending their life (an ideation group) released significantly lower cortisol upon awakening (CAR) and had a tendency towards flatter wake-peak to 12 hour (WP-12) cortisol slopes compared to individuals with no history of attempt or ideation. Moreover, childhood trauma was found to be associated with significantly lower CAR and a tendency towards flatter WP-12 cortisol slope and it had an indirect effect on suicide vulnerability group membership via lower daily CAR levels. The latter finding is particularly important as it shows, for the first time, that the effects of childhood trauma has indirect, as well as, direct effects on suicide vulnerability through lower levels of daily CAR.

[ insert Figure 4 about here ]

Taken together, the studies reviewed are important as they suggest that the experience of childhood trauma may predispose individuals to vulnerability to suicide in adulthood by leading to diminished HPA axis activity during awakening (and possibly a tendency towards a flatter diurnal profile across the day) as well as during stress. These findings are in keeping with a recent large scale meta-analysis by Adam and colleagues (2017) that showed flatter cortisol cycles were common to a wide range of mental and physical health outcomes. Moreover, these results are also consistent with the development of hypocortisolism posited by Fries et al (2005), as outlined earlier, which suggests that hypocortisolism occurs after a prolonged period of hyperactivity of the HPA axis due to chronic stress. Moreover, we have previously suggested that Lovallo’s (2013) conceptual model of addiction linking adverse life experiences in childhood and adolescence to adverse health outcomes in adulthood should be extended to suicide risk (O’Connor et al., 2018). Lovallo (2013) has argued that adverse life experiences cause modifications in frontolimbic brain function which may then lead directly to: 1) reduced stress reactivity, 2) altered cognition (characterised by a shift in focus to more short-term goals and impulsive response selection) and 3) unstable affect regulation. Lovallo (2013) has also suggested that these three negative consequences influence the development of a more impulsive behavioral style that may increase risk of addiction and the engagement in poor health behaviours. We believe that exhibiting a low or blunted CAR may be another negative consequence of the modification of brain function (Boehringer et al., 2015).

**Possible mechanisms linking stress and suicide risk**

The association between stress and suicide has been described in the models of suicide risk, and the role of the HPA axis in this relationship has been outlined above. However, there are likely to be multiple interrelated mechanisms that link stress and suicide. We will look at a few more possible pathways here that may help to answer the question: How does the experience of stress influence subsequent suicidal behaviour, sometimes decades later?

*Executive Function and Impulsivity*

One possible mechanism tying stress to suicide behaviour is executive function. Executive function is a broad term for a range of cognitive processes which manage and control thoughts, emotions and actions. These functions are required whenever we must pay attention to a task or are effortfully pursuing a goal; they help us to concentrate, consider possible courses of action, and make informed decisions. There are three core executive functions (Diamond, 2013): inhibition (this includes both the self-control of behaviour, as well was stopping interferences to thought necessary for selective attention), working memory (keeping information temporarily available for processing), and cognitive flexibility (the ability to switch from thinking about one concept to another, and also the ability to adapt thoughts or behaviours based on changes in the environment). The personality trait ‘impulsivity’ is related to executive function as it is characterised by behaviours which reflect impaired self-regulation. At the behavioural level, this might include poor planning, premature responding without considering the consequences of one’s actions, taking risks and an inability to delay gratification. These behaviours are suggested to originate from deficits in working memory, self-regulation of affect-motivation-arousal, internalisation of speech and behavioural analysis that affords hindsight, forethought, and goal-directed action (Barkley, 1997; Gvion & Apter, 2011). Impulsivity tends to lead to the underestimation of potential consequences of actions, has been shown to be positively associated with suicide risk (Brezo et al., 2006; Gvion & Apter, 2011; McGirr et al., 2009). Dysfunctional executive decision-making, such as cognitive rigidity, has also been suggested to result in suicidal mental states (Marzuk et al., 2005; for review see Bredemeier & Miller, 2015).

There is evidence to support the suggestion that both distal and proximal stress can have an effect on executive function. Greater levels of adverse life experience (such as physical and sexual abuse, separation from parents, and a family history of substance abuse) has been shown to predict lower working memory function, greater impulsive decision-making, and lower mental age (Lovallo, 2013; Lovallo et al., 2013). As rates of early adversity are high in individuals who have attempted suicide (O’Connor et al*.*, 2018), a mediated pathway is plausible where stressful experiences early in life alter cognitive function and that these altered thought processes can increase the risk of suicidal behaviours throughout the lifecourse.

However, a moderation pathway is also possible. Some aspects of executive control are considered heritable (Swan & Carmelli, 2002). McGirr et al. (2010) compared relatives of suicide completers with matched controls, and found no difference in baseline measures of executive function. However, performance on the Word-Colour Inhibition Test and Trail Making Test were differentially affected by a controlled laboratory stressor (the Trier Social Stress Test). Relatives of suicide completers failed to improve on executive function tests after the TSST, specifically on switching and inhibition conditions. This indicates a level of cognitive inflexibility in these individuals, but only after stress induction. McGirr and colleagues argue that cognitive inflexibility and a decreased ability to inhibit inappropriate action in response to real-life stressors could be potential factors that increase the risk of suicidal behaviour. These findings provide a possible moderation mechanism for the stress diathesis hypothesis, where ‘at risk’ individuals respond to stress with cognitions which could increase their risk of suicidal behaviour.

*Family history*

Suicidal behaviour aggregates in families (Brent et al., 1996, 2002; Kim et al*.*, 2005; McGirr et al., 2009, 2011). In a register-based case control study, Mittendorfer-Rutz et al. (2008) demonstrated that individuals whose sibling had attempted suicide were nearly 3.5 times more likely to attempt suicide themselves; a maternal suicide attempt carried a 2.7 times greater risk and paternal suicide attempt carried a 1.9 times greater risk. Genetic transmission of personality traits such as impulsivity has been one factor suggested to account for familial aggregation of suicidal behaviour in families (Mittendorfer-Rutz et al., 2008). However, it is difficult to tease out the relationships between stress, family history of suicide and suicidal behaviour because a family history of suicide can be a substantial source of stress in itself, as well as providing a potentially direct genetic/hereditary pathway to suicidal behaviour.

There is evidence that in a sample of depressed outpatients, a family history of suicide was associated with lower plasma cortisol levels (McGirr et al., 2011). This effect was independent of psychopathology and the individual’s previous suicide attempts, and suggests an overall down-regulation of HPA-axis activity in this group. However, from this we cannot determine where in the diurnal rhythm of cortisol the levels are reduced. Different points of this rhythm are implicated in different aspects of HPA functionality and reactivity; research focussing on HPA stress reactivity has used cortisol saliva samples alongside acute laboratory stressors to determine whether differences in cortisol stress reactivity exist between these two groups.

Evidence from first-degree family members of suicide completers shows low (or blunted) salivary cortisol responses to an acute laboratory stressor, compared to controls (McGirr et al., 2010). O’Connor et al. (2017) also found that having a family history of suicide was associated with the lowest cortisol response to an acute laboratory stressor. Melhem and colleagues (2016) found that offspring of parents who had attempted suicide exhibited lower levels of total cortisol output during an acute laboratory stressor compared to offspring of parents with mood disorder but had not attempted suicide, but they did not find significant differences in cortisol reactivity to the task between these groups. These studies tentatively suggest that having a family history of suicide is associated with blunted HPA axis stress reactivity, and are consistent with the idea that dysregulation of the stress response system may be a heritable risk factor for suicidal behaviour. Again, this dysregulation of the stress system would act as a moderation pathway, where the relationship between stress and suicidal behaviour is strengthened due to the dysregulated HPA axis response to stress in these individuals. Indeed, in a sample of suicide attempters, lower levels of cortisol in response to acute stress have been shown to predict higher levels of suicidal ideation one month later (O’Connor et al., 2017). Therefore, HPA axis dysregulation may exacerbate the stress-suicide relationship such that the link between stress and suicide is stronger for those with a family history of suicide.

However, it cannot be determined whether this dysregulation occurs through a genetic commonality between family members or whether it is an effect of the stress of losing a close family member to suicide. Do members of families with a history of suicide have a shared genetic vulnerability or diathesis, which increases the risk of suicide in the face of stress? Or has the stressful experience of losing a close relative to suicide caused the dysregulation of the HPA axis in these individuals? Further research is warranted, but will require carefully controlled groups to compare those highly affected by family history of suicide and those less affected, for example where the parental suicide attempt was before the child was born. Adoption studies could also provide valuable insights.

*Perinatal Influences and Epigenetics*

Familial influences on suicide risk may also work through adverse in-utero and perinatal conditions. In a recent systematic review, Orri and colleagues (2019) assessed family and parental characteristics during pregnancy and around the time of birth in relation to suicide, suicide attempt and suicide ideation throughout the lifespan. Factors associated with higher suicide risk included high birth order, teenage mothers, single mothers, low maternal and paternal education level, fetal growth and small for gestational age. Only one study in this review directly measured maternal stress, in the form of bereavement (Class et al*.*, 2014). This Swedish population-based study of over 2,000,000 offspring found that the death of a first degree relative of the mother during the first postnatal year increased the risk of suicide attempt and completed suicide in offspring. Orri and colleagues also argue that factors such as teenage mothers, single mothers, and low socioeconomic position at birth may reflect a wider adverse psychosocial environment which would be associated with greater levels of maternal stress both during pregnancy and the perinatal period. While other psychosocial mechanisms are likely to be at work, there is some evidence that maternal stress may influence foetal brain development through epigenetic (non-genetic influences on gene expression) or gene-by-environment interaction mechanisms.

There is evidence that prenatal anxiety is associated with higher levels of waking cortisol in children at age 10, suggesting that prenatal experiences can influence HPA activity in offspring (O’Connor et al., 2005). Turecki and colleagues (2012) outline a model to explain increased risk of suicide in individuals exposed to early-life adversity through HPA axis dysregulation (Figure 5). Early life stress is proposed to increase methylation (addition of a methyl group to a DNA nucleotide) of hippocampal glucocorticoid receptor (GR) genes, which disrupts the GR gene expression. One of the studies that support this suggestion demonstrated increased methylation of the GR promoter gene in adolescent children in cases where their mothers were exposed to intimate partner violence during pregnancy (Radtke et al*.*, 2011). The methylation status of the GR gene in the mothers was not affected by intimate partner violence, but the prenatal stress experienced appears to have had a long-lasting impact on the gene expression of their children. This may provide a mechanism to explain findings that prenatal stress alters HPA axis activity later in life (O’Connor et al., 2005). These hippocampal receptors play a crucial role in the negative feedback loop controlling cortisol levels, and thus alterations in the number and sensitivity of these receptors influences the body’s ability to regulate the amount of circulating cortisol. This, in turn, is proposed to lead to the development of emotional, behavioural and cognitive phenotypes (e.g. chronic anxiety, impulsivity) and cognitive alterations (e.g. executive function, as discussed above) which are associated with increased suicide risk. For comprehensive reviews of the animal and human research into the epigenetics of stress in the early years of life, see Roy and Dwivedi (2017), Turecki et al. (2012), and Turecki and Meaney (2016). For a review of the evidence linking epigenetic changes with suicidal behaviour, see Labonté and Turecki (2010).

[ insert Figure 5 about here ]

Epigenetic research has also suggested that the neuropeptide oxytocin, which is sensitive to environmental stress, may be implicated in the transmission of maternal stress during pre- and postnatal periods (Toepfer et al., 2018). Further investigation for the role of epigenetic mechanisms in suicidal behaviour comes from research assessing GR gene expression in post-mortem hippocampi obtained from suicide completers with a history of childhood abuse, suicide completers with no history of childhood abuse, and controls (McGowan et al., 2009; Labonte et al., 2012). These studies demonstrate reduced hippocampal GR gene expression in suicide victims with a history of childhood abuse in comparison to suicide victims with no history of abuse and controls, while there was no difference between the non-abused and control groups. This suggests that while childhood abuse is associated with epigenetic changes in gene expression which influences HPA function, but does not provide evidence for a link between these changes and risk of suicidal behaviour.

Using a whole genome-wide approach to investigate DNA methylation in the hippocampi of suicide completers, Labonte and colleagues (2013) confirmed their previous findings that promoter DNA methylation levels are greater in suicide completers compared to controls. Interestingly, they report increased levels of methylation in promoters of four specific genes known to be involved in cognitive processes related to executive function (e.g. learning, working memory, behaviour). Therefore, taken with previous findings that childhood abuse is related to DNA methylation, this provides initial evidence for an epigenetic mechanism where stress in childhood leads to changes in hippocampal gene expression which could cause impairments in executive function that increase the risk of suicide.

*Sleep*

Another mechanism by which stress could potentially affect suicide behaviours is through disruption to sleep. There is strong evidence that insomnia and nightmares are associated with increased suicide risk (Bernert et al., 2015; Nadorff et al., 2011; 2013; Pigeon et al., 2012). However, causality and third variable effects are hard to establish. Research to date has mainly focussed on psychological mediators of this effect, identifying defeat and entrapment, as well as emotional regulation, social isolation and negative appraisals as mediators of this effect (Russell et al., 2018; for review see Littlewood et al., 2017). However, it has also been suggested that disturbances in sleep may lead to cognitive impairments and impulsive decision making (Porras-Segovia et al., 2019). Interestingly, evidence suggests that the duration of sleep disturbance (e.g. for how long an individual has been experiencing nightmares) is a significant factor in risk of suicide, where longer durations are associated with increased risk (Golding et al., 2015; Nadorff et al., 2013).

The main issue with this body of literature is that it consists predominantly of cross-sectional studies which cannot determine the direction of the relationships between sleep and suicidal behaviours. A recently ecological momentary assessment study by Littlewood and colleagues (2019) addressed this issue and demonstrated a unidirectional relationship between sleep disturbance and suicidal thoughts. Objectively and subjectively determined short sleep duration, and poor sleep quality predicted more severe next-day suicidal thoughts; there was no relationship between suicidal ideation and sleep duration or quality the following night. This study establishes the causal direction of this day-to-day relationship, which is a valuable step in our understanding. However, reciprocal and bidirectional relationships are still possible along longer time scales and merit investigation.

High levels of stress are associated with both chronic insomnia symptoms and recurrent short sleep duration (Abell et al., 2016). Stress effects sleep not only in terms of sleep quality, but it also disrupts the EEG spectral profile of sleep in both healthy participants and patients with chronic insomnia (Ackermann et al., 2019; Hall et al., 2000). In insomnia patients, the tendency to experience stress-related intrusive thoughts is associated with poorer subjective sleep quality, and higher levels of subjective stress burden are associated with decreases in delta activity which is an indication of hyperarousal during sleep (Hall et al., 2000). Therefore, different aspects of stress may influence distinct characteristics of sleep. In another study with healthy participants, an acute laboratory-based stressor was used to investigate the immediate effects of psychosocial stress on napping; this form of acute stress increased sleep latency, but also reduced slow wave activity and enhanced alpha activity (Ackermann et al., 2019).

Sleep disruption also influences HPA axis activity. While some older research did not find associations between measures of sleep quality or insomnia with salivary cortisol, more recent research with improved methodologies have confirmed an effect of shorter sleep and poor sleep quality on diurnal cortisol (Castro-Diehl et al*.*, 2015). Cross-sectional research has also found that those who report frequent nightmares show a blunted CAR on a working day, but not on a leisure day (Nagy et al., 2015). In an impressive 10-year follow up in the Whitehall II study, Abell and colleagues (2016) provide evidence that recurrent short sleep (measured at 3 time points during the 10-year period) was associated with a flatter diurnal cortisol pattern, characterised by higher levels of cortisol later in the day. A steeper CAR was also observed in those who reported insomnia symptoms at all three timepoints and those reporting short sleep twice, compared to those who did not report sleep problems at any time point. These findings have yet to be related to suicide risk, but given the accumulating evidence for different aspects of HPA axis dysregulation in suicide risk and the potential pathways between stress, sleep, and cortisol, this seems a promising avenue for future research.

However, the inter-relations of these variables are complex and potentially reciprocal and therefore are not easy to disentangle. While it is possible that there is a direct pathway from stress to suicidal behaviour via sleep disturbance, it is likely that any such mechanism will also interact with the other variables we have mentioned here. For example, disruption to sleep patterns could influence executive function, and there is evidence that familial risk for insomnia can be measured through HPA axis dysregulation in response to stress (Drake et al*.*, 2017). Disruption to sleep also has been hypothesised as a stressor in itself, contributing to allostatic load (McEwen, 2006). This idea is consistent with the findings suggesting that duration of insomnia or nightmares is predictive of suicidal risk, as the cumulative effects of ongoing sleep disturbance leads to wear and tear on bodily systems. Research into the interconnections of these mechanisms could provide vital and effective insights for the development of interventions, through the identification of vulnerable populations and provision of targeted tools to reduce the risk of suicide in vulnerable populations.

**General conclusion**

This article has presented an overview of studies that demonstrate that stress and dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity, as measured by cortisol levels, are important additional risk factors for suicide. It has also highlighted the IMV model of suicide as a useful framework to understand suicide risk. Evidence for other stress-related putative suicide risk factors including childhood trauma, impaired executive function, impulsivity and disrupted sleep have been shown to play an important role together with family history of suicide, perinatal and epigenetic influences on suicide risk. In order to further improve our understanding of the precise pathways through which stress and HPA axis dysregulation contribute to suicide, there is a need for future research to investigate simultaneously the impact of distal *and* proximal determinants of suicidal behavior.

**References**

Abell, J. G., Shipley, M. J., Ferrie, J. E., Kivimäki, M., & Kumari, M. (2016). Recurrent short sleep, chronic insomnia symptoms and salivary cortisol: A 10-year follow-up in the Whitehall II study. *Psychoneuroendocrinology, 68*, 91-99. doi: 10.1016/j.psyneuen.2016.02.021

Ackermann, S., Cordi, M., La Marca, R. Seifritz, E., & Rasch, B. (2019). Psychosocial stress before a nap increases sleep latency and decreases early slow-wave activity. *Frontiers in Psychology, 10*, 20. doi: 10.3389/fpsyg.2019.00020

Adam, E. K., Quinn, M. E., Tavernier, R., McQuillan, M. T., Dahlke, K. A., & Gilbert, K. E. (2017). Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology,83,*25–41

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121*, 65–94.

Bernanke, J.A., Stanley, B.,H., & Oquendo, M.A. (2017). Toward fine-grained phenotyping of suicidal behavior: the role of suicidal subtypes. *Molecular Psychiatry*, 22, 1080 – 1081

Bernert, R. A., Kim, J. S., Iwata, N. G., & Perlis, M. L. (2015). Sleep disturbances as an evidence-based suicide risk factor. *Current Psychiatry Reports, 17*, 1–9.

Branley-Bell, D., O’Connor, D. B., Green, J. A., Ferguson, E., O’Carroll, R. E., & O’Connor, R. C. (2019). Distinguishing suicide ideation from suicide attempts: Further test of the Integrated Motivational-Volitional Model of Suicidal Behaviour. *Journal of Psychiatric Research*, 117, 100–107.

Bredemeier, K., & Miller, I. W. (2015). Executive function and suicidality: A systematic qualitative review. *Clinical Psychology Review, 40,* 170-183. doi:10.1016/j.cpr.2015.06.005

Brent, D. A., Bridge, J., Johnson, B. A., & Connolly, J. (1996). Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. *Archives of General Psychiatry, 53(12),* 1145-1152. doi: 10.1001/archpsyc.1996.01830120085015

Brent, D. A., Oquendo, M., Birmaher, B., Greenhill, L., Kolko, D., Stanley, B., *et al.* (2002). Familial pathways to early-onset suicide attempt: risk for suicidal behavior in offspring of mood-disordered suicide attempters. *Archives of General Psychiatry, 59(9),* 801-807. doi: 10.1001/archpsyc.59.9.801

Brezo, J., Paris, J., & Turecki, G. (2006). Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. *Acta Psychiatrica Scandinavica, 113*, 180–206. doi: 10.1111/j.1600-0447.2005.00702.x

Carroll, B., Martin, F., & Davies, B. (1968). Resistance to suppression by dexamethasone of plasma 11-OHCS levels in severe depressive illness. *British Medical Journal,* 3, 285.

Carpenter, L.L., Shattuck, T.T., Tyrka, A.R., Geracioti, T.D., & Price, L.H. (2011). Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology*, 214, 367-375.

Carpenter, L.L., Carvalho, J.P., Tyrka, A.R., Wier, L.M., Mello, A.F., Mello, M.F., Anderson, G.M., Wilkinson, C.W., & Price, L.H. (2007). Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry*, 62*,* 1080-1087.

Chang, B.P., Franklin, J.C., Ribeiro, J.D., Fox, K.R., Bentley, K.H., Kleinman, E.M., & Nock, M.K. (2016). Biological risk factors for suicidal behaviors: a meta-analysis. *Translational Psychiatry*, 6, e887.

Chatzittofis, A., Nordström, P., Hellström, C., Arver, S., Asberg, M., Jokinen J., 2013. CSF 5-HIAA, cortisol and DHEAS levels in suicide attempters. Eur Neuropsychopharmacology23, 1280–7.

Class, Q. A., Abel, K. M., Khashan, A. S., Ricket, M. E., Dalman, C., Larsson, H., *et al.* (2014). Offspring psychopathology following preconception, prenatal, and postnatal maternal bereavement stress. *Psychological Medicine, 44(1*), 71-84. doi:10.1017/S0033291713000780

Coryell, W., Schlesser, M.A. (1981). Suicide and the dexamethasone suppression test in unipolar depression. *American Journal of Psychiatry*,138, 1120-1121.

Coryell, W., Schlesser, M.A. (2001). The dexamethasone suppression test and suicide prediction. *American Journal of Psychiatry*, 158, 748-753.

Coryell, W., Young, E., & Carroll, B. (2006). Hyperactivity of the hypothalamic-pituitary-adrenal axis and mortality in major depressive disorder. *Psychiatry Research*,142, 99-104.

Diamond, A. (2013). Executive Functions. *Annual Review of Psychology, 64*, 135-168. doi:10.1146/annurev-psych-113011-143750

Drake, C. L., Cheng, P., Almeida, D. M., Roth, T. (2017). Familial risk for insomnia is associated with abnormal cortisol response to stress. *Sleep, 40(10)* doi: 10.1093/sleep/zsx143

Enns, M.W., Cox, B.J., Afifi, T.O., de Graff, R., ten Have, M. & Sareen, J. 2006. Childhood adversities and risk for suicide ideation and attempts: a longitudinal population-based study. *Psychological Medicine*, 36, 1769-1778.

Fries, E., Hesse, J., Hellhammer, J., Hellhammer, D.H. (2005). A new view of hypocortisolism. *Psychoneuroendocrinology,* 30, 1010-1016.

Gartland, N., O’Connor, D.B. Lawton, R & Bristow, M. (2014). Exploring day-to-day dynamics of daily stressor appraisals, physical symptoms and the cortisol awakening response. *Psychoneuroendocrinology*, 50, 130-138.

Giletta, M., Calhoun, C. D., Hastings, P. D., Rudolph, K. D., Nock, M. K., & Prinstein, M. J. (2015). Multi- level risk factors for suicide ideation among at-risk adolescent females: The role of hypothalamic- pituitary-adrenal axis responses to stress. *Journal of Abnormal Child Psychology, 43*, 807-820.

Golding, S., Nadorff, M. R., Winer, E. S., Ward, K. C. (2015). Unpacking sleep and suicide in older adults in a combined online sample. *J Clin Sleep Med, 11(12),* 1385 –1392.

Gvion, Y., & Apter, A. (2011). Aggression, impulsivity, and suicide behavior: A review of the literature. *Archives of Suicide Research, 15*, 93–112. doi: 10.1080/13811118.2011.565265

Hall, M., Buysse, D. J., Nowell, P. D., Nofzinger, E. A., Houck, P., Reynolds, C. F., Kupfer, D. J. (2000). Symptoms of stress and depression as correlates of sleep in primary insomnia. *Psychosomatic Medicine*, 62, 227-230. doi: 0033-3174/00/6202-0227

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., & Nemeroff, C.B. (2000). Pituitary–adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA, 284, 592–597.

Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., & Nemeroff, C.B. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology*, 33, 693-710.

Jokinen, J., & Nordstrom, P. (2008). HPA axis hyperactivity as suicide predictor in elderly mood disorder inpatients. *Psychoneuroendocrinology* 33, 1387-1393.

Jokinen, J., Nordstrom, P. (2009). HPA axis hyperactivity and attempted suicide in young adult mood disorder inpatients. *Journal of Affective Disorders*,116, 117-120.

Kim, C. D., Seguin, M., Therrien, N., Riopel, G., Chawky, N., Lesage, A. D., *et al.* (2005). Familial aggregation of suicidal behavior: a family study of male suicide completers from the general population. *American Journal of Psychiatry, 162(5),* 1017-1019. doi:10.1176/appi.ajp.162.5.1017

Kirschbaum, C., Pirke, K.M., & Hellhammer, D.H. (1993). The ‘Trier Social Stress Test’—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 28, 76-81.

Labonté, B., Suderman, M., Maussion, G., Lopez, J. P., Navarro-Sánchez, L., Yerko, V., et al., (2013). Genome-wide methylation changes in the brains of suicide completers. *American Journal of Psychiatry, 170*, 511-520.

Labonté, B. & Turecki, G. (2010). The epigenetics of suicide: Explaining the biological effects of early life environmental adversity. *Archives of Suicide Research, 14*, 291-310. doi:10.1080/13811118.2010.524025

Labonté, B., Yerko, V., Gross, J., Mechawar, N., Meaney, M. J., Szyf, M., *et al*. (2012). Differential Glucocorticoid Receptor Exon 1B, 1C, and 1H Expression and Methylation in Suicide Completers with a History of Childhood Abuse. *Biological Psychiatry, 72,* 41-48. doi:10.1016/j.biopsych.2012.01.034.

Lazarus, R.S. (1999). *Stress and emotion: a new synthesis*. London: Springer.

Lindqvist, D., Isaksson, A., Träskman-Bendz, L., Brundin, L. (2008). Salivary cortisol and suicidal behavior--a follow-up study. *Psychoneuroendocrinology* 33, 1061–8.

Lindqvist, D., Traskman-Bendz, L., & Vang, F. (2008). Suicidal Intent and the HPA-axis characteristics of Suicide Attempters with Major Depressive Disorder and Adjustment Disorder. *Archives of Suicide Research,* 12, 197-207.

Littlewood, D. L., Kyle, S. D., Carter, L., Peters, S., Pratt, D., & Gooding, P. (2019). Short sleep duration and poor sleep quality predict next-day suicidal ideation: an ecological momentary assessment study. *Psychological Medicine, 49,* 403-411. doi:10.1017/S0033291718001009

Littlewood, D., Kyle, S. D., Pratt, D., Peters, S., Gooding, P. (2017). Examining the role of psychological factors in the relationship between sleep problems and suicide. *Clinical Psychology Review, 54,* 1–16. doi:10.1016/j.cpr.2017.03.009

Lovallo, W. R. (2013). Early life adversity reduces stress reactivity and enhances impulsive behavior: Implications for health behaviors. *International Journal of Psychophysiology*, 90(1), 8-16. doi: 10.1016/j.ijpsycho.2012.10.006

Lovallo, W. R., Farag, N. H., Sorocco, K. H., Acheson, A., Cohoon, A. J., & Vincent, A. S. (2013). Early Life Adversity contributes to impaired cognition and impulsive behaviour: Studies from the Oklahoma Family Health Patterns Project. *Alcoholism: Clinical & Experimental Research, 37(4),* 616-623. doi:10.1111/acer.12016

Mann, J.J. (2013). The serotonergic system in mood disorders and suicidal behaviour. *Philosophical Transactions of the Royal Society London B: Biological Sciences*, 368, 20120537.

Mann, J.J., & Currier, D. (2007). A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. *Archives of Suicide Resesarch*,11, 3-16.

Mann, J.J., Waternaux, C., Haas, G.L., & Malone, K.M. (1999). Towards a clinical model of suicidal behaviour in psychiatric patients. *American Journal of Psychiatry*, 156, 181-189.

Mars, B., Heron, L., Klonsky, D., Moran, P., O’Connor, R.C., Tilling, K., Wilkinson, P., Gunnell, D. (2018). What distinguishes adolescents with suicidal thoughts from those who have attempted suicide? A population-based birth cohort study. *Journal of Child Psychology and Psychiatry.*

Marshall, B.D.L., Galea, S., Wood, E., & Kerr, T. (2013). Longitudinal associations between types of childhood trauma and suicidal behaviour among substance users: A cohort study. *American Journal of Public Health*, 103, e69-e75.

Marzuk, P. M., Hartwell, N., Leon, A. C., & Portera, L. (2005). Executive functioning in depressed patients with suicidal ideation. *Acta Psychiatrica Scandinavica, 112*, 294–301.

McEwen, B.S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338, 171-179.

McEwen, B.S., 2000. Allostasis and allostatic load: Implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108-124.

McEwen, B. S. (2006). Protective and damaging effects of stress mediators: central role of the brain. *Dialogues in Clinical Neuroscience, 8(4),* 367-381.

McGirr, A., Alda, M., Séguin, M., Cabot, S., Lesage, A., & Tureki, G. (2009). Familial aggregation of suicide explained by cluster B traits: a three-group family study of suicide controlling for major depressive disorder. *American Journal of Psychiatry, 166(10),* 1124-1134. doi: 10.1176/appi.ajp.2009.08111744

McGirr, A., Diaconu, G., Berlim, M. T., Pruessner, J. C., Sablé, R., Cabot, S., & Turecki, G. (2010). Dysregulation of the sympathetic nervous system, hypothalamic-pituitary-adrenal axis and executive function in individuals at risk for suicide. *Journal of Psychiatry & Neuroscience, 35(6),* 399-408.

McGirr, A., Diaconu, G., Berlim, M. T., Turecki, G. (2011). Personal and family history of suicidal behavior is associated with lower peripheral cortisol in depressed outpatients. *Journal of Affective Disorders, 131,* 368–373.

Melhem, N. M., Keilp, J. G, Porta, G., Oquendo, M. A., Burke, A., Stanley, B., *et al.* (2016). Blunted HPA axis activity in suicide attempters compared to those at high risk for suicidal behavior. Neuropsychopharmacology, 41, 1447-1456. doi:10.1038/npp.2015.309

Miller, G.E., Chen, E., Zhou, E.S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological Bulletin, 133, 25-45.

Mittendorfer-Rutz, E., Rasmussen, F., & Wasserman, D. (2008). Familial clustering of suicidal behaviour and psychopathology in young suicide attempters: A register-based nested case control study. *Social Psychiatry and Psychiatric Epidemiology, 43,* 28-36. doi:10.1007/s00127-007-0266-0

Nadorff, M. R., Nazem, S., Fiske, A. (2013). Insomnia symptoms, nightmares, and suicide risk: duration of sleep disturbance matters. *Suicide Life Threat Behav, 43(2),* 139 –149.

Nadorff, M. R., Nazem, S., Fiske, A. (2011). Insomnia symptoms, nightmares, and suicidal ideation in a college student sample. *Sleep*, *34(1),* 93–98.

Nagy, T., Salavecz, G., Simor, P., Purebl, G., Bódizs, R., Dockray, S., *et al.* (2015. Frequent nightmares are associated with blunted cortisol awakening response in women. Phyisology & Behavior, 147, 233-237. doi: 10.1016/j.physbeh.2015.05.001

Norman, W.H., Brown, W., Miller, I.W., Keitner, G.I., & Overholser, J. (1990). The dexamethasone suppression test and completed suicide. *Acta Psychiatrica Scandinavica,* 81, 120-125.

O’Connor, D.B., Branley-Bell, D., Green, J., Ferguson, E., O’Carroll, R., O’Connor, R.C. (2020). Effects of Childhood Trauma, Daily Stress and Emotions on Daily Cortisol Levels in Individuals Vulnerable to Suicide. *Journal of Abnormal Psychology*, in press.

O’Connor, D.B., Ferguson, E., Green, J., O’Carroll, R.E., & O’Connor, R.C. (2016). Cortisol and suicidal behavior: A meta-analysis. *Psychoneuroendocrinology*, 63, 370-379.

O’Connor, D. B., Green, J. A., Ferguson, E., O’Carroll, R. E., O’Connor, R. C. (2018). Effects of childhood trauma on cortisol levels in suicide attempters and ideators. *Psychoneuroendocrinology, 88,* 9-16.

O’Connor, D.B., Green, J., Ferguson, E., O’Carroll, R.E., & O’Connor, R.C. (2017). Cortisol reactivity and suicidal behavior: investigating the role of hypothalamic-pituitary-adrenal (HPA) axis responses to stress in suicide attempters and ideators, *Psychoneuroendocrinology*, 75, 183-191.

O’Connor, D.B., Hendrickx, H., Dadd, T., Talbot, D., Mayes, A., Elliman, T., Willis, T. & Dye, L. (2009). Cortisol Awakening Rise in Middle-aged Women in Relation to Chronic Psychological Stress. *Psychoneuroendocrinology*, 34, 1486-1494.

O’Connor, R.C. (2011). Towards an Integrated Motivational-Volitional of Suicidal Behaviour. In R O’Connor, S Platt, & J Gordon (Eds.) *International Handbook of Suicide Prevention: Research, Policy and Practice.* Wiley Blackwell

O’Connor, R.C. (2007). The relations between perfectionism and suicide risk: A systematic review. *Suicide and Life-Threatening Behavior*, 37, 698-714

O'Connor, R.C., Cleare, S., Eschle, S., Wetherall, K., Kirtley, O.J. (2016). The Integrated Motivational-Volitional Model of Suicidal Behaviour: An Update. In O'Connor, R.C., & Pirkis, J. (Eds.) (2016).  *The International Handbook of Suicide Prevention (2nd ed.).* Chichester: Wiley-Blackwell.

O'Connor, R.C., Kirtley, O.J. (2018). The Integrated Motivational-Volitional Model of Suicidal Behaviour. *Philosophical Transactions of the Royal Society B.*373: 20170268.

O’Connor, R.C., Nock, M. (2014). The psychology of suicidal behaviour. Lancet Psychiatry 1, 73–85.

O’Connor, R.C., Rasmussen, S., & Hawton, K. (2012). From Thoughts to Action: Distinguishing Adolescents Who Think About Self-harm From Those Who Engage in Self-harm. *British Journal of Psychiatry*, 200, 330-335.

O’Connor, T. G., Ben-Shlomo, Y., Heron, J., Golding, J., Adams, D., & Glover, V. (2005). Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological Psychiatry, 58*, 211–217. doi:10.1016/j.biopsych.2005.03.032

Orri, M., Gunnell, D., Richard-Devantoy, S., Bolanis, D., Boruff, J., Turecki, G., & Geoffroy, M. (2019). In-utero and perinatal influences on suicide risk: a systematic review and meta-analysis. *Lancet Psychiatry, 6(6)*, 477-492.

Pompili, M., Serafini, G., Innamorati, M., Moller-Leimkuhler, A.M., Giupponi, G., Girardi, P.... Lester, D. (2010). The hypothalamic-pituitary-adrenal axis and serotonin abnormalities: a selective overview for the implications of suicide prevention. European Archives of Psychiatry and Clinical Neuroscience, 260, 583-600.

Pigeon, W. R., Pinquart, M., & Conner, K. (2012). Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *Journal of Clinical Psychiatry, 73,* e1160–e1167.

Porras-Segovia, A., Pérez-Rodríguez, M. M., López-Esteban, P., Courtet, P., Barrigón, M. L, López-Castromán, J., *et al.* (2019). Contribution of sleep deprivation to suicidal behaviour: A systematic review. *Sleep Medicine Reviews, 44,* 37-47. doi: 10.1016/j.smrv.2018.12.005

Radtke, K. M., Ruf, M., Gunter, H. M., Dohrmann, K., Schauer, M., Meyer, A., & Elbert, T. (2011). Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. *Translational Psychiatry*, 1, e21. doi:10.1038/tp.2011.21

Roy, B. & Dwivedi, Y. (2017). Understanding epigenetic architecture of suicide neurobiology: A critical perspective. *Neuroscience & Biobehavior Reviews, 72*, 10-27. doi:10.1016/j.neubiorev.2016.10.031

Russell, K., Rasmussen, S., & Hunter, S. C. (2018). Insomnia and nightmares as markers of risk for suicidal ideation in young people: Investigating the role of defeat and entrapment. *Journal of Clinical Sleep Medicine, 14(5)*, 775-784. doi:10.5664/jcsm.7104

Sachiapone, M., Carli, V., Cuomo, C., & Roy, A. (2007). Childhood trauma and suicide attempts in patients with unipolar depression. *Depression and Anxiety*, 24, 268-272.

Sapolsky, R.M., Romero, L.M., & Munck, A.U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*, 55-89.

Schotte, D.E., & Clum, C.A. (1987). Problem-solving skills in psychiatric patients. *Journal of Consulting & Clinical Psychology*, 55, 49-54.

Smeets, T., Cornelisse, S., Quaedflieg, C., Meyer, T., Jelicic, M., & Merckelbach, H. (2012). Introducing the Maastricht Acute Stress Test (MAST): A quick and non-invasive approach to elicit robust autonomic and glucocorticoid stress responses. *Psychoneuroendocrinology*, 37, 1998–2008.

Swan, G. E., & Carmelli, D. (2002). Evidence for genetic mediation of executive control: A study of aging male twins. *Journal of Gerontology: Psychological Sciences, 57B(2)*, 133-143.

Toepfer, P., Heim, C., Entringer, S., Binder, E., Wadhwa, P., & Buss, C. (2017). Oxytocin pathways in the intergenerational transmission of maternal early life stress. *Neuroscience & Biobehavioral Reviews*, 73, 293-308. doi:10.1016/j.neubiorev.2016.12.026

Turecki, G., Ernst, C., Jollant, F., Labonté, B., & Mechawa, N. (2012). The neurodevelopmental origins of suicidal behavior. *Trends in Neurosciences, 35(1),* 14-23. doi:10.1016/j.tins.2011.11.008

Turecki, G. & Meaney, M. J. (2016). Effects of the social environment and stress on glucocorticoid receptor gene methylation: A systematic review. *Biological Psychiatry*, 79, 87-96. doi:10.1016/j.biopsych.2014.11.022.

van Heeringen, C., Bijttebier, S., & Godfrin, K. (2011). Suicidal brains: A review of functional and structural brain studies in association with suicidal behaviour. *Neuroscience and Biobehavioral Reviews*, 35, 688-98.

van Heeringen, K., & Mann, J.J. (2014). The neurobiology of suicide. *Lancet Psychiatry,* 1, 63-72.

van Orden, K.A., Witte, T.K., Cukrowicz, K.C., Braithwaite, S.R., Selby, E.A., Joiner, T.E. Jr. (2010). The interpersonal theory of suicide. *Psychological Review*,117,575–600.

Wetherall, K., Cleare, S., Eschle, S., Ferguson, E., O'Connor, D.B., O'Carroll, R., O'Connor, R.C. (2018). From ideation to action: differentiating between those who think about suicide and those who attempt suicide in a national study of young

adults. *Journal of Affective Disorders, 241, 475 – 483*

Westrin, A. Ekman, R., Träskman-Bendz, L. (1999). Alterations of corticotropin releasing hormone (CRH) and neuropeptide Y (NPY) plasma levels in mood disorder patients with a recent suicide attempt. *European Neuropsychopharmacology* 9, 205–11.

Williams, J.M.G. (2001). *Suicide and attempted suicide. Understanding the cry of pain*. London: England: Penguin.

Yehuda, R., Kahana, B., Binder-Brynes, K., Southwick, S.M., Mason, J.W., & Giller, E.L. (1995). Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. *American Journal of Psychiatry* 152, 982-986.

Figure 1. Integrated Motivational-Volitional Model of Suicidal Behaviour (O’Connor, 2011; O’Connor & Kirtley, 2018)



Figure 2. Summary of moderating effects of age showing that where the average age of the sample was below 40 years the association was positive, whereas it was negative for samples where the average age was equal to or above 40 years.

p < .001

p < .001

p < .001

p < .001

Note: Effect size = association between naturally fluctuating cortisol levels and suicide attempt history; AM = samples collected before midday, PM = samples collected in the afternoon or evening

Figure 3. Effects of suicide vulnerability group on cortisol reactivity to stress (n = 145)

MAST

Note: Error bars represent the standard error of the mean. MAST was delivered between 0 and 10 mins (see above) and cortisol measures taken at the beginning of the stress task (0 mins), at +10, +20, +30 and +40 min post-task.

Figure 4. Effects of childhood trauma levels on cortisol reactivity to stress in a combined attempt and ideation group (n = 100). The results show that individuals exposed to the highest number of childhood traumas release the lowest levels of cortisol in response to acute laboratory stressor

Figure 5