CHAPTER FIVE

Stress, cortisol and suicide risk

Daryl B. O'Connor[a,*], Nicola Gartland[a], Rory C. O'Connor[b]
[a]School of Psychology, University of Leeds, Leeds, United Kingdom
[b]Suicidal Behavior Research Laboratory, Institute of Health & Wellbeing, University of Glasgow, Glasgow, United Kingdom
[*]Corresponding author: e-mail address: d.b.oconnor@leeds.ac.uk

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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.
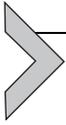
1. Introduction

Every 40s 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, Waternaux, Haas, & Malone, 1999; O'Connor, 2011; O'Connor & Nock, 2014; O'Connor & Kirtley, 2018; van Heeringen & 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, Ernst, Jollant, Labonté, & Mechawa, 2012; van Heeringen, Bijttebier, & Godfrin, 2011; van Heeringen & 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 & 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 this 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 mobilization, as well as regulating the magnitude and duration of inflammatory responses (Sapolsky, Romero, & Munck, 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, 2000; Miller, Chen, & Zhou, 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.

1.1 Stress–diathesis models of suicidal behavior

Stress–diathesis models have a long history in the field of suicide research (see O'Connor, Ferguson, Green, O'Carroll, & O'Connor, 2016; O'Connor, Cleare, Eschle, Wetherall, & Kirtley, 2016). More than 30 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 behavior in the presence of stress (O'Connor, 2007).

Another diathesis-stress model, developed by Mann and colleagues, was the clinical model of suicidal behavior (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 characterized 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.

1.2 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 Fig. 1). The first phase, the pre-motivational phase, outlines
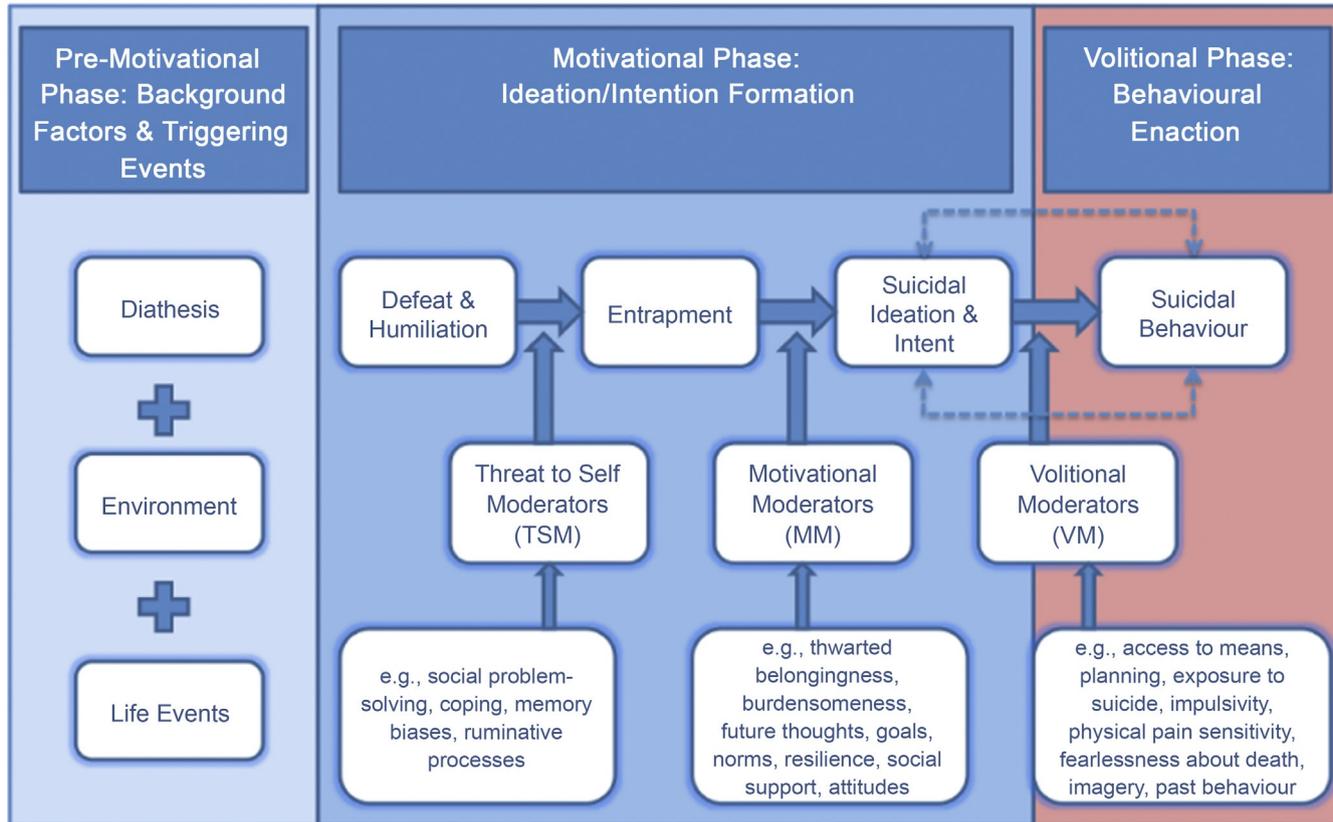
Fig. 1 Integrated motivational–volitional model of suicidal behavior (O'Connor, 2011; O'Connor & Kirtley, 2018).

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 behavioral 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 behavioral enaction (O'Connor, Rasmussen, & Hawton, 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 behavior or self-harm (Branley-Bell et al., 2019; Mars et al., 2019; 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.
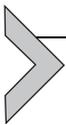
2. Cortisol and suicide risk

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 & Currier, 2007; Pompili et al., 2010) using the Dexamethasone Suppression Test (DST; Carroll, Martin, & Davies, 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.

2.1 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 11 am) and then plasma cortisol levels being assessed the following day in the morning (8 am) and afternoon (4 pm). 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 & Schlesser, 1981; Coryell, Young, & Carroll, 2006; Jokinen & Nordstrom, 2008, 2009; Norman, Brown, Miller, Keitner, & Overholser, 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 hospitalized 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 behavior 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 behaviors was inconclusive with regards to the prediction of future suicide behaviors (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, while DST research has contributed enormously to knowledge regarding HPA axis dysregulation and suicide vulnerability, findings remain inconsistent and contradictory (Chang et al., 2016; McGirr, Diaconu, Berlim, & Turecki, 2011). Pharmacological manipulation has also been criticized as it may not adequately mimic the size of the endogenous HPA response to naturally occurring stressors (Burke, Davis, Otte, & Mohr, 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, Green, Ferguson, O'Carroll, & O'Connor, 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 behaviors.

2.2 Naturally fluctuating cortisol and suicidal behavior

The second broad area of research investigating the HPA axis and suicidal behavior has focused on exploring the relationship between naturally fluctuating (or baseline) cortisol levels and suicide behaviors. However, before outlining this research, it is important to note that cortisol has a distinct pattern over any 24 h period. The diurnal pattern of cortisol production is characterized 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., Adam et al., 2017; O'Connor et al., 2020, 2009).

Similar to the findings from the DST studies, research that has explored the associations between naturally fluctuating cortisol and different aspects of suicide behaviors have yielded inconsistent findings. For example, Westrin, Ekman, and Träskman-Bendz (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, Isaksson, Träskman-Bendz, and Brundin (2008) and Lindqvist, Traskman-Bendz, and Vang (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, Ferguson, et al., 2016; O'Connor, Cleare, et al., 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 behavior and (ii) to identify moderators of this relationship. The systematic literature identified 27 studies ($N = 2226$; 779 suicide attempters and 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 Fig. 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; $r = 0.234$, $P < 0.001$), and where the mean age was 40 or above the association was negative (i.e., lower cortisol was associated with suicide attempts; $r = -0.129$, $P < 0.001$).

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
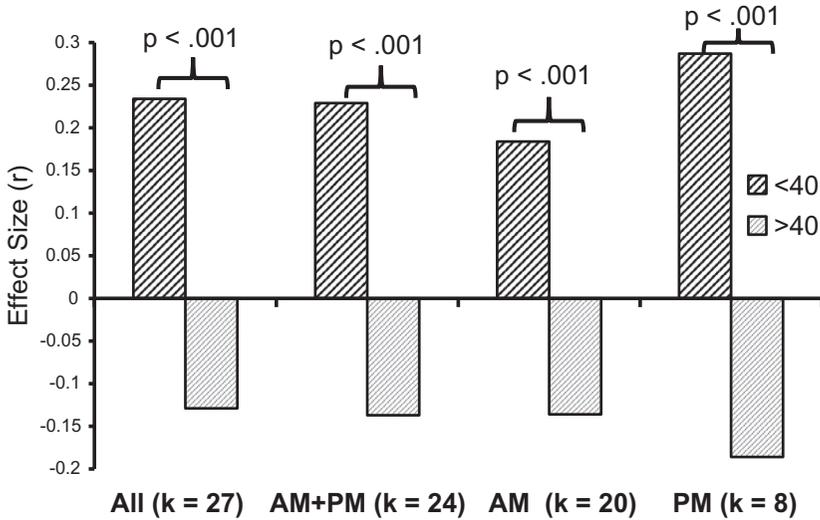
Fig. 2 Summary of moderating effects of age showing that where the average age of the sample was below 40 years the association was positive, whereas it was negative for samples where the average age was equal to or above 40 years. Note: Effect size = association between naturally fluctuating cortisol levels and suicide attempt history; AM = samples collected before midday, PM = samples collected in the afternoon or evening.

for younger people it is positive and that the relationship between cortisol and suicide attempts is more nuanced and complicated than past research has recognized. 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, Hesse, Hellhammer, and Hellhammer (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 (hyperreactivity 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 utilizing 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, O'Connor, Lawton, & Bristow, 2014) to capture the full profile of cortisol, in doing so, use appropriate measurement (e.g., accuracy of sampling, accounting for variables known to influence cortisol, etc).

2.3 Cortisol reactivity to laboratory stress and suicide behavior

The third broad area investigating the HPA axis and suicidal behavior 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, Green, Ferguson, O'Carroll, & O'Connor, 2017). A leading study in this area was conducted by McGirr et al. (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, Pirke, & Hellhammer, 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 Fig. 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.

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
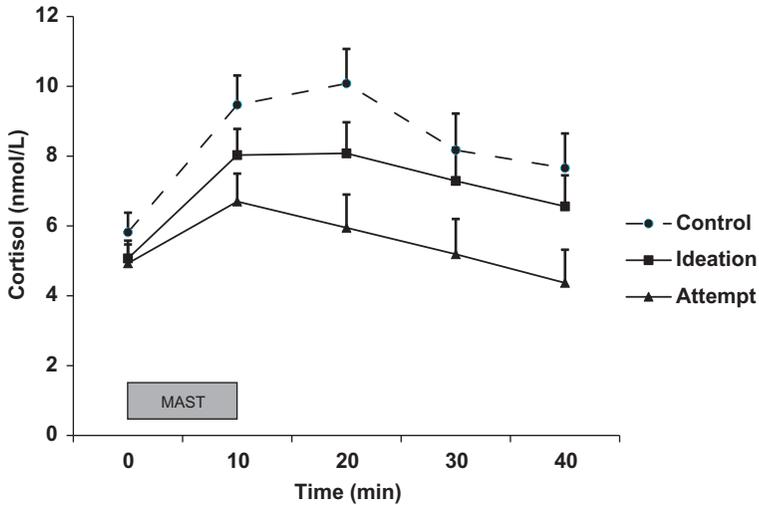
Fig. 3 Effects of suicide vulnerability group on cortisol reactivity to stress ($n = 145$). Note: Error bars represent the standard error of the mean. MAST was delivered between 0 and 10 min (see above) and cortisol measures taken at the beginning of the stress task (0 min), at +10, +20, +30 and +40 min post-task.

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 utilize 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.
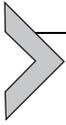
3. Childhood trauma—Cortisol—Suicide risk

Childhood trauma has been identified as an important variable in the etiology of suicide risk. For example, Marshall, Galea, Wood, and Kerr (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, Carli, Cuomo, and Roy (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.

3.1 Childhood trauma and the hypothalamic-pituitary-adrenal axis

Research has begun to focus on the links between childhood trauma and altered dynamics of the HPA axis. In the context of depression, Heim et al. (2000) and Heim, Newport, Mletzko, Miller, and Nemeroff (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 decreased cortisol 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, Shattuck, Tyrka, Geracioti, & Price, 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 increased cortisol 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, Farag, Sorocco, Cohoon, & Vincent, 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 et al. (2020, 2018) 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 Fig. 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
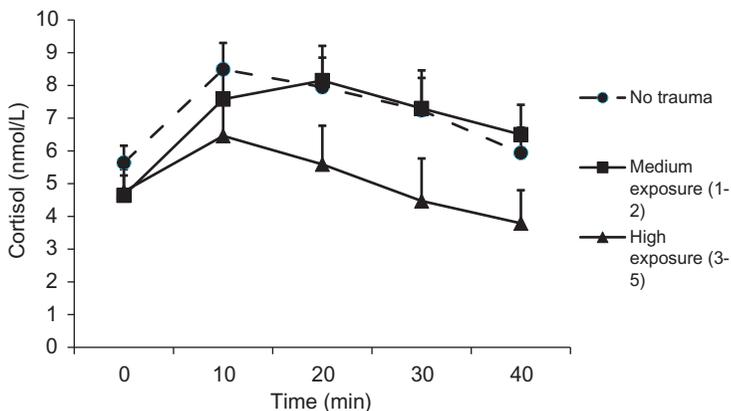
Fig. 4 Effects of childhood trauma levels on cortisol reactivity to stress in a combined attempt and ideation group ($n = 100$). The results show that individuals exposed to the highest number of childhood traumas release the lowest levels of cortisol in response to acute laboratory stressor.

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 toward flatter wake-peak to 12 h (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 toward 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.

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 toward 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 et al. (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 (characterized 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 behaviors. We believe that exhibiting a low or blunted CAR may be another negative consequence of the modification of brain function (Boehringer et al., 2015).
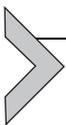
4. Possible mechanisms linking stress and suicide risk

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 behavior, sometimes decades later?

4.1 Executive function and impulsivity

One possible mechanism tying stress to suicide behavior 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 behavior, 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 behaviors based on changes in the environment). The personality trait "impulsivity" is related to executive function as it is characterized by behaviors which reflect impaired self-regulation. At the behavioral 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 behaviors are suggested to originate from deficits in working memory, self-regulation of affect–motivation–arousal, internalization of speech and behavioral 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, Paris, & Turecki, 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, Hartwell, Leon, & Portera, 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 behaviors 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-Color 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 behavior. 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 behavior.

4.2 Family history

Suicidal behavior aggregates in families (Brent, Bridge, Johnson, & Connolly, 1996; Brent et al., 2002; Kim et al., 2005; McGirr et al., 2009, 2011). In a register-based case control study, Mittendorfer–Rutz, Rasmussen, and Wasserman (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 behavior in families (Mittendorfer–Rutz et al., 2008). However, it is difficult to tease out the relationships between stress, family history of suicide and suicidal behavior 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 behavior.

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 focusing 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 et al. (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 behavior. Again, this dysregulation of the stress system would act as a moderation pathway, where the relationship between stress and suicidal behavior 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 1 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.

4.3 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 et al. (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 fetal 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 et al. (2012) outline a model to explain increased risk of suicide in individuals exposed to early-life adversity through HPA axis dysregulation. 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 cru-cial 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, behavioral 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 behavior, see Labonté and Turecki (2010).

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., 2017). Further investigation for the role of epigenetic mechanisms in suicidal behavior 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 (Labonté et al., 2012; McGowan et al., 2009). 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 behavior.

Using a whole genome-wide approach to investigate DNA methylation in the hippocampi of suicide completers, Labonté et al. (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, behavior). 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.

4.4 Sleep

Another mechanism by which stress could potentially affect suicide behaviors is through disruption to sleep. There is strong evidence that insomnia and nightmares are associated with increased suicide risk

(Bernert, Kim, Iwata, & Perlis, 2015; Nadorff, Nazem, & Fiske, 2011, 2013; Pigeon, Pinquart, & Conner, 2012). However, causality and third variable effects are hard to establish. Research to date has mainly focused 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, Rasmussen, & Hunter, 2018; for review, see Littlewood, Kyle, Pratt, Peters, & Gooding, 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, Nadorff, Winer, & Ward, 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 behaviors. A recently ecological momentary assessment study by Littlewood et al. (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, Shipley, Ferrie, Kivimäki, & Kumari, 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, Cordi, La Marca, Seifritz, & Rasch, 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 (Ackemann 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 et al. (2016) provide evidence that recurrent short sleep (measured at three timepoints during the 10-year period) was associated with a flatter diurnal cortisol pattern, characterized 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 behavior 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, Cheng, Almeida, & Roth, 2017). Disruption to sleep also has been hypothesized 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.
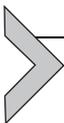
5. General conclusion

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 puta-
tive suicide risk factors including childhood trauma, impaired executive func-
tion, 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 sui-
cide, there is a need for future research to investigate simultaneously the
impact of distal and proximal determinants of suicidal behavior.

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