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Cortisol reactivity and suicidal behavior: Investigating the role of hypothalamic-pituitary-adrenal axis responses to stress in suicide attempters and ideators

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ABSTRACT

Every 40 s a person dies by suicide somewhere in the world. The causes of suicidal behavior are not fully understood. Dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity, as measured by cortisol levels, is one potential risk factor. The current study aimed to investigate whether cortisol reactivity to a laboratory stress task differentiated individuals who had previously made a suicide attempt from those who had thought about suicide (suicide ideators) and control participants. One hundred and sixty participants were recruited to a previous attempt, a suicidal ideation or a control group. Participants completed background questionnaires before completing the Maastricht Acute Stress Test (MAST). Cortisol levels were assessed throughout the stress task. Measures of suicide behavior were measured at baseline, 1 month and 6 month follow-up. Participants who had made a previous suicide attempt exhibited significantly lower aggregate cortisol levels during the MAST compared to participants in the control group; suicide ideators were intermediate to both groups. This effect, however, was driven by participants who made an attempt within the past year, and to some degree by those with a family history of attempt. Participants who made a suicide attempt and had a family history of suicide exhibited the lowest levels of cortisol in response to stress. Finally, 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 attempter group. These results are consistent with other findings indicating that blunted HPA axis activity is associated with some forms of suicidal behavior. The challenge for researchers is to elucidate the precise causal mechanisms linking stress, cortisol and suicide risk.

1. Introduction

Every 40 s a person dies by suicide somewhere in the world (WHO, 2014). Researchers have been exploring the causes of suicidal behavior for many decades with a view to identifying targets for suicide prevention. To this end, 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 and Nock, 2014; van Heeringen and Mann, 2014; van Orden et al., 2010). Central to many of these models is a stress-diathesis component, which states that suicidal behavior is a result of an interaction between acutely stressful life events and a susceptibility to suicide (a diathesis). Stress-diathesis explanations of behavior (and illness) typically have three aspects: a predispositional vulnerability factor, a stressful life event(s) or trigger(s) and protective factors that may shield the individual from developing the illness (or in this case, engaging in suicidal behavior). In terms of a vulnerability factor, data from post-mortem, neuroimaging and in-vivo studies are emerging that a trait diathesis is not only manifested in impairments of the serotonergic and noradrenergic neurotransmitter systems, in structural brain abnormalities and via epigenetic pathways but also in dysregulation of hypothalamic-pituitary-adrenal (HPA) axis stress response activity (Mann, 2013; Turecki et al., 2012; van Heeringen et al., 2011; van Heeringen and Mann, 2014).

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Cortisol is the primary effector hormone of the HPA axis stress response system, and has received extensive empirical investigation. In the context of suicide research, the majority of previous work has focused on assessing HPA axis functioning through pharmacological manipulation of the stress system (e.g., see Coryell and Schlesser, 2001; Coryell et al., 2006; Mann and Currier, 2007; Pompili et al., 2010). However, recently researchers have turned their attention to investigating other aspects of the cortisol response, such as cortisol reactivity to laboratory stressors (e.g., Giletta et al., 2015; McGirr et al., 2010). McGirr et al. (2010) explored the extent to which dysregulation of the HPA axis to a laboratory stressor was a heritable risk factor for suicidal behavior. In this study, a small sample of first-degree relatives of suicide completers and matched controls were compared on their cortisol reactivity to a well-established psychosocial stressor known as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). The results showed that the first-degree relatives exhibited a blunted cortisol (and α amylase) response to stress. In addition, this study also measured executive function and found that participants who had a first-degree relative who had completed or attempted suicide did not improve on measures of inhibition upon repeated testing after the TSST. Taken together, these authors have suggested that their findings indicate that blunted cortisol reactivity to stress may represent a trait marker (or phenotype) of suicide risk and impairment of aspects of executive function may be a consequence of dysregulation that increases vulnerability to suicide. These findings are undoubtedly important, however, as the authors acknowledge, the design utilised cannot rule out the possibility that the observed effects were accounted for by the impact of the traumatic loss of a close family member on the HPA axis (and may not represent a trait diathesis per se). Therefore, important next steps for this line of research are: i) to investigate differences in cortisol reactivity to stress in individuals who have attempted suicide with and without a family history of suicide and, ii) to draw comparisons with individuals who have thought about taking their own life (suicide ideators), but have not translated these intentions into action (cf., Dhingra et al., 2015; O'Connor, 2011).

More recently, two studies have been published that have used the TSST to examine HPA axis responses to stress in vulnerable, at risk groups (Giletta et al., 2015; Melhem et al., 2016). Giletta and colleagues explored the extent to which cortisol reactivity to stress was associated with lifetime history of suicide ideation (i.e., developing suicidal thoughts) and whether reactivity predicted future suicidal ideation in at-risk adolescent females. The results of this study found that adolescents who exhibited heightened cortisol responses to stress were more likely to report a lifetime history of suicide ideation and they were approximately 16 times more likely to report suicide ideation 3 months later. This study also found a subsample of adolescents who exhibited a blunted response to stress in which low cortisol reactivity also predicted future suicide ideation. However, when compared to those who exhibited a heightened response, the likelihood of suicide ideation was substantially lower. This research has numerous strengths including the relatively large sample size and the prospective design. Nonetheless, its focus on female adolescents and suicide *ideation* only limits the extent to which the findings can be generalised to actual suicide attempts and to vulnerable populations more generally.

Melhem et al. (2016) conducted the second of the recent studies utilising the TSST and this study examined cortisol responses to stress in a large sample of adult offspring of parents with mood disorder. The results of this research 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, surprisingly, there were no significant differences between groups on their measure of cortisol reactivity to stress. Taken together, these results suggest that blunted HPA axis activity may increase risk for suicide attempt among vulnerable individuals.

The conflicting results of these three key cortisol reactivity studies highlight the complexity of attempting to understand the causes of suicidal behavior and the interplay between a myriad of different influences. A number of factors may account for these mixed findings including deviations in the measurement of cortisol levels, differences in the nature of the samples recruited (e.g., first-degree relatives of suicide completers versus at-risk adolescents), variations in cumulative exposure to stress and the age of participants. In terms of the latter, a recent meta-analysis of naturally fluctuating cortisol levels and suicidal behavior showed that cortisol was associated with suicide attempts in an age-dependent fashion (O'Connor et al., 2016). Relatedly, variations in the cumulative exposure to chronic stress over a life course may account for differences in observations of enhanced secretion compared to blunted secretion in vulnerable individuals (cf., McEwen's notion of allostatic load, McEwen, 1998, 2000). Moreover, in line with a stress-diathesis approach, it is also likely that the time elapsed since any acutely stressful event(s) or trigger(s) will influence cortisol reactivity. In their influential review, Miller et al. (2007) highlighted the importance of the temporal features of stressors and showed that time of onset of stress was negatively associated with HPA axis activity. More specifically, they found that the greater the amount of time that had elapsed since the stressor was initially encountered, the lower participants' morning cortisol and total daily cortisol output (which will also include cortisol reactivity to stress). These authors argued that the HPA axis exhibits initial activation in the form of elevated cortisol release and following prolonged exposure to the stressors, they theorized that, this activity reduces and cortisol secretion rebounds to less than normal. Therefore, in the current study, we were also interested in exploring whether the time since suicide attempt (i.e., within the last 12 months versus more distant history of suicide attempts) was related to cortisol reactivity to stress in the laboratory.

To summarise, the primary aim of the current study was to determine whether heightened or blunted cortisol reactivity to stress was associated with a history of suicide ideation and/or suicide attempt in comparison to healthy controls. Secondary aims were: i) to explore whether family history of suicidal behavior and the time since suicide attempt (i.e., within the last 12 months versus more distant history of suicide attempts) were related to cortisol reactivity to stress and ii) to investigate whether cortisol reactivity to stress predicted later suicide ideation or attempt at 1 month and 6 month follow-up.

2. Method

2.1. Design and participants

One hundred and sixty participants (100 females) were recruited to a previous attempt (n = 49), a suicidal ideation but no attempt (n = 55) and a control group (n = 48) based upon established measures of suicidal behavior (see below). Participants were aged between 18 and 62 years (M = 26.84 years, SD = 9.32) with 73.8% identified as Caucasian. Participants were enrolled to the study in response to a local advertising campaign on websites (e.g., Gumtree, Twitter), via poster, flyers and emails. Eligible participants were required to be at least 18 years old and to understand English. Suicide ideation and attempt were assessed using the Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock et al., 2007) and the Beck Scale for Suicide Ideation (Beck et al., 1979,