



Research paper

Toward subtyping of suicidality: Brief suicidal ideation is associated with greater stress response

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ABSTRACT

Background: Suicide is a heterogeneous phenomenon, and thus defining more homogeneous subgroups may help in understanding its underlying biology and ultimately in its prevention. Suicidal ideation is far more common than suicidal behavior and predicts future suicide attempts. Hypothalamic–pituitary–adrenal (HPA)-axis reactivity has been implicated in individuals with suicidal ideation but findings are mixed with some studies showing increased and others demonstrating decreased reactivity. This suggests that dysregulation of HPA-axis is related to a specific character of suicidal ideation. We hypothesized that individuals with brief suicidal ideation are more stress responsive than those with longer/continuous ideation.

Methods: Thirty-five individuals with major depressive disorder (MDD) and 23 healthy volunteers (HVs), aged 18–65 years, underwent the Trier Social Stress Test (TSST). Salivary cortisol was measured at 6 time-points before and during TSST. Total severity and duration of current suicidal ideation were assessed using the Beck Scale for Suicidal Ideation (SSI). Brief suicidal ideators (N = 18), longer/continuous ideators (N = 17) and HVs were compared regarding cortisol response, baseline cortisol and total output.

Results: Participants with brief suicidal ideation had greater cortisol response compared to those with longer/continuous ideation and HVs, even after controlling for relevant covariates. However, total SSI score was not associated with cortisol response. Baseline cortisol and total output were not related to overall severity or duration of suicidal ideation.

Limitations: The cross-sectional design and modest sample limit generalizability of the results.

Conclusions: Hyper-responsiveness of HPA-axis to social stress is associated with brief suicidal ideation, possibly defining a pathway for exploring the biological subtyping of suicidal individuals.

1. Introduction

Suicide is a worldwide problem resulting in the death of over 800,000 people every year (WHO, 2016). Suicidal behavior is a heterogeneous phenomenon with complex underlying biology and risk factors (Chaudhury et al., 2016; Mann and Currier, 2007; van Heeringen and Mann, 2014). Defining more homogeneous subgroups may improve the understanding of its underlying biology and ultimately aid in prediction and prevention of future suicide.

Suicidal ideation is the first step on a path toward dying by suicide (Nock et al., 2008). Despite the importance of suicidal ideation in

predicting future suicide attempts (Fawcett et al., 1987; Kessler et al., 1999; Oquendo et al., 2004), little empirical research has been conducted on its dimensions/patterns. Suicidal thoughts can range from transient thoughts that life is not worth living (Nock and Banaji, 2007) to persistent rumination about death (Oquendo et al., 2003), or even manifest as an intense delusional preoccupation with self-destruction (Goldney et al., 1989). Importantly, some data suggest that individuals with brief, fleeting suicidal ideation have a comparable risk for future suicide attempts to those with persistent ideation (Wilcox et al., 2010). Community (Reinherz et al., 2006) as well as clinical (Pfeffer et al., 1993) cohort studies found that adolescents with suicidal thoughts,

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even if mild or of an apparently low severity, are more likely to have serious suicidal behavior in adulthood. Witte et al. (2005) found that fluctuation of suicidal ideation over time is a potent predictor for previous suicide attempts. Hall et al. (1999) reported that over two thirds of individuals who made serious suicide attempts requiring hospitalization had only brief suicidal ideation with no specific plan prior to their attempt. The biological correlates of these brief, fluctuating thoughts of killing oneself are largely unknown.

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis has been suggested to increase the risk for suicidal behavior (Mann, 2003; Turecki, 2005; van Heeringen and Mann, 2014). Although some studies report that HPA axis hyperactivity, as assessed by non-suppression on the dexamethasone suppression test (DST), predicts completed suicide (Coryell and Schlessler, 2001; Mann et al., 2006; Yerevanian et al., 2004), and to a lesser extent, future suicide attempts (Jokinen et al., 2008; Jokinen and Nordstrom, 2009), others do not (Black et al., 2002; Fountoulakis et al., 2004; Maes et al., 1989; Pitchot et al., 2008). A few DST studies have examined the association of HPA axis activity with suicidal ideation, and, again, their results are mixed. Both HPA axis hyper-responsivity (López-Ibor et al., 1985) as well as hypo-responsivity (Pfennig et al., 2005) have been found in relation to suicidal thoughts. In an effort to understand these mixed results, Lindqvist et al. (2008) examined the relationship between suicide intent and HPA axis reactivity using the DST and reported that subjects with low suicide intent had greater cortisol response.

As a pharmacologic manipulation, the DST may not accurately depict functioning of the HPA axis in response to social and environmental stressors (McGirr et al., 2011), such as those produced by staged-situation laboratory stressors (e.g., Giletta et al., 2015; Keilp et al., 2016; McGirr et al., 2010; Melhem et al., 2016; Wilson et al., 2016)), like the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993). Some TSST studies have found lower pre-task baseline cortisol (Keilp et al., 2016; Melhem et al., 2016) and blunted total cortisol output (Melhem et al., 2016; O'Connor et al., 2017a) in suicide attempters, but no differences in cortisol response to stress. O'Connor et al. (2017a), in turn, found that lower cortisol reactivity predicted elevated suicidal thoughts at 1-month follow up in suicide attempters, but not in ideators who did not attempt suicide. However, Giletta et al. (2015) reported that both hyper-responsivity as well as hypo-responsivity (at a trend level) were associated with suicidal ideation. A next logical step is to examine the relationship between cortisol response to social stress and the character of suicidal ideation, particularly its duration.

In the current study, we examined the relationship between HPA axis reactivity using the TSST and current suicidal ideation in individuals with major depressive disorder (MDD). Stress-responsive individuals likely have increased emotional reactivity and are proposed to develop sudden, transient suicidal thoughts following stressful life events (Bernanke et al., 2017). Thus, we hypothesized that those with brief, fleeting suicidal ideation would show greater HPA axis reactivity, as indicated by elevated levels of cortisol response rather than baseline or total cortisol output (Pruessner et al., 2003), compared to those with longer or continuous periods of ideation.

2. Methods

2.1. Participants

Participants were recruited through the Molecular Imaging and Neuropathology Division (MIND) Clinic at Columbia University (New York, NY, SA). This study was approved by the New York State Psychiatric Institute Institutional Review Board and all participants gave their written informed consent. Thirty-five participants who met the DSM-IV (American Psychiatric Association, 1994) criteria for MDD and have current suicidal ideation, and 23 healthy volunteers (HVs) were included. Depressed participants were classified as brief suicidal ideators (N = 18) or longer/continuous ideators (N = 17), using the

time dimension item on the Beck Scale for Suicidal Ideation (SSI) (Beck et al., 1979) (see below for details). Inclusion criteria for depressed participants were assessed through clinical interview and included: 1) 18–65 years of age; 2) DSM-IV diagnosis of MDD; and 4) capacity to provide informed consent. Exclusion criteria included: 1) unstable medical condition; 2) current alcohol or substance use disorder (past diagnosis allowed if in remission for ≥ 6 months); 3) bipolar disorder or schizophrenia (comorbid anxiety disorders were not excluded); 5) marked cognitive impairment that would interfere with participation. Criteria for HVs were similar except for the required absence of psychiatric history (specific phobia was permitted) or family history of a mood or psychotic disorder or suicidal behavior in a first-degree relative.

2.2. Clinical assessment

Lifetime Axis I DSM-IV diagnoses were assessed using the Structured Clinical Interview for DSM-IV (SCID I) (First et al., 1995). Self- and clinician rated current severity of depressive symptoms was evaluated with the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Hamilton Depression Rating Scale-17 item (HDRS) (Hamilton, 1960), respectively. Hopelessness was assessed with the Beck Hopelessness Scale (Beck et al., 1974).

Suicide history was assessed with the Columbia Suicide History Form (Oquendo et al., 2003). Suicidal ideation was evaluated with the Beck Scale for Suicidal Ideation (Beck et al., 1979), a 19-item scale that assesses thoughts, feelings, and plans regarding suicide. Item 6 on this scale assesses the time dimension of suicidal ideation. The duration of suicidal ideation on this item is classified into 3 categories: 1) brief, fleeting periods, 2) longer periods, and 3) continuous (chronic) or almost continuous. Longer and continuous ideators were then added together into a single group.

2.3. Trier Social Stress Test (TSST)

The TSST is a well-established procedure used to study psychological and physiological indices of stress response (Kirschbaum et al., 1993). The procedure involves administering a 5-min personal introduction speech followed by 5 min of a speeded mental arithmetic task, in the presence of a test administrator and two observers who serve as the confederates. The administrator and observers respond neutrally to the participant and provide stern feedback for computation errors. The test was performed at the same time for all participants in order to control for diurnal variation in cortisol levels: mid-afternoon at 2.30 p.m., when cortisol levels are declining to improve the signal to baseline ratio (Kudielka et al., 2004). Saliva samples were obtained at 6 time points: –15, and –5 min before the procedure began, and then at 4 intervals of time from the start of the task: 15, 25, 35, and 45 min. Subjective mood was evaluated using the Profile of Mood States (POMS; (McNair et al., 1992)) at –20, 10, and 40 min.

2.4. Salivary Samples Collection and Assay

Saliva was collected via the Sarstedt Salivette Synthetic Swab saliva collection system (Catalogue # 51.1534.500 Sarstedt, Newton, NC 28658, USA). Samples were stored at -30°C until assayed for cortisol by radioimmunoassay. Primary antibodies raised against cortisol-3-O-carboxymethylxime-BSA and iodine labeled cortisol were purchased from MP Biomedicals. Cortisol standards were purchased from Sigma Chemical, anti-rabbit globulin serum in conjunction with polyethylene glycol was used for separation of the bound and free fractions. All samples and standards were analyzed in duplicate. The intra and inter-assay coefficient of variation was 4.7% at 1 ng/ml and 7.4% at 0.25 ng/ml, respectively.

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