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Preliminary communication

Increased fear-potentiated startle in major depressive disorder patients with lifetime history of suicide attempt

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ABSTRACT

Background: Suicide is a common reason for psychiatric emergency and morbidity, with few effective treatments. Anxiety symptoms have emerged as potential modifiable risk factors in the time before a suicide attempt, but few studies have been conducted using laboratory measures of fear and anxiety. We operationally defined fear and anxiety as increased startle reactivity during anticipation of predictable (fear-potentiated startle) and unpredictable (anxiety-potentiated startle) shock. We hypothesized that a lifetime history of suicide attempt (as compared to history of no suicide attempt) would be associated with increased fear-potentiated startle.
Methods: A post-hoc analysis of fear- and anxiety-potentiated startle was conducted in 28 medication-free patients with Major Depressive Disorder (MDD) divided according to suicide attempt history.
Results: The magnitude of fear-potentiated startle was increased in depressed patients with lifetime suicide attempts compared to those without a lifetime history of suicide attempt ($F(1,26)=5.629$, $p=.025$). There was no difference in anxiety-potentiated startle by suicide attempt history.
Limitations: This is a post-hoc analysis of previously analyzed patient data from a study of depressed inpatients. Further replication of the finding with a larger patient sample is indicated.
Conclusions: Increased fear-potentiated startle in suicide attempters suggests the role of amygdala in depressed patients with a suicide attempt history. Findings highlight the importance of anxiety symptoms in the treatment of patients at increased suicide risk.

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1. Introduction

Suicidal behavior is a leading cause of death and morbidity (Centers for Disease Control and Prevention, 2013) and there are few, if any, effective treatments for patients at risk. Anxiety has emerged as a potential modifiable risk factor for later suicidal behavior (Fawcett et al., 1990; Hawton et al., 2013; Sareen et al., 2005). In a nationally representative sample, anxiety disorders, such as post-traumatic stress disorder (PTSD), were significantly associated with the transition from suicidal thoughts to suicide attempt, an association which was not found for depression (Nock et al., 2010). Anxiety sensitivity, meaning the fear of the physical, social or cognitive consequences of anxiety, is a demonstrated risk factor for suicide attempts in the context of depression (Capron et al., 2013); cognitive behavioral treatment for anxiety sensitivity has been associated with reduced suicidal thoughts and behavior (Capron et al., 2014).

While anxiety is an important symptom and treatment target for suicidal behavior, most of the published research has assessed anxiety through the use of self-report measures or clinical diagnosis of an anxiety disorder. The use of paradigms that assess changes in fear and anxiety for suicide research is relatively rare and primarily measure aversive reactivity to minor threats. For example, one study of affectively modulated startle reflex (to suicide-related, positive and negative visual stimuli) found no differences between depressed controls, ideators, and attempters (Smith et al., 2010). Another found no difference on acoustic startle reflex between depressed suicide attempters and healthy controls (Quednow et al., 2006). To our knowledge, there has been no

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investigation of an anxiety- or fear-related paradigm with the potential of *actual* threat in the context of suicidal thoughts and behavior.

Another concern in studying anxiety is the heterogeneity of aversive responses to threat. As an example, *fear* can be considered a brief response in anticipation to a proximal threat. In contrast, *anxiety* is considered to be a more sustained response to unpredictable stress. Fear and anxiety have been shown to have different neural correlates, with fear mediated by the amygdala and anxiety mediated by the bed nucleus of the stria terminalis (BNST) (Davis et al., 2010). Fear and anxiety have been investigated empirically by measuring startle reactivity during the threat of predictable and unpredictable shock, respectively (Schmitz and Grillon, 2012). In this paradigm, fear and anxiety are operationally defined as the increase in startle magnitude from a safe condition to periods of predictable (i.e., fear-potentiated startle) and unpredictable (i.e., anxiety-potentiated startle) shock anticipation, respectively. This paradigm has been used as a marker of post-traumatic stress disorder (PTSD) and panic disorder (Grillon et al., 2009; Grillon et al., 2008) and has demonstrated anxious anticipation in patients with MDD, (Grillon et al., 2013), but has never been used in the study of suicide risk.

We reanalyzed data from a previous investigation in patients with Major Depressive Disorder (MDD) (Grillon et al., 2013) to examine the extent to which suicide influenced fear- and anxiety-potentiated startle. Lifetime history of suicide attempt was used as a between-subject factor, as previous attempt is a significant suicide risk factor (Suominen et al., 2004) and anxiety symptoms may be particularly associated with suicidal behavior in patients with depression. We hypothesized that there would be increased fear-potentiated startle in MDD patients with a history of suicide attempts, due to the clinical findings of amygdala pathology in suicidal individuals (Anisman et al., 2008; Hrdina et al., 1993; Maheu et al., 2013) as well as the incidence of negative stressful events in the time immediately before many suicide attempts (Bagge et al., 2013; Cooper et al., 2002). Preliminary findings will have implications for neurological and clinical treatment targets in patients at risk for suicide.

2. Methods

2.1. Participants

Following written informed consent, 28 adult participants between the ages of 18–55 with MDD were enrolled into the protocol, as approved by the Combined Neuroscience Institutional Review Board (CNS-IRB) of the National Institutes of Health (NIH) in accordance with the Declaration of Helsinki. All participants were screened through the Experimental Therapeutics and Pathophysiology Branch (ETPB) of the National Institute of Mental Health (NIMH) Bethesda, Maryland, USA for participation in treatment protocols. Diagnoses were assessed by psychiatrists through clinical interview and confirmed with the Structured Clinical Interview for DSM-IV Diagnoses (SCID) (First et al., 1997), and all participants had a current, primary diagnosis of MDD without psychotic features, lasting at least 4 weeks in duration. Suicide attempt histories were gathered via clinical interview with participants.

All participants were deemed to be in good physical health following an extensive medical history, physical examination, hematologic laboratory evaluation, electrocardiogram, urinalysis, and toxicology screening. Exclusion criteria included patients with a comorbid substance abuse or dependence disorder (excluding caffeine or nicotine) in the 3 months prior to screening, positive urine toxicology screen, history of antidepressant- or substance-induced hypomania or mania, serious unstable medical disorders or conditions, or concomitant treatment with psychotropic medications or electroconvulsive therapy in the 2 weeks prior to the experiment. Females could not be pregnant or nursing.

2.2. Study design, stimuli, and physiologic responses

A previously published methodological report details the threat of shock paradigm (Schmitz and Grillon, 2012). This paradigm has successfully been used in several articles examining startle potentiation in anxious (Grillon et al., 2006; Grillon et al., 2009) and depressed (Grillon et al., 2013) participants while anticipating shocks. Briefly, participants were exposed to three conditions: no shock (N), predictable shock (P), and unpredictable shock (U), or, the NPU-threat test. Startle reactivity was measured with an electromyograph (EMG) throughout the experiment via eyeblink electrodes that were superficially placed on the skin below the left eye; EMG data was then digitized (1000 Hz) and amplified (bandwidth 30–500 Hz). Initially, participants were habituated to the startle response by receiving a total of nine acoustic startle stimuli every 18–23 s via headphones. All acoustic startle stimuli were white noise sounds (40-ms duration, 103-dB). Superficial shock electrodes were then unilaterally attached medially to the supine wrist. A shock work-up was initiated to set the intensity of shock to a mildly painful level. Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, London, England).

Explicit instructions were then given to participants for the NPU-threat test conditions. A total of three conditions lasting 150-s in duration were administered (Fig. 1 for schematic representation). During each condition, an 8-s cue was presented four times on a computer monitor facing the participants. A green circle cue represented the N condition, a red square for P, and a blue triangle for U. Depending on the condition being tested, the following written instructions were continuously displayed on the computer screen: “no shock (N),” “shock only during shape (P),” or “shock at any time (U).” Therefore, the cues signaled the possibility of receiving a shock only in the P condition but the cues had no signal value in the N and U conditions. Each participant was exposed to two blocks of three N, two P, and two U in either the order of P–N–U–N–U–N–P or U–N–P–N–P–N–U. Participants received a total of eight shocks during the session: two in each of the P and U conditions. When delivered in the P conditions, shocks were at the end of the cue; in the U conditions, they were

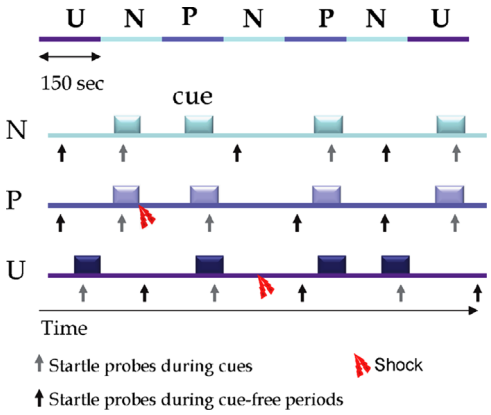

Fig. 1. Schematic representation of sequences of stimulus presentation during each condition in one block of the NPU-threat test. The top of the figure represents a complete block, including two P (predictable), two U (unpredictable) and three N (no shock) conditions (order U–N–P–N–P–N–U as shown; or, alternatively administered as P–N–U–N–U–N–P). The remaining figure shows each condition, including cues (8-s duration), startle probes presented during cues (grey arrow pointing up) or during cue-free periods (dark arrow pointing up), and shocks. Image originally adapted from reference (Grillon et al., 2009) and taken from Grillon et al. (2013).