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Research paper

# Neurophysiological correlates of suicidal ideation in major depressive disorder: Hyperarousal during sleep

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ABSTRACT

*Background:* Suicide is a major public health concern, and a barrier to reducing the suicide rate is the lack of objective predictors of risk. The present study considers whether quantitative sleep electroencephalography (EEG) may be a neurobiological correlate of suicidal ideation.

*Methods:* Participants included 84 (45 female, mean age=26.6) adults diagnosed with major depressive disorder (MDD). The item that measures thoughts of death or suicide on the Quick Inventory of Depressive Symptomatology (QIDS) was used to classify 47 participants as low suicidal ideation (24 females, mean age=26.1) and 37 as high suicidal ideation (21 females, mean age=27.3). Data were obtained from archival samples collected at the University of Michigan and University of Texas Southwestern Medical Center between 2004 and 2012. Sleep EEG was quantified using power spectral analysis, and focused on alpha, beta, and delta frequencies.

*Results:* Results indicated that participants with high compared to low suicidal ideation experienced 1) increased fast frequency activity, 2) decreased delta activity, and 3) increased alpha-delta sleep after adjusting for age, sex, depression, and insomnia symptoms.

*Limitations:* Limitations include the exclusion of imminent suicidal intent, a single suicidal ideation item, and cross-sectional archival data.

*Conclusions:* This is one of the first studies to provide preliminary support that electrophysiological brain activity during sleep is associated with increased suicidal ideation in MDD, and may point toward central nervous system (CNS) hyperarousal during sleep as a neurobiological correlate of suicidal ideation.

## 1. Introduction

Suicide is a leading cause of death worldwide, with nearly one million incidents per year occurring at an alarming rate of one suicide every 40 s (World Health Organization, 2014). Despite being identified as a priority condition by the World Health Organization, the suicide rate has been rising. Indeed, from 2000 to 2009, the annual suicide rate increased by nearly 30% (Center for Disease Control, 2014). The evidence is clear: predictors of suicide must be identified to change the trajectory of the global suicide rate. While extant research has identified a range of predictors across various domains, the neurobiological correlates of suicide risk are not well defined. Among a number of mechanisms, sleep disturbance has emerged as an important contributor to the relationship between suicide and psychiatric disorders.

There is substantial evidence that subjective sleep disturbance is related to suicidal ideation and behavior including death from suicide (Bernert et al., 2015; Bernert and Joiner, 2007; Bernert and Nadorff, 2015; McCall et al., 2010; Perlis et al., 2015; Pigeon et al., 2012). Sleep electroencephalography (EEG) has been identified as a tool to identify

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potential biomarkers for disorders closely related to suicide such as major depressive disorder (Armitage et al., 2006; Benca et al., 1992; Cheng et al., 2015; Goldschmied et al., 2014; Steiger and Kimura, 2010). Further, findings from a meta-analysis indicate that sleep EEG abnormalities may also represent a transdiagnostic psychophysiological mechanism that cuts across disorders (Baglioni et al., 2016). A growing literature indicates that sleep EEG abnormalities are related to suicide. Longer sleep onset latency and alterations in REM activity have been linked previously to greater suicide risk (Agargun and Cartwright, 2003; Sabo et al., 1991; Singareddy and Balon, 2001). This research has been extended by recent studies that report less non-REM (NREM) stage 4 sleep, lower sleep efficiency, and increased awakenings among individuals with suicidal ideation (Ballard et al., 2016; Bernert et al., 2016).

The existing studies on sleep EEG abnormalities and suicide have provided critical evidence that alterations in sleep macroarchitecture, or global patterns of sleep stages, are related to suicide risk. While useful as a generalized summary of sleep, analyses of sleep macroarchitecture have been criticized for construing sleep as occurring in discrete stages (Armitage, 1995). Indeed, physiological phasic and tonic details are lost when a single stage score is assigned to several electrophysiological events that may have occurred during a single scoring period (Armitage et al., 1992). Alternatively, quantitative sleep EEG (or sleep microarchitecture) may be a more powerful method of measuring sleep as a neurobiological event, as it describes electrophysiological brain activity across different EEG frequencies, which could increase specificity in differentiating patients from healthy individuals (Armitage and Hoffmann, 2001; Augustinavicius et al., 2014; Benca et al., 1992). Measuring sleep microarchitecture could provide further evidence for a neurobiological correlate of suicidal ideation, and may help to clarify how sleep disturbance is related to suicidal ideation.

Intrusions of fast frequency EEG activity (i.e., alpha and beta activity) during sleep may be indicative of central nervous system (CNS) hyperarousal (Nofzinger et al., 2004; Perlis et al., 2001a; Riemann et al., 2010), and may be one potential mechanism related to suicidal ideation (McCall and Black, 2013). Hyperarousal has been observed in disorders associated with suicidal ideation such as MDD, insomnia, PTSD, autism spectrum disorder, and chronic pain disorders (Armitage, 1995; Cervena et al., 2014; Germain and Nielsen, 2003; Kupfer et al., 1989; Mazurek and Petroski, 2015; Merica et al., 1998; Merica and Gaillard, 1992; Moldofsky, 2001; Nofzinger, 2005a; Nofzinger et al., 2000; Perlis et al., 2001b, 1997; Riemann et al., 2010, 2001; Woodward et al., 2000). In MDD in particular, both increased whole night alpha and beta activity have been described in patients compared to healthy controls (Armitage, 1995; Armitage et al., 1992; Armitage and Hoffmann, 2001). Additionally, increased whole night power in the 10- to 28-Hz frequency range (which contains alpha and beta activity) has been observed in patients with delusional depression compared to controls (Kupfer et al., 1989). Hyperarousal, and particularly whole night beta activity, in depression appears to be linked to relative glucose metabolism in the ventromedial prefrontal cortex, which is hypothesized to interfere with brain processes related to sleep regulation (Nofzinger et al., 2000). This evidence suggests that hyperarousal is an important contributor to sleep disturbance in MDD and other disorders related to suicidal ideation. However, it remains unclear if intrusions of fast frequency EEG activity during sleep are also a neurobiological correlate of suicidal ideation.

Reduced slow frequency EEG activity (e.g., delta activity) may also reflect hyperarousal (Germain et al., 2004; Ho et al., 1996). Abnormal delta activity has consistently been observed in MDD (Armitage, 1995; Armitage et al., 2000a, 2000b; Cheng et al., 2015; Goldschmied et al., 2014; Kupfer et al., 1986; Lotrich and Germain, 2015), as well as a range of other disorders including insomnia (Buysse et al., 2008; Dijk, 2010; Merica et al., 1998), alcohol dependence (Brower et al., 2011), and schizophrenia (Hoffmann et al., 2000). Decreased delta activity may also be further compounded by the presence of fast frequency activity during periods of sleep that typically contain slow frequency delta activity. Research has begun to describe the presence of "alpha-delta" sleep in patients with MDD and chronic fatigue syndrome, which appears to be linked to physical pain symptoms and daytime impairment (Hauri and Hawkins, 1973; Jaimchariyatam et al., 2011; Manu et al., 1994). A similar phenomenon may occur in individuals with suicidal ideation whereby cortical hyperarousal combines with decreased delta activity and results in a higher ratio of alpha to delta activity over the night.

The preceding evidence suggests that hyperarousal is an important contributor to sleep disturbance in disorders closely related to suicide such as MDD or insomnia. Although there is evidence for this process in other disorders, it remains unclear whether hyperarousal during sleep may also be related to suicide. The present study aims to test whether high compared to low suicidal ideation is related to differing levels of hyperarousal during sleep among participants with MDD, above and beyond insomnia and depression symptom severity. Based on previous research in disorders related to suicide, it was hypothesized that participants with high compared to low suicidal ideation would experience (1) increased alpha and beta activity across the night, (2) decreased delta activity across the night, and (3) increased alpha-delta sleep across the night.

## 2. Methods

### 2.1. Material and methods

#### 2.1.1. Data sourcing

Data were obtained from archival samples collected at the University of Michigan at Ann Arbor and University of Texas Southwestern Medical Center at Dallas recorded under standardized protocols examining sleep in depression between 2004 and 2012 (Armitage et al., 2000a; Cheng et al., 2015; Goldschmied et al., 2015; Liscombe et al., 2002). Archival data was used based on its value as a cost-effective method of exploring novel research questions while maximizing sample size. All participants in the original studies met criteria for MDD based upon the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and were in a current depressive episode (First et al., 2002). All participants were free of psychiatric or sleep medications for a minimum of 2 weeks. Subjects were asked to refrain from alcohol and drug use prior to the study. Participants maintained regular sleep schedules and completed sleep diaries for a minimum of 5 days prior to overnight polysomnography (PSG). Exclusionary criteria for the original studies included psychiatric comorbidities, such as lifetime histories of substance dependence, bipolar disorder, psychosis, anorexia, and bulimia. Individuals reporting acute and imminent suicidal intent were immediately referred for clinical intervention and excluded from study participation. Individuals were also excluded for current shift-work, or sleep disorders (e.g., obstructive sleep apnea, narcolepsy, or bruxism). The research protocols described were approved by the Institutional Review Board at the respective institutions. All participants signed an informed consent document prior to undergoing study procedures.

#### 2.1.2. Participants

The present study included 84 (45 females, mean age =26.6) adults diagnosed with major depressive disorder (MDD). Participants were included in the present sample if baseline polysomnography data and the Quick Inventory of Depressive Symptomatology (QIDS) were available. All participants had baseline PSG data and thirteen individuals excluded because of missing QIDS data.

#### 2.1.3. Instruments

Participants were administered the 16-item self-report QIDS within two weeks of polysomnography. The QIDS assessed depressive symp-