Biological Psychiatry: GOS

# Archival Report

# The Dynamic Relationship Between Alpha and Beta Power and Next-Day Suicidal Ideation in Individuals With Treatment-Resistant Depression

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## ABSTRACT

**BACKGROUND:** Nocturnal wakefulness has emerged as a potential predictor of short-term suicide risk. This analysis used dynamic temporal patterns in alpha and beta power and global sleep metrics to explore the possible link between next-day suicidal ideation (NDSI) and wakefulness measures in unmedicated participants with treatment-resistant depression.

**METHODS:** Thirty-three medication-free participants with treatment-resistant depression completed overnight polysomnography. Alpha and beta spectral power as functions over time were used to represent arousal-related components of the dynamic sleep process. A functional data analytic approach (multilevel functional principal component analysis [MFPCA]) was used to preserve the oscillatory nature of the data; MFPCA PC scores were then associated with NDSI. Associations between NDSI and polysomnography-defined wakefulness after sleep onset, sleep efficiency, and total sleep time were also evaluated.

**RESULTS:** NDSI had the strongest relationship with the second beta PC score (slope = 0.09 [90% credible interval, 0.03 to 0.14]), which represented an oscillating pattern that reflected disturbed sleep. The first PCs from both alpha and beta MFPCAs represented the overall magnitude of power and were most closely associated with traditional polysomnography metrics but were not related to NDSI. Results were equivocal for wakefulness after sleep onset with NDSI and did not support a relationship between NDSI and either sleep efficiency or total sleep time, highlighting the value of information contained in oscillating electroencephalogram patterns for identifying physiological links between nocturnal wakefulness and NDSI.

**CONCLUSIONS:** This study leveraged the dynamic nature of wakefulness-related electroencephalogram frequencies and provides a potential electrophysiological link between suicidal ideation and wakefulness during sleep in individuals with treatment-resistant depression.

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Sleep difficulties have recently emerged as a potential predictor of both long- and short-term suicide risk independent of psychiatric diagnosis (1–3). Specifically, nocturnal wakefulness is a near-term suicide risk factor, as the midnight to 5:00 AM hours are associated with the highest rates of suicide death when accounting for time awake (4,5). This connection with next-day suicidal ideation (NDSI) is supported by self-report measures (6) as well as by actigraphy-defined nocturnal wakefulness associations (7). A previous polysomnography (PSG) study from our laboratory found that SI was associated with less non–rapid eye movement (NREM) stage 4 sleep, lower sleep efficiency (SE), and higher wakefulness after sleep onset (WASO) in individuals with major depressive disorder (MDD) and bipolar disorder (8). Another study focusing on nocturnal wakefulness between midnight and 5:00 AM found that PSG-based wakefulness in the 4:00 AM hour was associated with NDSI (9). Finally, a recent review of 11 studies found that suicidal individuals evaluated using PSG had increased sleep latency in three studies and altered REM activity in seven studies (10). Taken together, the findings suggest that wakefulness over the course of the night is associated with both higher risk of suicide death and near-term SI, but the precise contributions of the physiological and neurological signals remain undefined.

Hyperarousal and insomnia are included in several recent theories of the acute suicide crisis, including suicide crisis syndrome and acute suicidal affective disturbance (11,12). In these syndromes and/or potential diagnoses, a constellation of symptoms is associated with the time just before a suicide attempt, suggesting many pathways to the suicide crisis as well as opportunities for intervention. Sleep disturbances are ideal modifiable symptoms, given that a robust literature already exists on the underlying neurobiology of sleep as well as on effective treatments that could be repurposed to treat suicidal patients. While it is unlikely that insomnia directly causes suicidal thoughts, understanding the neurobiological link between




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suicide risk and sleep disturbance would provide additional insight into the acute suicide crisis. For example, an imbalance between wake-promoting and sleep-promoting neural circuits can manifest through insomnia and nocturnal wakefulness. As characterized by the "flip-flop" switch model of sleep and wakefulness (13), such an imbalance could reflect disruptions between circuits that involve wakefulness-promoting projections from the upper brain stem into the thalamus, hypothalamus, basal forebrain, and cerebral cortex (the ascending reticular activating system) as well as between circuits that involve sleep-promoting areas such as the ventrolateral preoptic nucleus (14). In particular, animal models of insomnia have demonstrated that both arousal and sleep-promoting regions are simultaneously activated during sleep in rats with stress-induced insomnia (15). In humans with insomnia, sleep electroencephalogram (EEG) findings similarly suggest a simultaneous sleep and wakefulness process. Specifically, individuals with insomnia demonstrate increased overnight beta and alpha power, indicating alert and relaxed wakefulness, respectively (16–18), though it should be noted that this relationship has yet to be linked with suicidal thoughts.

This study sought to determine the association between nocturnal wakefulness and NDSI in medication-free individuals with treatment-resistant depression (TRD), a patient group that is more likely to experience insomnia and to have a high rate of suicidal behavior (19,20). In addition to objective (PSG) measures that summarize wakefulness with a single value, dynamic semicontinuous electrophysiological signals from alpha (8–12 Hz) and beta (18–26 Hz) waveforms known to be associated with alertness and wakefulness were also used. The inclusion of the latter allowed the more direct assessment of arousal as a brain process that could then be related to NDSI. To our knowledge, no studies have specifically explored the relationship between NDSI and the waveforms associated with alert and relaxed wakefulness; while such a relationship cannot be determined to be causal, the findings could further elucidate the link between nocturnal wakefulness and suicide risk.

## METHODS AND MATERIALS

### Participants

Participants were drawn from a previously published randomized controlled crossover trial of ketamine in unmedicated TRD (21). The current study included 33 participants with MDD ($n$ = 20; 61% female; mean age = 35.97 years [SD = 9.8 years]) (see Table S1 for additional demographic information). All participants were inpatients admitted voluntarily to a psychiatric inpatient unit over the course of their participation in the clinical trial; PSG was collected the night before the first infusion of either ketamine or placebo. Participants were eligible for the clinical trial if they were 18 to 65 years of age, were diagnosed with recurrent MDD without psychotic features on the Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Version, and had not responded to at least one antidepressant medication during the current depressive episode. In addition, participants were required to have a score of at least 20 on the Montgomery–Åsberg Depression Rating Scale (MADRS) (22) at screening and before PSG. Suicidal thoughts were permitted in this study unless the participants were considered to be at imminent suicide risk or endorsed a score of more than 4 on the MADRS suicide item, in which case they were removed from the protocol and received clinical treatment. The aims of the clinical trial were to evaluate the biological mechanisms of action of ketamine; all participants were free of psychotropic medications for at least 2 weeks (5 weeks for fluoxetine, 3 weeks for aripiprazole) before baseline assessment and PSG and were considered to be in good physical health based on medical history, physical exam, blood labs, electrocardiogram, chest x-ray, urinalysis, and toxicology. Furthermore, all participants had PSG results without an abnormal finding of first REM episode preceding first NREM episode. All participants provided written informed consent, and the study was approved by the National Institutes of Health Combined Neuroscience Institutional Review Board (NCT00088699).

### Clinical Ratings

Ratings were obtained the morning after PSG, before administration of ketamine or placebo. SI was measured using a factor score derived from the results of a previously published exploratory factor analysis (23). Briefly, this factor score is based on the MADRS suicide item, the Beck Depression Inventory suicide item, and the Beck Depression Inventory pessimism item. Scores range from 0 to 1, with higher scores representing greater SI. MADRS total score with the MADRS suicide item removed was used to measure the overall severity of depressive symptoms. All the information necessary to calculate factor scores prior to the PSG was not available, but clinical consensus ratings that included the MADRS suicide item were collected from the week before the PSG. The consensus MADRS SI item (CMSI) (scores from 0 [no SI] to 6 ["Explicit plans for suicide when there is an opportunity. Active preparations for suicide."]) was available for 26 of the 33 participants and was used to evaluate the stability of SI ratings.

### PSG and Spectral Estimation

Overnight PSG was performed the night before the clinical assessments and followed a night of sleep adaptation to the PSG with one exception; that participant completed the PSG 2 nights before the clinical assessments and without an adaptation night. EEGs were recorded using a Nihon-Kohden system (Neurofax version 05-50; Nihon-Kohden) and Polysmith Acquisition and Review Software (version 4.0.25.0; Nihon-Kohden). Electrooculograms and submental electromyograms were used to evaluate eye movements and muscle activity, respectively. All EEGs were scored by reviewers blinded to diagnosis using guidelines established by Rechtschaffen and Kales (24). Further description of the summary PSG scores and power spectral density estimates can be found in the Supplemental Methods.

### Statistical Methods

Next-day SI was regressed on WASO, SE, and total sleep time (TST). For each of these three models (one per measure), sex, age, and next-day MADRS total score (summed without the SI item) were included as covariates.

**Functional Data Analysis.** Power spectral density time series data were aligned from all participants at sleep onset

(defined as the first epoch of stage 2 sleep; average onset = 1:37 AM). A total of 5.4 hours (648 30-second epochs) of post–sleep onset recordings were used in order to include the minimum observed post–sleep onset duration. One participant's data were omitted from all functional data analyses because they had a particularly short post–sleep onset PSG recording.

Two multilevel functional principal component analyses (MFPCAs) (25) were conducted: one included four alpha (8.0–11.99 Hz) frequencies (alpha MFPCA) per participant and one included eight beta (18.0–25.99 Hz) frequencies (beta MFPCA) per participant (see Figure S1 for a schematic of the data analysis pipeline). Multiple frequencies were included, rather than averages within alpha and beta bands, in order to minimize the extent to which the time series data were collapsed and simplified and because evidence suggests that frequency within a band may vary relative to magnitude or intercept (26). Briefly, MFPCA permits multiple time series per person and takes into account the semicontinuous nature of the data by treating each frequency for each person as a function of time. Eigendecomposition of smoothed covariance matrices generates eigenfunctions or curves that represent the primary orthogonal axes or latent patterns of variation evident in sleep processes at both the within- and between-subjects level, similar to variance estimation in mixed-effects models. In MFPCA, each time series is approximated with a few eigenfunctions or PCs that meet predefined criteria for total variance accounted as well as for the variance accounted for per PC. Thresholds were initially set at the between-persons level (level 1) at a combination of at least 90% total variance explained and a minimum of 5% variance accounted for per PC after setting the maximum allowable number of PCs to 30. However, because this combination did not exist in the data, our threshold was set at a minimum of 5% variance accounted for per PC. Once the number of PCs was set, the eigenfunctions were calculated and the PC scores were estimated; these were normalized to a mean of 0 and an SD of 1. Every participant had a PC score for each PC, and the PC scores could be interpreted as weights that measure how much a person's alpha or beta temporal dynamics were like those represented by the corresponding PCs. Additional details of the equations used to estimate the relationship between NDSI and PCs can be found in the Supplemental Methods.

Given the difficulties associated with null hypothesis significance testing, $p$ values, and power when conducting secondary data analyses from clinical trials (27,28), a Bayesian approach to parameter estimation was used for all regression models. Weakly informative Gaussian priors ($b \sim N0, 1$) were used for all regression slope coefficients, and half-Cauchy priors were used for $\sigma$. Trace plots were used to assess Markov chain Monte Carlo performance for each parameter, and posterior predictive check plots were used to assess whether the model was a reasonable fit to the data. The following statistics are reported for point estimates and hypotheses: posterior means for slope coefficients with 90% credible intervals, posterior probabilities (e.g., evidence in favor of a hypothesis such as a nonzero positive or nonzero negative association with NDSI), and evidence ratios (ERs) (e.g., evidence in favor of a positive relationship/slope vs a negative relationship/slope or vice versa). All Bayesian models were run using the brms package (29) in R (Version 3.6; R Foundation for Statistical Computing).

Pearson correlations with bootstrapped confidence were used to explore the relationships between MFPCA PC scores (level 1) and global sleep summary metrics. Because average alpha and beta power are often used to measure arousal in the insomnia literature, MFPCA PC scores were also correlated with alpha and beta power averaged (per person) over the same time and frequencies used for the MFPCA analyses. Post hoc analyses were conducted using the CMSI and focused on providing conceptual guard rails to limit any causal implications specifically related to sleep metrics that appeared to be related to NDSI. To do this, the similarity between SI measured before and after the PSG was assessed, and variations were explored in the relationship between arousal and SI measured before versus after the PSG. Last, we determined whether including the CMSI (SI measured before the PSG) altered the meaning of positive findings.

## RESULTS

### Sample Characteristics

Average WASO was 23.3 minutes, although considerable variability in this measure was noted (range, 30 seconds to 83 minutes). Average TST was 6.57 hours (range, 5.03–7.45 hours). The participants were, on average, moderately depressed (mean MADRS score without SI item = 30.94 [SD = 4.26]), and 61% reported a lifetime suicide attempt. Additional details are provided in Table 1.

### Regression Results

The relationship between WASO and NDSI was essentially flat (slope = 0.003 [90% credible interval, 0.00 to 0.01]), with a posterior probability that the estimated slope was $>0$ = 0.92 (i.e., 92% of the posterior distribution was associated with slope values $>0$) and an ER of 12.9. The results did not support a relationship between NDSI and either TST (slope = −0.015 [90% credible interval, −0.09 to 0.06], ER = 0.58, posterior probability = 0.37) or SE (slope = −0.001 [90% credible interval, −0.01 to 0.01], ER = 0.54, posterior probability = 0.35).

### Functional PC Analysis

For the alpha MFPCA, a three-component solution accounted for 82% of the total variance at the between-persons level. The first component (alpha PC1) accounted for 68% of the total variance, which represented a somewhat constant shift in alpha power over time. The second and third alpha MFPCA PCs (alpha PC2 and PC3) accounted for 8% and 6% of the total variance, respectively, and represented oscillatory patterns in alpha power over time (see Figure 1). A similar pattern was observed at the between-persons level for the beta MFPCA results. The first three PCs (referred to as beta PC1, PC2, and PC3) accounted for 79% of the total variance. The first beta PC accounted for 64% of the total variance and represented a constant shift in beta power over time. The second and third components accounted for 9% and 6% of the variance, respectively, and represented oscillatory patterns with varying degrees of increasing and

**Table 1. Clinical and Sleep-Related Characteristics of the Study Sample (*N* = 33)**

| | Mean (SD) | Median | Minimum | Maximum |
|---|---|---|---|---|
| PSG Measures | | | | |
| WASO, min | 23.3 (19.34) | 18.0 | 0.50 | 83.00 |
| Sleep efficiency, % | 87.76 (7.72) | 89.2 | 69.36 | 97.16 |
| Stage 1 duration, min | 30.56 (15.18) | 28.5 | 7.50 | 62.00 |
| Stage 2 duration, min | 234.27 (34.7) | 228.0 | 183.00 | 313.00 |
| Stage 3 duration, min | 24.89 (24.16) | 17.0 | 0.00 | 90.50 |
| REM duration, min | 103.45 (28.51) | 101.0 | 55.50 | 162.50 |
| TST, hours | 6.57 (0.7) | 6.8 | 5.03 | 7.45 |
| REM latency, hours | 1.13 (0.75) | 0.9 | 0.32 | 3.73 |
| Clinical Measures | | | | |
| MADRS total score[a] | 30.94 (4.26) | 31.0 | 22.00 | 40.00 |
| Suicidal ideation factor score[b] | 0.38 (0.18) | 0.4 | 0.06 | 0.72 |

MADRS, Montgomery–Åsberg Depression Rating Scale; PSG, polysomnography; REM, rapid eye movement; TST, total sleep time; WASO, wakefulness after sleep onset.

[a]Suicide item omitted from total score.

[b]Calculated from a previous exploratory factor analysis (23), the suicidal ideation factor score combines the MADRS suicide item, the Beck Depression Inventory suicide item, and the Beck Depression Inventory pessimism item.

decreasing power over time (see Figure 1). Most of the variability in the data was accounted for by person-to-person variability rather than by frequency-to-frequency variation within people (level 2) (0.89 for alpha MFPCA and 0.98 for beta MFPCA), indicating relatively little variation between frequencies within an individual.

## Regression Analyses

Alpha MFPCA PC2 had a negative relationship with NDSI (greater decline in alpha over time related to lower NDSI) (Figure 2), although the results could not rule out a flat relationship (slope = −0.07 [90% credible interval, −0.14 to 0.00], ER for nonzero negative relationship = 19.9, posterior probability of slope <0 = 0.95). The direction of the PC2 slope remained negative after removing an outlier visible in Figure 2 (see Figure S2 for the plot with the outlier removed) (slope = −0.17 [90% credible interval, −0.29 to −0.05]). Weaker support was observed for the relationship between NDSI and MFPCA alpha PC1 and PC3 (PC1 slope = −0.01 [90% credible interval, −0.03 to 0.02], ER for nonzero negative relationship = 2.14, posterior probability = 0.68; PC3 slope = −0.02 [90% credible interval, −0.01 to 0.07], ER for nonzero negative relationship = 1.71, posterior probability of slope <0 = 0.63).

Beta MFPCA PC2 scores were strongly positively related with NDSI (slope = 0.09 [90% credible interval, 0.03 to 0.14], ER = 214.38, posterior probability of slope >0 = 99.9), such that greater NDSI corresponded to a pattern of increasing beta power over the 5.4 hours of post–sleep onset. A flat relationship between NDSI and beta MFPCA PC3 (slope = −0.06 [95% credible interval, −0.13 to 0.01], ER = 13.43, posterior probability slope <0 = 0.93) could not be ruled out, and the results did not support a relationship between NDSI and PC1 (slope = 0.01 [90% credible interval, −0.01 to 0.03], ER = 2.8, posterior probability slope >0 = 0.74).

As a supplemental analysis, alpha and beta MFPCA PC scores were correlated with MADRS score with the SI item removed; all bootstrapped 95% confidence intervals crossed zero (see Figure S3). Additional analyses of the relationship

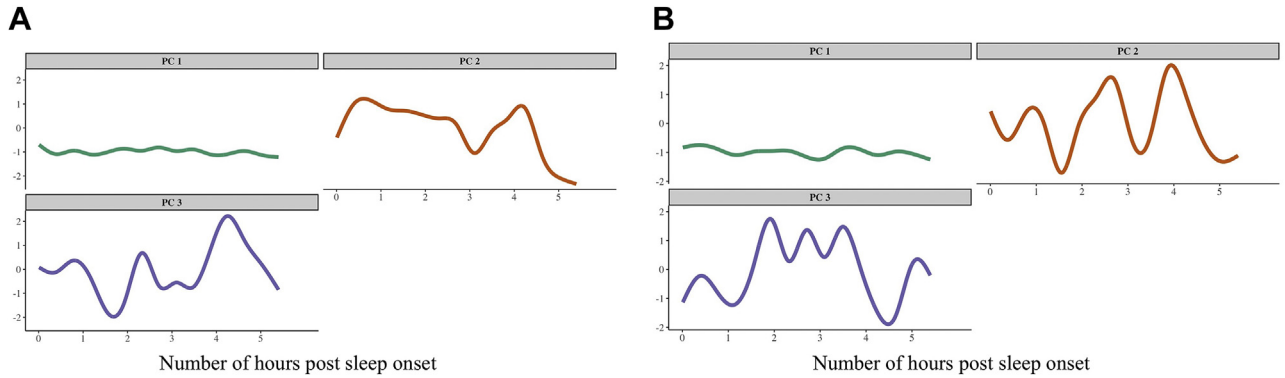


**Figure 1.** Results from multilevel functional principal component (PC) analysis of alpha and beta power. The three PCs/eigenfunctions from each multilevel functional PC analysis, **(A)** alpha and **(B)** beta, are depicted. The y-axis reflects relative increases (higher values) and decreases (lower values) in power.

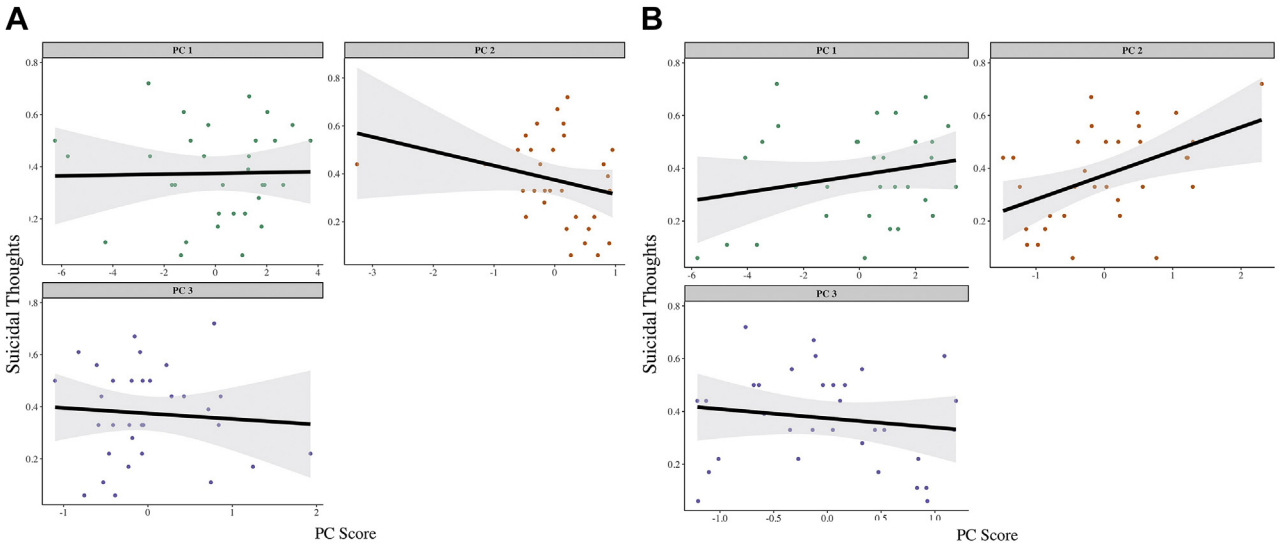


**Figure 2.** Relationship between principal component (PC) scores and next-day suicidal ideation (NDSI). Scatter plots with regression lines (shaded region is 95% confidence interval) show the relationship between NDSI (y-axis) and PC scores from **(A)** alpha and **(B)** beta multilevel functional PC analyses (x-axes). NDSI was assessed using previously derived exploratory factor analysis scores (23). The direction of the relationship between NDSI and alpha PC2 scores remained negative after removing the outlying data point (Figure S2).

between beta MFPCA PC scores and anxiety disorder diagnoses can be found in the Supplemental Results.

## Correlations Between PC Scores and Alpha and Beta Power

To evaluate the overlap between PC scores and average alpha and beta power, which are more commonly used in the research literature, Pearson correlations with bootstrapped confidence intervals are presented in Table 2. Beta MFPCA PC1 scores were strongly negatively correlated with average beta power ($r$ = −0.985; bootstrapped 95% CI, −0.99 to −0.98), such that greater beta power was associated with lower beta PC1 scores (see Figure 3). Similarly, alpha PC1 scores were strongly negatively correlated with average alpha power ($r$ = −0.84; 95% CI, −0.92 to −0.67), such that greater alpha power was associated with lower alpha PC1 scores. The remaining correlation coefficients between PC scores and average alpha and beta power averaged over the night were hard to distinguish from zero (see Table 2). In addition, average

**Table 2. Correlations Between PC Scores and PSG Metrics of Wakefulness**

| | Beta MFPCA PC Scores | | | Alpha MFPCA PC Scores | | |
|---|---|---|---|---|---|---|
| | $r$ | Lower 95% CI Limit | Upper 95% CI Limit | $r$ | Lower 95% CI Limit | Upper 95% CI Limit |
| PC1 vs. WASO | −0.67[a] | −0.79 | −0.44 | −0.59[a] | −0.80[a] | −0.32[a] |
| PC1 vs. Sleep Efficiency | 0.39[a] | 0.15 | 0.63 | 0.38 | −0.06 | 0.71 |
| PC1 vs. TST | 0.15 | −0.12 | 0.53 | 0.21 | −0.32 | 0.52 |
| PC1 vs. Average Beta Power | −0.98[a] | −0.99 | −0.98 | – | – | – |
| PC1 vs. Average Alpha Power | – | – | – | −0.84[a] | −0.92 | −0.67 |
| PC2 vs. WASO | −0.07 | −0.49 | 0.48 | −0.30 | −0.69 | 0.53 |
| PC2 vs. Sleep Efficiency | −0.09 | −0.52 | 0.31 | 0.14 | −0.42 | 0.43 |
| PC2 vs. TST | −0.05 | −0.43 | 0.38 | 0.31 | −0.25 | 0.59 |
| PC2 vs. Average Beta Power | 0.00 | −0.40 | 0.32 | | | |
| PC2 vs. Average Alpha Power | | | | 0.01 | −0.39 | 0.65 |
| PC3 vs. WASO | −0.3 | −0.63 | 0 | 0.13 | −0.24 | 0.43 |
| PC3 vs. Sleep Efficiency | −0.06 | −0.35 | 0.34 | 0.17 | −0.03 | 0.35 |
| PC3 vs. TST | 0.04 | −0.27 | 0.43 | 0.02 | −0.26 | 0.31 |
| PC3 vs. Average Beta Power | 0.00 | −0.37 | 0.40 | – | – | – |
| PC3 vs. Average Alpha Power | – | – | – | −0.01 | −0.28 | 0.30 |

MFPCA, multilevel functional principal component analysis; PC, principal component; PSG, polysomnography; TST, total sleep time; WASO, wakefulness after sleep onset.

[a]CIs do not include zero.

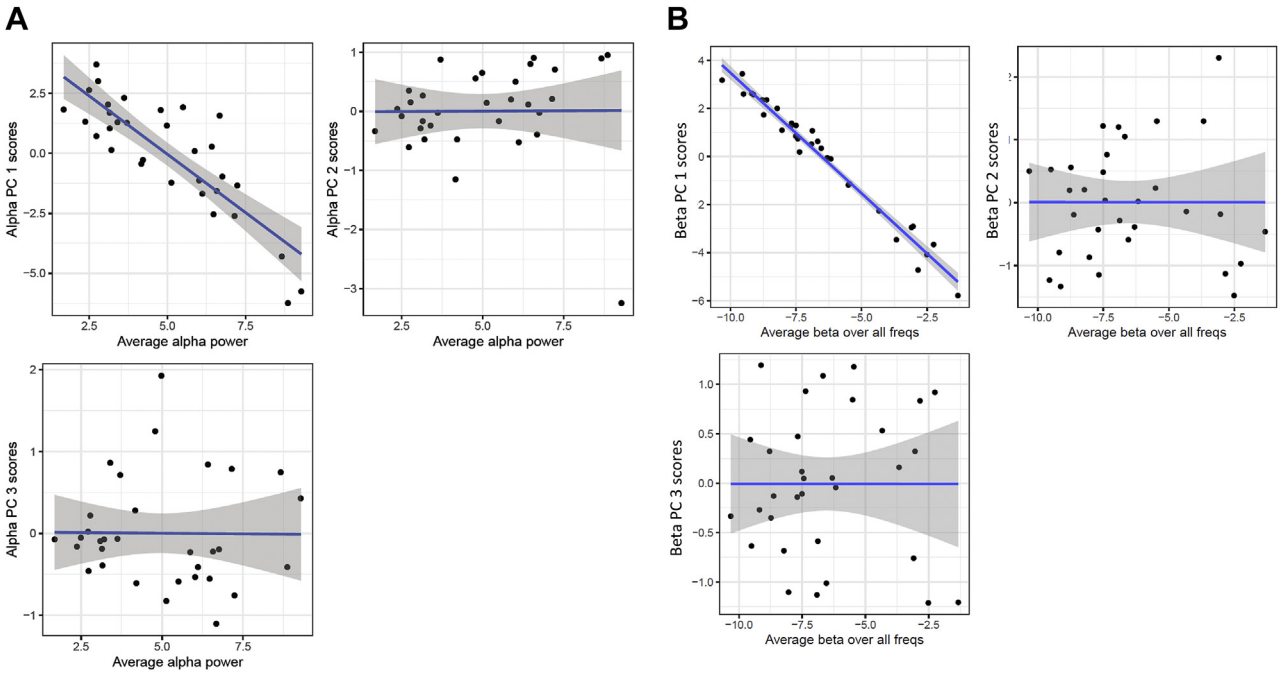


**Figure 3.** Alpha and beta principal component (PC) scores compared with average alpha and beta power. Scatter plots with regression lines (shaded region is 95% confidence interval) show the relationship between **(A)** alpha and **(B)** beta multilevel functional PC analyses. PC scores with the respective average alpha and beta power (units are in dB/Hz). freq, frequency.

alpha and beta power were not associated with NDSI (data are not shown but are available upon request).

## Correlations Between PC Scores and WASO, Sleep Efficiency, and TST

The relationship between PC scores and traditional PSG metrics is also presented in Table 2. Lower beta MFPCA PC1 scores (reflecting higher beta power) were associated with greater WASO values (more time awake) ($r$ = −0.67; bootstrapped 95% CI, −0.79 to −0.40) and lower SE ($r$ = 0.39; bootstrapped 95% CI, 0.15 to 0.63). In parallel fashion, lower alpha MFPCA PC1 scores (reflecting higher alpha power) tended to be associated with greater WASO values ($r$ = −0.59; 95% CI, −0.80 to −0.32). However, the results did not support a relationship between alpha PC1 and SE, nor was a relationship detected between any PC2 or PC3 scores and WASO, SE, or TST, suggesting that these scores identify electrophysiological activity distinct from traditional PSG metrics.

## Relationship Between Beta PC2 and Sleep Hypnogram

Given the strong relationship between NDSI and beta PC2 score, a post hoc, qualitative visual inspection of hypnograms from 3 participants with the highest beta PC2 scores and 3 participants with the lowest beta PC2 scores was conducted (Figure S4). The aim was to better understand how beta PC2 might connect to cycling between wake, REM, and non-REM sleep stages. Expert review (W.D.) of the hypnograms suggested that individuals with the highest beta PC2 scores generally had more disrupted and fragmented sleep, less slow-wave activity, and reduced overall rhythmic activity relative to the participants with the lowest beta PC2 scores.

## Post Hoc Analyses: Relationship Between Beta PC2, SI Prior to the PSG (CMSI), and NDSI

Spearman's correlation coefficients indicated that SI before (CMSI) and after (NDSI) the PSG were positively related (Spearman's $\rho$ = 0.66; bootstrapped 95% CI, 0.42 to 0.85), and that the CMSI was also positively, albeit not significantly (Spearman's $\rho$ = 0.17; bootstrapped 95% CI, −0.22 to 0.58), related to beta PC2 scores. In comparison, a significant relationship was observed between NDSI and beta PC2 scores (Spearman's $\rho$ = 0.43; bootstrapped 95% CI, 0.12 to 0.70), suggesting possible similarity in the direction of the relationship between beta PC2 scores and SI measures before and after the PSG. Additionally, when the CMSI was added in the model with the three beta PC scores and covariates as independent variables and NDSI as the outcome, the relationship between beta PC2 and NDSI was not meaningfully altered when controlling for pre-PSG SI ratings (see Table S2 for results of this analysis).

## DISCUSSION

By leveraging fluctuations in electrophysiological activity in alpha and beta power, the present study was able to identify temporal electrophysiological dynamics related to NDSI in a sample of medication-free participants with TRD. While the specific dynamic patterns should be interpreted with caution, the findings do suggest that electrophysiological patterns of wakefulness and alertness, as represented by beta power, are

associated with NDSI. This is a potentially critical step toward understanding the neurobiological processes related to suicide risk and sleep difficulties, lending further support of the presence of insomnia and hyperarousal in the acute suicide crisis. This relationship could not be explained by correlating the beta power findings with clinical assessments conducted before the PSG, suggesting a potential state-dependent relationship; however, the study design could not ascertain a causal relationship between sleep disruption and suicide risk. These results are also consistent with previous analyses that found an association between wakefulness between 4:00 and 5:00 AM and NDSI (9) and cannot be explained by the relationship between severity of depressive symptoms or average electrophysiological activity in alpha and beta power.

Our findings imply a potential imbalance between wake-promoting and sleep-promoting neural circuits in individuals with NDSI. Overnight alpha and beta power activity was previously linked with overall central nervous system hyperarousal in many psychiatric diagnoses also associated with SI, including MDD (16). Specifically, beta activity during sleep was found to be inversely associated with both slow-wave sleep and delta power (a marker of deep sleep) (30), as well as with relative cerebral glucose metabolism in the ventromedial prefrontal cortex and the right lateral inferior occipital cortex in participants with MDD and healthy volunteers (31). Beta power has also been associated with cortisol secretion, suggesting a link with the hypothalamic-pituitary-adrenal axis (32). Confirming this relationship, previous analyses of participants with MDD found that higher levels of SI were associated with increased fast frequency (alpha) power, decreased delta power, and increased alpha/delta sleep, indicating central nervous system hyperarousal (33). Because suicide risk is also associated with daytime hyperarousal, including increased anxiety (34), fear-potentiated startle (34), and alterations in hypothalamic-pituitary-adrenal axis function (35), results from the present study fit into current neurobiological theories of suicide while also providing a more precise potential electrophysiological target for suicide risk detection and intervention.

Importantly, the relationship between SI and arousal would not have been detected within this sample without an approach that included information contained in the temporal patterns and dynamics of electrophysiological activity. Consistent with this notion, the present study found no evidence to support the relationship between NDSI and either alpha or beta PC1, both of which entailed relatively minimal temporal fluctuations and could instead be understood as shrinkage estimators of average power (25). Both alpha and beta PC1 also had the strongest relationship with two global sleep metrics (WASO and TST) that similarly lacked convincing support for relationships with NDSI. Complementing PC1, most of the remaining PCs represented oscillating patterns over the course of the night, often echoing the expected 90-minute REM-NREM cycles. Together, PC1 and the temporally varying PCs encompassed two main sleep phenomena: decreased arousal level (each PC1) and cycling between increased and decreased levels of arousal (each PC2 and each PC3). In particular, beta PC2, which was most closely associated with NDSI, presented as a rhythmic oscillating pattern with gradually increasing power peaks as the night progressed. A visual inspection of the hypnograms from the individuals with the highest and lowest beta PC2 scores suggested that individuals whose beta oscillations were more like the pattern represented by PC2 (higher beta PC2 scores) tended to have more disrupted and fragmented sleep and less deep sleep (Figure S4). While the specific dynamic patterns represented by the PCs should be interpreted with caution until they are reproduced in an independent sample, our results suggest the possibility that increasing arousal over the night may be part of a larger process that underlies poor sleep quality and increases risk of NDSI.

Our results may also help inform the search for urgently needed, modifiable, near-term risk factors for suicidal thoughts and behaviors. Specifically, wakefulness-related biomarkers could be useful in clinical trials of sleep or insomnia-focused interventions to treat suicide risk. To date, the treatment literature for SI and insomnia has been mixed; for example, in the REST-IT (Reducing Suicidal Ideation Through Insomnia Treatment) trial for SI, zolpidem-CR reduced insomnia symptoms in a sample of suicidal patients, but a significant reduction in SI was only found on one of the two SI outcome measures (36). Secondary analyses suggested that the greatest reductions in treatment effects were found in those individuals with the most severe insomnia. In addition, an uncontrolled trial of cognitive behavioral therapy for insomnia in suicidal veterans showed a relationship between reduction in insomnia and improvement in SI (37), but other randomized clinical trials have yet to demonstrate similar results (38). Initial findings from the ketamine literature similarly suggest that SI response to ketamine is associated with normalization of nocturnal wakefulness (39), but these results have not yet been replicated using markers of alpha and beta power. It is possible that more precise biomarkers of wakefulness and arousal could help determine which individuals at risk of suicide are most likely to respond to sleep-focused interventions.

The study is associated with several strengths, including use of an unmedicated sample who were inpatients for the duration of the study. Additionally, there was little indication that the beta PC2 scores were related to CMSI ratings obtained a week before the PSG; however, lower power (there were fewer participants with CMSI ratings, and the CMSI is a single ordinal item as compared with the continuous NDSI)—as well as more time between the PSG and the CMSI—make it difficult to compare these correlation coefficients. Several potential limitations also exist. First, this is a secondary analysis of clinical trial data drawn from individuals with TRD rather than SI more specifically. TRD in this context was defined as failure to respond to one antidepressant trial, which is a lower threshold than other definitions of TRD in the literature, which include failure to respond to two trials; however, even with this inclusion criterion, the average number of failed trials in this sample was 6.4 (SD = 3.4). It will be critical to determine whether the relationships between SI and alpha and beta power occur similarly across psychiatric diagnoses, as TRD has been linked to both suicide risk and insomnia (19,20). For example, while the present study found no evidence of a significant relationship between alpha and beta oscillations and depressive symptoms (without SI), it is possible that this relationship could differ across other psychiatric diagnoses known to affect both suicide risk and sleep patterns, such as bipolar disorder or posttraumatic

stress disorder. Second, because no estimates of uncertainty for PC scores were available, it is unclear how stable these findings would be in a second sample. Given the magnitude of individual differences in these data, however, it is possible that the shared underlying structure evident in the PCs represents basic aspects of sleep dynamics present in all adults. Third, data were lacking regarding homeostatic sleep state and sleep apnea diagnosis, both of which are potential sources of noise in PSG data. Future analyses could include wrist actigraphy to assess the presence of homeostatic sleep state and daytime activity. Although no difference in beta PC2 scores was detected between participants with an anxiety disorder and those without an anxiety disorder, it is possible that comorbid anxiety could play a role in the relationship between beta PC and NDSI outcome. Last, all studies were conducted on a psychiatric inpatient unit; this milieu impacts sleep by imposing regular wake-up times, meetings, unit activities, and observation checks, thus limiting generalizability.

In summary, this evaluation into the dynamic changes in nighttime alpha and beta power demonstrated that oscillations in the beta frequency band were associated with NDSI. While the results require replication and are not thought to reflect a causal relationship, they further underscore the association between arousal and wakefulness over the course of the night and suicide risk. Practical implications of the results for clinicians include the detailed assessment of sleep disruptions in patients at risk for suicide as a potential suicide risk factor. Further evaluation of the relationship between the neurobiology of sleep-related arousal and suicide risk is indicated.

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CAZ is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorder. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Rapid Antidepressant Effects of Ketamine in Major Depression; https://clinicaltrials.gov/ct2/show/NCT00088699; NCT00088699.

## ARTICLE INFORMATION

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