Clinical Neurophysiology 156 (2023) 272–280

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

# EEG wakefulness regulation in transdiagnostic patients after a recent suicide attempt

Annia Rüesch [a,*], Cheng-Teng Ip [b], Anna Bankwitz [a], Tania Villar de Araujo [a], Christoph Hörmann [a], Atalìa Adank [a], Georgios Schoretsanitis [c,d,e], Birgit Kleim [a,f], Sebastian Olbrich [a]

[a] University of Zurich, Psychiatric University Hospital Zurich, Department of Psychiatry, Psychotherapy and Psychosomatics, Zurich, Switzerland
[b] Center for Cognitive and Brain Sciences, University of Macau, Taipa, Macau SAR, China
[c] Psychiatric University Hospital Zurich, Zurich, Switzerland
[d] The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, NY, USA
[e] Department of Psychiatry, Zucker School of Medicine at Northwell/Hofstra, Hempstead, NY, USA
[f] University of Zurich, Institute of Psychology, Experimental Psychopathology and Psychotherapy, Zurich, Switzerland

## HIGHLIGHTS

- We assessed EEG wakefulness regulation with the Vigilance Algorithm Leipzig in transdiagnostic patients after a suicide attempt.
- A distinct vigilance pattern was observed in patients, characterized by a steep climb of vigilance during the first 3 minutes.
- Significant correlations of suicidal ideation with the vigilance slope and stage A1 could serve as markers of suicidal behavior.

## ARTICLE INFO

*Article history:*
Accepted 22 August 2023
Available online 6 September 2023

*Keywords:*
Suicide attempts
Wakefulness regulation
Vigilance Algorithm Leipzig (VIGALL)
Resting-state EEG
Biomarker

## ABSTRACT

*Objective:* Decades of research have not yet produced statistically reliable predictors of preparatory behavior eventually leading to suicide attempts or deaths by suicide. As the nature of suicidal behavior is complex, it is best investigated in a transdiagnostic approach, while assessing objective markers, as proposed by the Research Domain Criteria (Cuthbert, 2013).
*Methods:* A 15-min resting-state EEG was recorded in 45 healthy controls, and 49 transdiagnostic inpatients with a recent (<6 months) suicide attempt. Brain arousal regulation in eyes-closed condition was assessed with the Vigilance Algorithm Leipzig (VIGALL) (Sander et al., 2015).
*Results:* A significant incline of median vigilance and vigilance slope was observed in patients within the first 3-min of the EEG recording. Additionally, a significant positive correlation of self-reported suicidal ideation with the vigilance slope over 15-min recording time, as well as a significant negative correlation with EEG vigilance stage A1 during the first 3-min was found.
*Conclusions:* Transdiagnostic patients with a recent suicide attempt show a distinct vigilance regulation pattern. Further studies including a control group consisting of patients without life-time suicide attempts are needed to increase the clinical utility of the findings.
*Significance:* These findings might serve as potential objective markers of suicidal behavior.


## 1. Introduction

One substantial challenge in suicide risk assessment is the lack of objective and reliable predictors. While psychological theories of suicidal thoughts and behavior (STB) (Joiner, 2005; Klonsky et al., 2016; 2017; 2018; Mann, 2003; O'Connor, 2011; O'Connor and Kirtley, 2018; Rudd, 2000; Schotte and Clum, 1982, 1987; Van Orden et al., 2010; Wenzel and Beck, 2008) provide a solid mechanistic framework to understand suicidal behavior, they have not yet yielded statistically reliable predictors (Bhatt et al., 2018; Franklin et al., 2017). However, supplementary screening tools to assist with clinicians' suicide risk assessments are urgently needed as a worldwide estimate of 10 to 14 million suicide attempts each year is reported (WHO, 2019). The difficulties in the prediction of preparatory actions that eventually lead to a suicide attempt or death by suicide originate from the complex nature of STB

* Corresponding author at: Psychiatric University Hospital Zurich, Lenggstrasse 31, CH-8032 Zurich, Switzerland.
*E-mail address:* anniacarolina.rueesch@uzh.ch (A. Rüesch).

https://doi.org/10.1016/j.clinph.2023.08.018
1388-2457/© 2023 International Federation of Clinical Neurophysiology. Published by Elsevier B.V.

(Glenn and Nock, 2014). Often, individuals who suffer from suicidal ideations do not disclose their intentions to die by suicide (Bernecker et al., 2019). This constitutes a serious bias for suicide risk assessment through self-report psychometric instruments. Consequently, existing clinical suicide risk evaluation tools have been criticized for their low sensitivity and low positive predictive value (Kessler et al., 2020; Nock, 2016). A recent study by Randall et al. (2019) found that the clinician's opinion as well as two standardized suicide assessment questionnaires predicted future suicidal behavior with only a low to moderate accuracy. Furthermore, most individuals who experience suicidal ideation to not ever carry out actions to end their own life (Klonsky et al., 2017). Finally, while suicidal behavior primarily occurs in the context of mental illness, psychiatric diagnoses themselves are criticized to lack validity. As psychiatric diagnoses are mainly based on psychopathological syndromes with a high overlap between clinical entities, they are inadequate conceptualizations of underlying pathophysiological causes (Ghaemi, 2018; Stein and Reed, 2019). In addition, many patients who display STB are diagnosed with several comorbidities (Park et al., 2018). To conclude, the previously discussed difficulties in suicide risk assessment call for reliable objective, ideally transdiagnostic predictors, which can be easily implemented in the clinical practice, such as biomarkers (Garcia-Gutierrez et al., 2020; Venigalla et al., 2017). Analogously, a transdiagnostic and phenotype-based approach which aims to overcome a merely descriptive, symptom-based definition of mental disorders is proposed by the Research Domain Criteria (RDoC) (Cuthbert and Insel, 2013).

In the context of STB, disturbed arousal regulation is a particularly interesting biomarker. Specifically, in a recent meta-analysis by Glenn et al. (2018) "arousal and regulatory systems" were named as promising biomarkers within the RDoC, with a statistically significant relationship to suicidality. Furthermore, increased STB are linked with a heightened arousal on a behavioral level (Rudd, 2000), and several of the modulatory systems involved in brain arousal regulations (Brown et al., 2012; Oken et al., 2006; Sander et al., 2015), such as the serotonergic system (Sudol and Mann, 2017), and the hypothalamo pituitary adrenal (HPA) axis (Johnston et al., 2022; O'Connor et al., 2017), have been associated with suicidal behavior. However, current research on the relation between arousal regulation and suicide attempts is scare. Hereby, EEG can provide an easy and objective method to examine brain activity as well as brain arousal. Notably, eyes-closed resting-state EEG is clinically feasible to be applied to a vulnerable patient population.

The resting-state EEG "vigilance model" (Oken et al., 2006; Sander et al., 2015) provides a comprehensive framework to interpret psychiatric symptoms in the context of brain arousal regulation. The vigilance model understands wakefulness regulation as an autoregulation of behavior, allowing adaptation of brain arousal to situational requirements. EEG-based vigilance can be assessed by the application of the Vigilance Algorithm Leipzig (VIGALL) to resting-state EEG data. Hereby, VIGALL classifies electrophysiological wakefulness patterns into distinct categories, which reflect the transition from full awareness to the onset of sleep. These categories encompass EEG frequency band measurements, cortical activity distributions assessed with source localization tools, and eye movements. Hereby, higher vigilance stages are characterized by dominant alpha-activity that slowly decreases with declining vigilance. Lower vigilance stages are defined by the appearance of slow eye movements (SEM), followed by increased delta- and theta-band activity. The on-set of sleep is marked by the appearance of typical EEG sleep pattern, such as K-complexes and sleep spindles. Vigilance dysregulation is hypothesized to be a pathogenic factor in several mental illnesses. While a steadily declining vigilance towards sleep-onset is typically observed in healthy subject under eyes-closed condition, a "hyperstable vigilance" was found in depressed patients (Hegerl and Hensch, 2014; Hegerl et al., 2012; Ip et al., 2021; Olbrich et al., 2012). Hereby, a "hyperstable" vigilance is characteristic by a delayed or missing decline of wakefulness towards lower vigilance stages, resulting in an EEG recording almost exclusively dominated by alpha frequency activity. Oppositely, a "unstable" or "labile" vigilance, marked by an almost immediate drop of EEG vigilance from full wakefulness to lower vigilance stages, and the appearance of EEG sleep patterns as soon as the eyes are closed, was observed in patients diagnosed with mania or attention-deficit/hyperactivity disorder (ADHD) (Berger et al., 2021; Hegerl et al., 2009) as well as in patients with borderline personality disorder (Hegerl et al., 2008). The vigilance model framework links arousal regulation with clinical symptoms on the behavioral level. Studies (Hegerl and Hensch, 2014; Hegerl et al., 2012) suggest that typical symptoms of depression, such as withdrawal, avoidance of sensations, and difficulties to fall asleep, can be understand as effort to autoregulate a "hyperstable" vigilance. Contrastingly, the experience-seeking behavior in ADHD and mania might be driven by behavioral attempts to stabilize vigilance regulation (Hegerl et al., 2009). Furthermore, a recent study by Jawinski et al. (2021) has connected low EEG arousal to higher scores in the NEO personality dimensions extraversion, openness to experience, and the sub-item impulsiveness. Notably, EEG vigilance has been proposed as a candidate biomarker to inform medical treatment decisions in psychiatric patients (Hegerl and Hensch, 2017; Ip et al., 2021; Olbrich et al., 2016).

However, the vigilance regulation framework has not yet been investigated in the context of suicidal behavior. Previous EEG research on STB is restricted to frequency band analysis in healthy or depressed individuals, and the reported results are conflicting. Lower frontal beta and gamma activation as well as higher occipital alpha power during resting-state condition has been reported in individuals who suffer from suicide ideation or a history of life-time suicide attempts (Benschop et al., 2019), but only the results for alpha power were replicated (Krepel et al., 2021). Further studies connected, in contrast, higher gamma power (Arikan et al., 2019), or higher frontal theta power (Lee et al., 2017) with suicidal ideation, while Dolsen et al. (2017) associated higher alpha power and higher levels of suicidal ideation in sleep EEG. Importantly, within the context of wakefulness arousal and sleep, higher alpha activation is generally associated with higher wakefulness stages, while theta and delta activity is predominately found during deeper wakefulness stages. Taken together, the investigation of vigilance regulation in mental health patients with STB not only provides further clarification on dominant frequency band rhythms, but also offers an insight into the dynamic frequency band changes over time. However, suicidal ideation has been reported to be a "weak predictor" of consecutive suicidal acts (Hawton et al., 2022). So far, a preceding suicide attempt is considered to have the strongest prediction value of future suicide attempt (Franklin et al., 2017; WHO, 2019). This implies that the pathophysiology of STB is best studied in patients after a recent suicide attempt. Furthermore, as STB is not restricted to patients diagnosed with depression, a transdiagnostic study group is needed.

The aim of this paper is to investigate the association between EEG vigilance and STB to detect possible STB-specific pattern in a diagnostically heterogeneous sample of in-patients with a recent (<6 month) suicide attempt, compared to healthy controls without a life-time history of mental illness or suicide attempts. Based on the previous literature on resting-state or sleep EEG in patients with suicidal thoughts and behavior, we expect to find a greater number of higher vigilance stages in patients after a suicide attempt.

## 2. Materials and methods

### 2.1. Design and participants

Study data were collected over a period of three years within the wards and outpatient settings of the Psychiatric University Hospital Zurich, the largest mental health care provider in Switzerland, with a catchment area of approximately 1.2 million people. 49 adult patient (≥18 years) with a recent suicide attempt (within the past six months) consented to study participation. Suicide attempts were defined as behavior with an intent to die (e.g., intoxication with medication and/or drugs, jumping from elevated grounds or in front of a vehicle, attempts to hang, suffocate or drown oneself, or the intended use of fire weapons), or as behavior involving a high risk of eventual death (e.g., intentional speeding on the highway, repeated drug overdosing), following the definition of Wolfersdorf and Etzersdorfer (2011). Within the framework of the overarching study project, all patients were randomized to receive a short psychotherapeutic intervention, specifically targeted at patients with a recent suicide attempt (ASSIP – Attempted Suicide Short Intervention Program (Gysin-Maillart et al. (2016)). Therefore, patients under the influence of acute psychosis, diagnosed with dementia or other severe cognitive impairments, and patients exhibiting chronical non-suicidal self-harming behavior were not considered eligible. Likewise, patients undergoing current electroconvulsive therapy and patients who executed suicidal acts during an episode of acute psychosis or under the influence of delusional thoughts were not included into the study. In addition to the psychiatric patients, 45 healthy controls were recruited from the general public via online advertisement. Before study participation, the controls were screened for exclusion criteria involving life-time suicide attempts, history of psychiatric illness, or chronic medical conditions. Patients' prescribed medication as well as psychiatric and somatic diagnoses were recorded from the electronic medical files at the assessment day. All study participants were provided with extensive details on the study and signed informed consent before participation. The study was carried out in accordance with the Declaration of Helsinki 2008 and was approved by the Ethics Commission of the Canton Zürich (Kantonale Ethikkommission Zürich). The study was registered under the project ID: 2019-01616.

### 2.2. Clinical assessment and diagnostic procedures

All study participants were instructed to fill out the German version of the Beck scale for suicide ideation (BSS) right before the recording of the EEG. The BSS is a standardized questionnaire used to assess the severity of suicidal ideation. Items measuring past and active suicidal ideation, suicide intentions during the past seven days, and history of suicide attempts, are rated on a 3-point scale ranging from 0 to 2. A maximum of 38 points can be reached (Beck et al., 1979).

The German 21-items version of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Strauß and Schumacher, 2004) was assessed with patients and controls to record the presence and severity of depressive symptoms on the day of the recording. The sum scores are interpreted as followed: 0 to 7 points: no depressive symptoms, 8 to 16 points: mild depressive symptoms, 17 to 23 points: moderate depressive symptoms, and scores over 24 points: severe depressive symptoms (Sharp, 2015).

To confirm the psychiatric diagnoses of the patients, respectively, to screen healthy controls for the presence of current or past psychiatric symptoms, the Mini International Neuropsychiatric Interview, German Version 5.0.0 (Sheehan et al., 1998) was conducted with all study participants. Furthermore, medical and life–time suicide attempt history was recorded together with demographic and socioeconomic data.

### 2.3. EEG recording

Electroencephalographic measurements were obtained using the eego™ recording software and the amplifier model EE-225 (ANT Neuro, Hengelo, Netherlands). The 15-min eyes-closed resting state EEG was recorded with 64 Ag/AgCI electrodes, placed on a waveguard™ cap (ANT Neuro GmbH, Netherlands) according to an extended international 10–20 system, at a sampling rate of 4 kHz. Additionally, signals for horizontal and vertical eye movement were recorded by a drop led electrode affixed on the infraorbital region of left eye, and two bipolar electrodes attached near the outer canthus of each eye respectively. Electrode impedances were kept under 50kΩ. The EEGs were recorded between 10:00 a.m. and 03:00 p.m. in a dimly lit room, while temperature was kept constant at around 22 °C. Prior to the recording, the participants received instructions to keep their eyes closed, relax their body, and remain still during the time of recording.

### 2.4. EEG processing and classification of vigilance stages

The eyes-closed resting-state EEG data were pre-processed using BrainVision Analyzer 2 (BrainVision Analyzer 2, 2019). Out of the recorded 64 channels, 25 were selected according to the VIGALL 2.1 manual (https://research.uni-leipzig.de/vigall). A FIR bandpass filter with cut-off frequencies of 0.5 Hz and 70 Hz, as well as a 50 Hz notch filter were applied. Likewise, electrooculogram channels were filtered with only a low-pass of 70 Hz and a 50 Hz notch filter to retain slow eye movement. Thereafter, all channels were re-referenced from CPz channel to average. Subsequently, the EEG data were segmented into 1-second epochs and visually screened for artefacts. Technical and muscular artefacts were marked, but not removed to maintain the full 15-min sample. Before running the independent component analysis for the correction of eye-movement artefacts, the EEG data were downsampled to 500 Hz. Lastly, the data were visually screened and sleep elements (sleep-spindles and K-complexes, as defined by Rodenbeck et al. (2006)) were marked.

In the next step, for each participant, the EEG-vigilance stages for every 1-sec epoch over the whole 900-sec time series (15*60) were automatically classified by the Vigilance Algorithm Leipzig plug-in of the BrainVision Analyzer (VIGALL 2.0, 11, 12), following the classification rules defined by Bente (1977), Roth (1961), and Santamaria and Chiappa (1987). Hereby, seven different vigilance stages were differentiated: Stage 0 marks the highest arousal in a state of alertness, followed by, in a declining order, relaxed wakefulness (stages A1, A2, A3), drowsiness (B1, B2/3) and sleep onset (stage C) (see Fig. 1). The A stages are defined by alpha dominance that gradually shifts from occipital regions (A1) to central and temporal (A2), and lastly to mainly frontal (A3) cortical regions with increasing relaxation. Epochs with no alpha activity are classified as stage 0 if there is no simultaneous occurrence of horizontal slow eye movement (SEM) (Santamaria and Chiappa, 1987) or as stage B1, if the epochs contain low amplitude activity with SEM. With progressive relaxation delta and theta activity become dominant. This is classified as stages B2/3. Vigilance stage C is classified based on the manually marked grapho-elements such as K-complexes and sleep-spindles (Rechtschaffen and Kales, 1968; Sander et al., 2015).

For the data analysis, the SEM criterium was set to 75 µV with a 12-s rolling window length to detect any horizontal SEM in the recording. Due to the low presences of A2 and A3 stages, they are combined in the following analysis, similar to Olbrich et al. (2016) and Ip et al. (2021), resulting in 6 vigilance stages. Each stage was assigned to a numerically value, stage 0 (6), A1 (5), A2/3 (4), B1 (3), B2/3 (2) and C (1). For the present study, we calculated the outcome variables "median vigilance", "median slope" and the percentages of different vigilance stages for each minute of the EEG recording, resulting in 15 1-min blocks. Median vigilance values indicate the median wakefulness arousal level during rest, while the median slope addresses vigilance changes over time. A lower slope index indicates a steeper vigilance decline, or, respectively, increase. The selected variables have been test-retested and are considered standard parameters in EEG vigilance analysis (Huang et al., 2015; Ip et al., 2021; Olbrich et al., 2016).

### 2.5. Statistical analyses

Three separate repeated measures analyses of variance (ANOVA) were performed for the VIGALL outcome parameters median vigilance, median slope, and the percentages of all vigilance stages (0, A1, A2/3, B1, B2/3). Due to the very low presence of stage C (see Fig. 2), indicating sleep onset, this vigilance stage was excluded from the analysis. For each VIGALL outcome, recording blocks (15 * 1-min block) were included as a within-subject factor, while group (patients after a recent suicide attempt vs. healthy controls) was defined as a between-subject factor. The design of the analysis plan followed statistical models applied in Ip et al. (2021) and Olbrich et al. (2012), where a 2–3-min block was used to assess predictive markers. A 3-min block thus resamples a clinical measure that can be achieved during most in-hospital EEG recordings. However, the Vigilance Algorithm Leipzig (Hegerl and Hensch, 2014) also uses a lengthier resting state recording to increase the validity of the measure. Consequentely, the 15-minute block corresponds to the standard measurement proposed in the VIGALL manual.

Therefore, the first 3-min of the recording and the whole 15-min recording block were performed separately in the ANOVA model. Subsequently, Bonferroni's correction was used for multiple comparisons and post hoc analyses. Degrees of freedom were corrected by Greenhouse-Geisser correction when necessary. Furthermore, to investigate the association between EEG vigilance and patients' current suicidal ideation, and depression scores, partial correlations between the VIGALL outcomes and the patients BSS sum scores, respectively, the patients HDRS scores, were performed. Age was included as a covariate in all models. Mean median vigilance (over time, one mean per minute), median slope, and mean percentages of all vigilance stages were used for the correlational analysis. The significance level was set to $p$ <.05 for median vigilance and median slope, and to $p$ <.01 for the percentages of vigilance stages to control for type I error, following previous study (Ip et al., 2021) (Supplementary Material, S.1-S.4). Group differences in age and psychometric measures were tested using independent sample t-test. Group differences in sex were investigated using Pearson's chi statistic test. Additional statistical analyses between mood disorder diagnosis, psychotropic medication, and vigilance regulation were performed and the details of each statistical model were given in the Supplementary Material (S.3-S.6).

## 3. Results

### 3.1. Sociodemographic characteristics

The included 49 patients were between 19 and 62 years old, while the 45 controls covered an age range of 18 to 67 years. The listed diagnoses were based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (WHO, 2004). At admission, the patients had been diagnosed with the following psychiatric disorders: F1: mental and behavioral disorders due to psychoactive substance use (37%), F2: schizophrenia, schizotypal and delusional disorders (8%), F3: mood disorders (63%), F4: neurotic, stress-related and somatoform disorders (43%), F5: behavioral syndromes associated with physiological disturbances and physical factors (4%), F6: disorders of adult personality and behavior (43%), and F9: behavioral and emotional disorder with onset usually occurring in childhood and adolescence (12%). Additionally, 65% of patients had one or several psychiatric comorbidities. For each patient, all psychiatric diagnoses were recorded. Patients' psychotropic medication was extracted from their electronic medical files. At the day of the EEG recording,

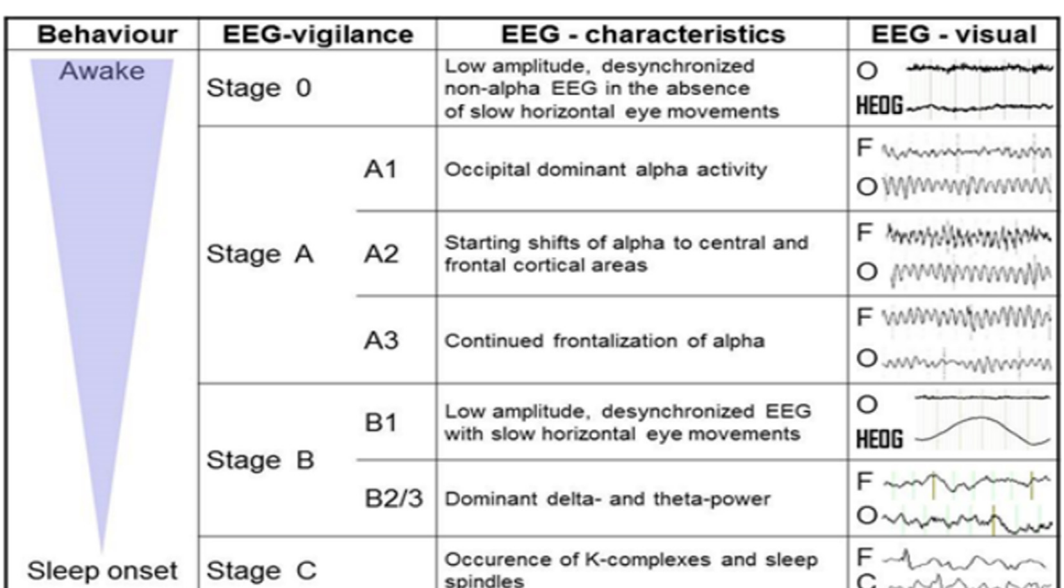


**Fig. 1. EEG-vigilance stages.** Note. EEG-vigilance stages with their EEG-characteristics and the corresponding behavior. F = frontal cortical areas. O = occipital cortical areas. C = central cortical areas. HEOG = horizontal electrooculogram. Reprinted from the Vigilance Algorithm Leipzig (VIGALL) Manual, 2017, p. 6.

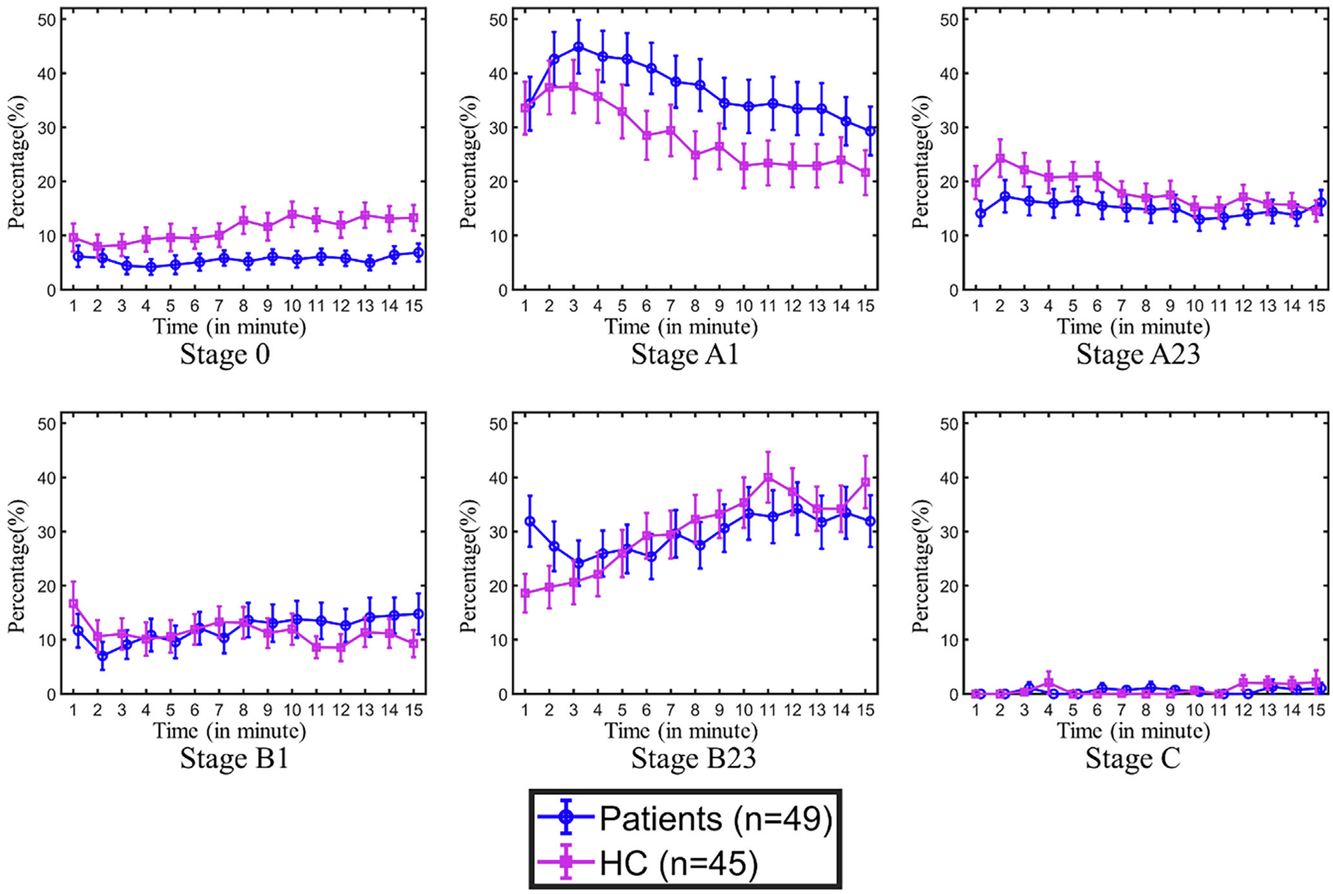


**Fig. 2. Vigilance stages of patients after a recent suicide attempt and healthy controls.** Note. The mean percentage and the corresponding error bars (representing ± 1 standard error) between patients after a recent suicide attempt and healthy controls. HC = Healthy controls.

67% of the patients took antidepressants, 30% neuroleptics, and 17% benzodiazepines or anxiolytics. Further demographic information as well as the BSS suicidality scores and HDRS depression scores are displayed in Table 1.

### 3.2. Median vigilance

A significant main effect of recording blocks was found for median vigilance in the 15-min-block ($F$ (14, 1274) = 6.42, $p$ <.001). When assessing the median vigilance at the first 3-min-block, there was a significant interaction between the recording blocks of median vigilance and group ($F$ (2, 182) = 6.61, $p$ =.003). The analyses of simple effects revealed that patients after a recent suicide attempt had an increasing median vigilance within the first 3-min-block ($p$ values < 0.001, see Fig. 3). No significant main group effect was found for median vigilance in the first 3-min-block ($p$ =.57) nor in the 15-min-block ($p$ =.69). No significant correlation between median vigilance (averaged across the first 3 min-bloc k/15 min-block) and BSS was found in patients with current STB ($p$ values > 0.26). Median vigilance of patients with current STB was also not significantly correlated with HDRS depression scores in either of the blocks.

### 3.3. Median slope

A significant group effect was observed for median slope in the first 3-min-block ($F$ (1, 91) = 8.36, $p$ =.005, see Fig. 4a), indicating that patients after a recent suicide attempt had less propensities for lower vigilance stages compared to healthy controls (0.27 vs −0.03 stage/min). However, the group effect of median slope was not sustained when the 15-min-block was evaluated ($p$ =.27, Fig. 4b). In patients, there was a significant positive partial correlation between median slope and BSS in the 15-min-block ($r$ (43) = 0.30, $p$ =.04, Fig. 5a). Opposingly, no significant partial correlations between median slope and HDRS depression scores were found in either the 3-min or the 15-min block.

### 3.4. Percentages at vigilance stage

The results of the ANOVA showed a significant main effect of recording block at stage A1 ($F$ (14, 1274) = 10.51, $p$ <.001, Fig. 2b) and B2/3 ($F$ (14, 1274) = 8.79, $p$ <.001, Fig. 2e) in the 15-min-block, but not in the 3-min-block ($p$ values > 0.21). There were significant interactions between recording block and group in the 15-min-block ($F$ (14, 1274) = 4.15, $p$ =.002) in stage B2/3. The analysis of simple effects showed that healthy controls had an increasing prevalence of stage B2/3 after 6 min ($p$ values < 0.017) while patients had no significant difference of stage B2/3 prevalence during the whole recording time ($p$ values > 0.11, Fig. 2). Furthermore, a significant negative partial correlation between mean percentages of stage A1 and BSS was found for patients with acute STB in the first 3-min-block ($r$ (43) = −0.37, $p$ = 0.01, Fig. 5b). No such partial correlations were observed between any of the mean percentages of the stages or the HDRS scores.

## 4. Discussion

The goal of this paper was to investigate the association between EEG vigilance and STB to detect possible STB-specific EEG patterns in a diagnostically heterogeneous group of patients

**Table 1**
Demographic and clinical characteristics.

| | *Patients* | *Controls* | | | |
|---|---|---|---|---|---|
| **Demographics** | | | *df* | *t* / $X^2$ | *p*-value |
| *n* | 49 | 45 | | | |
| Age, *M* (*SD*) | 34 (14) | 34 (13.7) | 91 | −0.0193 | 0.9846 |
| Sex, female (%) | 26 (53 %) | 26 (58 %) | 1 | 0.0634 | 0.8011 |
| **BSS** | | | *df* | *t* | *p*-value |
| *n* | 48 | 45 | | | |
| *M* (*SD*) | 12.8 (8.71) | 0.10 (0.49) | 46 | 9.972 | <0.0001*** |
| **HDRS** | | | *df* | *t* | *p*-value |
| *n* | 42 | 45 | | | |
| *M* (*SD*) | 19.3 (8.49) | 1.3 (1.61) | 43 | 13.518 | <0.0001*** |

*Note*. *n* = number, *M* = mean, *SD* = standard deviation, *df* = degrees of freedom, $X^2$ = Pearson's chi-square test, *t* = t-test for independent samples. BSS = Beck Scale for Suicide Ideation, HDRS = Hamilton Depression Rating Scale, *p <.05, **p <.01, ***p <.001.

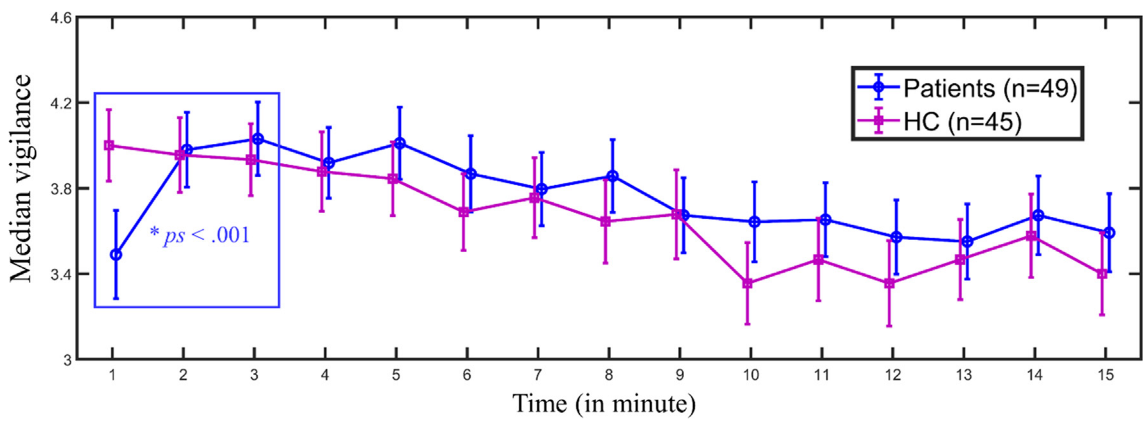


**Fig. 3. Median vigilance of patients after a recent suicide attempt and healthy controls.** Note. Median EEG vigilance over the course of 15-min. Error bars represent ± 1 standard error. The rectangular box highlights median vigilance within the first 3-min. HC = Healthy controls.

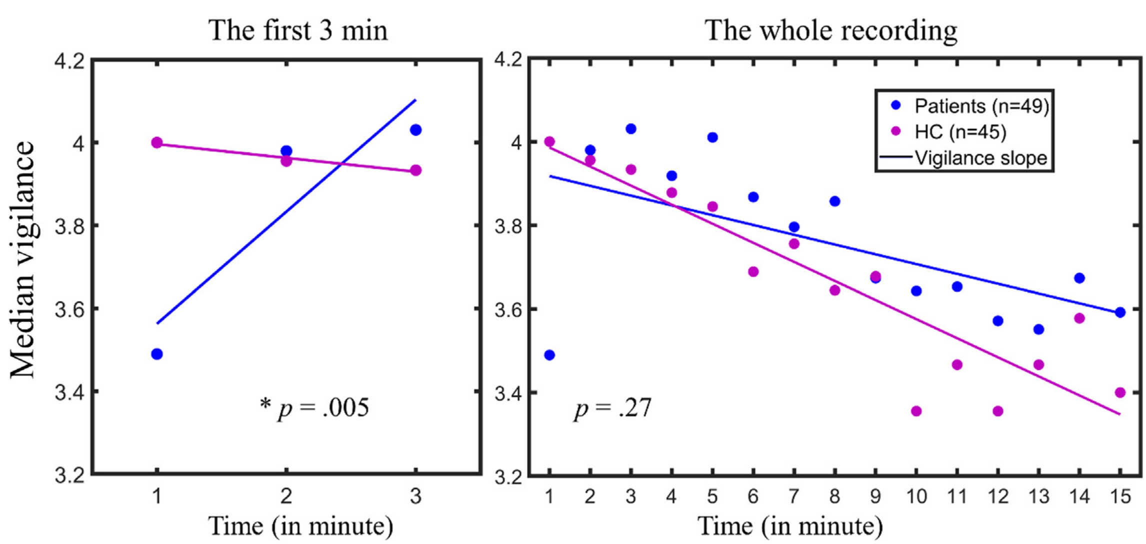


**Fig. 4. Vigilance slope of patients after a recent suicide attempt and healthy controls.** Note. Vigilance slope within 3-min (4a) and over the course of 15-min (4b). HC = Healthy controls. *p* = p-value.

after a recent suicide attempt. Concerning median vigilance, the statistical analysis showed a significant change in the EEG wakefulness arousal level over the span of the whole recording time for both study groups, indicating a slow but steady decline of vigilance towards sleep onset. Hence, patients' median vigilance regulation did not significantly differ from healthy controls and, notably the evidence for a hyperstable vigilance typically found in depressed individuals was not as pronounced as initially hypothesized. While previous studies on depressed patients observed a delayed or missing decline of wakefulness towards lower vigilance stages, this specific pattern was not found in patients after a recent suicide attempt. Interestingly, a significant difference between the two groups was found within the first 3 minutes of the recording. On average, patients showed a significantly lower median vigilance at the beginning of the recording session, followed by a steep rise of vigilance which afterwards reclined at the approximately same

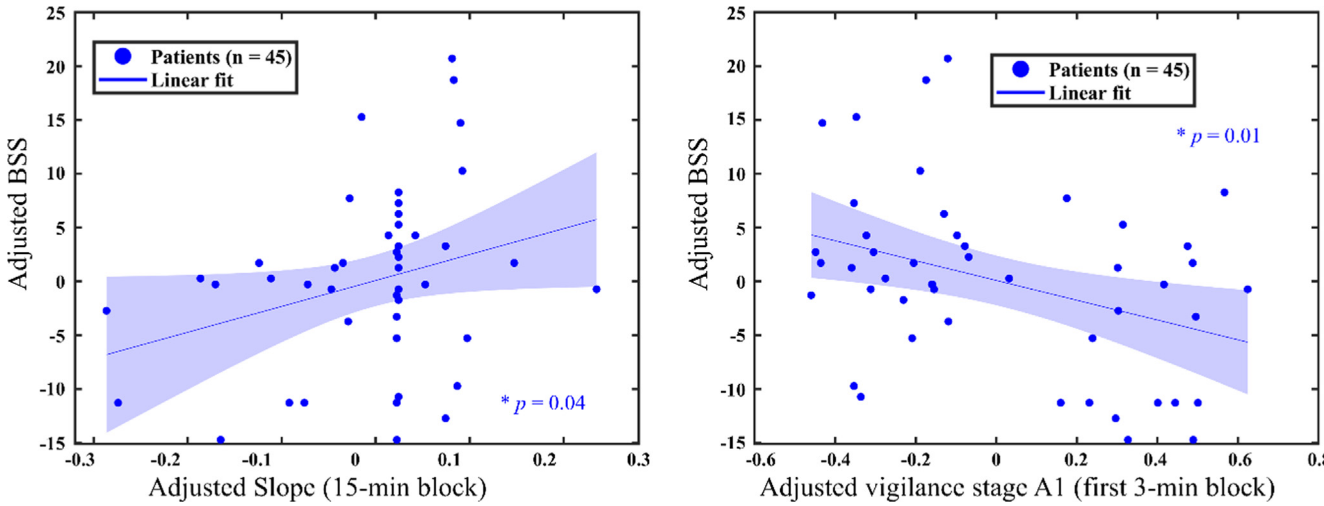


**Fig. 5. Associations between VIGALL measures and the Beck Scale for Suicide Ideation (BSS).** Note. Association between the Beck Scale for Suicide Ideation (BSS) and the mean vigilance slope over 15-min (5a), respectively vigilance stages A1 within the first 3-min (5b). The data were adjusted for age. *p* = p-value.

rate as the median vigilance in healthy controls. The findings for the vigilance slope mirror the previously stated results, with a significant increase of the vigilance slope for patients during the first 3 minutes. While Fig. 2 depicts fewer low vigilance stages in patients after a suicide attempt, this difference was not found to be statistically significant. Lastly, the analysis of the different vigilance stages showed, that patients had a significantly lower propensity to stage B2/3, the last vigilance stage before sleep onset. Oppositely, controls had an increased prevalence of lower vigilance stage B2/3 halfway during recording time at minute 6.

Previous literature on vigilance regulation has associated fewer low vigilance stages with symptoms of depression. While patients with heterogeneous diagnostic backgrounds were recruited for the presented study, their HDRS scores, measured on the assessment day, demonstrated that all patients experienced depressive symptoms to a certain extent (see Table 1). However, no significantly higher median vigilance was found in patients, and additional statistical analyses did not find a significant impact of mood disorder diagnosis, nor psychotropic medication, on vigilance regulation. One explanation of this outcome may be that the effects of depression on vigilance regulation may have been diminished by patients with other vigilance regulation subtypes.

In conclusion, these findings may indicate that the wakefulness regulation pattern found in this study, particularly the initial steep increase of vigilance, might be a unique characteristic in patients after a recent suicide attempt. Interestingly, a similar time-course of mean vigilance was found in a study investigating EEG resting-state vigilance in personality traits (Jawinski et al., 2021). A steep rise of vigilance at the beginning of the EEG recording was observed in individuals exhibiting lower levels of extraversion and openness. Specific personality trait, such as neuroticism (McDaniel et al., 2022; Soltaninejad et al., 2014), introversion (Wenzel and Beck, 2008), aggression and impulsivity (Mann et al., 1999), have long been proposed as risk factors of STB. Therefore, the steep rise of vigilance might reflect a relationship between STB and introversion or lower levels of openness in patients after a recent suicide attempt.

In addition to the initial steep rise of vigilance, a significant positive correlation was found between self-reported STB on the day of the recording and the vigilance slope over the whole recording duration, as well as a negative correlation with percentage of A1 stages during the first 3 minutes (Fig. 4). This indicated that higher levels of suicidal ideation are related with a higher slope index, suggesting a slower decline of vigilance in patients. Likewise, higher suicidal ideation scores are associated with less A1 stages at the beginning of the recording. Both of these parameters could be possible markers of suicidal behavior. Especially, since vigilance regulation has been reported to be inter-individually stable with trait-character, although it can be modulated by state factors (e.g., lack of sleep, nicotine, or caffeine intake) (Hegerl et al., 2008). Within the context of RDoC, transdiagnostic EEG vigilance markers could help to stratify patients in subgroups, and to inform clinical suicide risk management by providing an advanced understanding of the underlying pathophysiology of STB (Olbrich and Conradi, 2016; Rakus et al., 2021). EEG vigilance as a trait marker of STB might facilitate the detection of predispositions and therefore allow early pharmacological or psychotherapeutic interventions (Lema et al., 2018).

However, further studies are needed, also including a control group of transdiagnostic psychiatric patients without life-time suicide attempts, to stratify subgroups in mental health disorders and analyze the clinical usefulness of these markers. Only when the reported patterns distinguish between patients with history of STB versus patients without history of STB, these markers have a specific clinical value. Further limitations concern the inclusion of medicated patients. Currently, within the overarching study project, a variety of additional data is collected, allowing the investigation of possible diagnostic and predictive electrophysiological (e.g., heartrate variability, Rüesch et al. (2022)), clinical, socioeconomic, and neuropsychological predictors of STB.

## 5. Conclusions

An initial steep rise of vigilance within the first 3 minutes of a resting-state EEG recording could be an indication of a STB-specific wakefulness regulation pattern in patients after a recent suicide attempt. The positive correlation of self-reported suicidal ideation with the vigilance slope, as well as the negative correlation with A1 vigilance stages within the first 3 minutes, indicate that EEG wakefulness regulation might serve as a potential marker of suicidal behavior. To consolidate the clinical value of these findings, further studies are needed, including a control group of neuropsychiatric patients without suicidal thoughts and behavior.

## Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

## Acknowledgements

This study was funded by the Hans and Marianne Schwyn Foundation Zurich, Switzerland. The study sponsors had no involvement in the collection, analysis, and interpretation of data or in the writing of the manuscript.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.08.018.

## References

Arikan MK, Gunver MG, Tarhan N, Metin B. High-Gamma: A biological marker for suicide attempt in patients with depression. J Affect Disord 2019;254:1–6. https://doi.org/10.1016/j.jad.2019.05.007.
Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: The Scale for Suicide Ideation. J Consult Clin Psychol 1979;47(2):343–52.
Benschop L, Baeken C, Vanderhasselt M-A, Van de Steen F, Van Heeringen K, Arns M. Electroencephalogram resting state frequency power characteristics of suicidal behavior in female patients with major depressive disorder. J Clin Psychiatry 2019;80(6):5459.
Bente D. Vigilanz: Psychophysiologische Aspekte. In: Schlegel B, editor. Verhandlungen der Deutschen Gesellschaft für innere Medizin 83. Munich: J. F. Bergmann-Verlag; 1977.
Berger C, Duck A, Perin F, Wunsch K, Buchmann J, Kolch M, et al. Brain arousal as measured by EEG-assessment differs between children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and depression. Front Psych 2021;12. https://doi.org/10.3389/fpsyt.2021.633880 633880.
Bernecker SL, Zuromski KL, Gutierrez PM, Joiner TE, King AJ, Liu H, et al. Predicting suicide attempts among soldiers who deny suicidal ideation in the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). Behav Res Ther 2019;120. https://doi.org/10.1016/j.brat.2018.11.018 103350.
Bhatt M, Perera S, Zielinski L, Eisen RB, Yeung S, El-Sheikh W, et al. Profile of suicide attempts and risk factors among psychiatric patients: A case-control study. PLoS One 2018;13(2):e0192998.
Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of sleep and wakefulness. Physiol Rev 2012;92(3):1087–187. https://doi.org/10.1152/physrev.00032.2011.
Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med 2013;11(126). https://doi.org/10.1186/1741-7015-11-126.
Dolsen MR, Cheng P, Arnedt JT, Swanson L, Casement MD, Kim HS, et al. Neurophysiological correlates of suicidal ideation in major depressive disorder: Hyperarousal during sleep. J Affect Disord 2017;212:160–6. https://doi.org/10.1016/j.jad.2017.01.025.
Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X, et al. Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. Psychol Bull 2017;143(2):187–232. https://doi.org/10.1037/bul0000084.
Garcia-Gutierrez MS, Navarrete F, Sala F, Gasparyan A, Austrich-Olivares A, Manzanares J. Biomarkers in psychiatry: concept, definition, types and relevance to the clinical reality. Front Psych 2020;11:432. https://doi.org/10.3389/fpsyt.2020.00432.
Ghaemi SN. After the failure of DSM: Clinical research on psychiatric diagnosis. World Psychiatry 2018;17(3):301–2. https://doi.org/10.1002/wps.20563.
Glenn CR, Kleiman EM, Cha CB, Deming CA, Franklin JC, Nock MK. Understanding suicide risk within the Research Domain Criteria (RDoC) framework: A meta-analytic review. Depress Anxiety 2018;35(1):65–88. https://doi.org/10.1002/da.22686.
Glenn CR, Nock MK. Improving the short-term prediction of suicidal behavior. Am J Prev Med 2014;47(3 Suppl 2):S176–80. https://doi.org/10.1016/j.amepre.2014.06.004.
Gysin-Maillart A, Schwab S, Soravia L, Megert M, Michel K. A novel brief therapy for patients who attempt suicide: A 24-months follow-up randomized controlled study of the attempted suicide short intervention program (ASSIP). PLoS Med 2016;13(3):e1001968.
Hamilton M. A rating scale for depression. J Neurol Neurosurg 1960;23(1):56.
Hawton K, Lascelles K, Pitman A, Gilbert S, Silverman M. Assessment of suicide risk in mental health practice: shifting from prediction to therapeutic assessment, formulation, and risk management. Lancet Psychiatry 2022;9(11):922–8. https://doi.org/10.1016/S2215-0366(22)00232-2.
Hegerl U, Hensch T. The vigilance regulation model of affective disorders and ADHD. Neurosci Biobehav Rev 2014;44:45–57. https://doi.org/10.1016/j.neubiorev.2012.10.008.
Hegerl U, Hensch T. Why do stimulants not work in typical depression? Aust N Z J Psychiatry 2017;51(1):20–2. https://doi.org/10.1177/0004867416676369.
Hegerl U, Sander C, Olbrich S, Schoenknecht P. Are psychostimulants a treatment option in mania? Pharmacopsychiatry 2009;42(5):169–74. https://doi.org/10.1055/s-0029-1220888.
Hegerl U, Stein M, Mulert C, Mergl R, Olbrich S, Dichgans E, et al. EEG-vigilance differences between patients with borderline personality disorder, patients with obsessive-compulsive disorder and healthy controls. Eur Arch Psychiatry Clin Neurosci 2008;258(3):137–43. https://doi.org/10.1007/s00406-007-0765-8.
Hegerl U, Wilk K, Olbrich S, Schoenknecht P, Sander C. Hyperstable regulation of vigilance in patients with major depressive disorder. World J Biol Psychiatry 2012;13(6):436–46. https://doi.org/10.3109/15622975.2011.579164.
Huang J, Sander C, Jawinski P, Ulke C, Spada J, Hegerl U, Hensch T. Test-retest reliability of brain arousal regulation as assessed with VIGALL 2.0. Neuropsychiatr Electrophysiol 2015;1:13. https://doi.org/10.1186/s40810-015-0013-9.
Ip CT, Ganz M, Dam VH, Ozenne B, Ruesch A, Kohler-Forsberg K, et al. NeuroPharm study: EEG wakefulness regulation as a biomarker in MDD. J Psychiatr Res 2021;141:57–65. https://doi.org/10.1016/j.jpsychires.2021.06.021.
Jawinski P, Markett S, Sander C, Huang J, Ulke C, Hegerl U, et al. The big five personality traits and brain arousal in the resting state. Brain Sci 2021;11(10):1272. https://doi.org/10.3390/brainsci11101272.
Johnston JN, Campbell D, Caruncho HJ, Henter ID, Ballard ED, Zarate CA. Suicide biomarkers to predict risk, classify diagnostic subtypes, and identify novel therapeutic targets: 5 years of promising research. Int J Neuropsychopharmacol 2022;25(3):197–214. https://doi.org/10.1093/ijnp/pyab083.
Joiner TE. Why people die by suicide. Cambridge, MA: Harvard University Press; 2005.
Kessler RC, Bossarte RM, Luedtke A, Zaslavsky AM, Zubizarreta JR. Suicide prediction models: a critical review of recent research with recommendations for the way forward. Mol Psychiatry 2020;25(1):168–79. https://doi.org/10.1038/s41380-019-0531-0.
Klonsky ED, May AM, Saffer BY. Suicide, suicide attempts, and suicidal ideation. Annu Rev Clin Psychol 2016;12:307–30. https://doi.org/10.1146/annurev-clinpsy-021815-093204.
Klonsky ED, Qiu T, Saffer BY. Recent advances in differentiating suicide attempters from suicide ideators. Curr Opin Psychiatry 2017;30(1):15–20. https://doi.org/10.1097/YCO.0000000000000294.
Klonsky ED, Saffer BY, Bryan CJ. Ideation-to-action theories of suicide: a conceptual and empirical update. Curr Opin Psychol 2018;22:38–43. https://doi.org/10.1016/j.copsyc.2017.07.020.
Krepel N, Benschop L, Baeken C, Sack AT, Arns M. An EEG signature of suicidal behavior in female patients with major depressive disorder? A non-replication. Biol Psychol 2021;161. https://doi.org/10.1016/j.biopsycho.2021.108058 108058.
Lee SM, Jang KI, Chae JH. Electroencephalographic Correlates of Suicidal Ideation in the Theta Band. Clin EEG Neurosci 2017;48(5):316–21. https://doi.org/10.1177/1550059417692083.
Lema YY, Gamo NJ, Yung K, Ishizuka K. Trait and state biomarkers for psychiatric disorders: Importance of infrastructure to bridge the gap between basic and clinical research and industry. Psychiatry Clin 2018;72(7):482–9. https://doi.org/10.1111/pcn.12669.
Mann JH, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry 1999;156(2):181–9. https://doi.org/10.1176/ajp.156.2.181.
Mann JJ. Neurobiology of suicidal behaviour. Nat Rev Neurosci 2003;4(10):819–28. https://doi.org/10.1038/nrn1220.
McDaniel CJ, DeShong HL, Rufino K, Nadorff MR. The synergistic effects of neuroticism and extraversion on suicidal ideation, single attempts, and multiple attempts in an inpatient sample. J Pers Disord 2022;36(6):717–30. https://doi.org/10.1521/pedi.2022.36.6.717.
Nock MK. Recent and needed advances in the understanding, prediction, and prevention of suicidal behavior. Depress Anxiety 2016;33(6):460–3. https://doi.org/10.1002/da.22528.
O'Connor DB, Green JA, Ferguson E, O'Carroll RE, O'Connor RC. Cortisol reactivity and suicidal behavior: Investigating the role of hypothalamic-pituitary-adrenal axis responses to stress in suicide attempters and ideators. Psychoneuroendocrinology 2017;75:183–91. https://doi.org/10.1016/j.psyneuen.2016.10.019.
O'Connor RC. The integrated motivational-volitional model of suicidal behavior. Crisis 2011;32(6):295–8. https://doi.org/10.1027/0227-5910/a000120.
O'Connor RC, Kirtley OJ. The integrated motivational-volitional model of suicidal behaviour. Phil Trans R Soc B 2018;373:20170268. https://doi.org/10.1098/rstb.2017.0268.
Oken BS, Salinsky MC, Elsas SM. Vigilance, alertness, or sustained attention: physiological basis and measurement. Clin Neurophysiol 2006;117(9):1885–901. https://doi.org/10.1016/j.clinph.2006.01.017.
Olbrich S, Conradi J. Future of clinical EEG in psychiatric disorders: Shifting the focus from diagnosis to the choice of optimal treatment. Clin Neurophysiol 2016;127(1):17–8. https://doi.org/10.1016/j.clinph.2015.06.018.
Olbrich S, Sander C, Minkwitz J, Chittka T, Mergl R, Hegerl U, Himmerich H. EEG vigilance regulation patterns and their discriminative power to separate patients with major depression from healthy controls. Neuropsychobiology 2012;65(4):188–94. https://doi.org/10.1159/000337000.
Olbrich S, Trankner A, Surova G, Gevirtz R, Gordon E, Hegerl U, Arns M. CNS- and ANS-arousal predict response to antidepressant medication: Findings from the randomized iSPOT-D study. J Psychiatr Res 2016;73:108–15. https://doi.org/10.1016/j.jpsychires.2015.12.001.
Park S, Lee Y, Youn T, Kim BS, Park JI, Kim H, Lee HC, Hong JP. Association between level of suicide risk, characteristics of suicide attempts, and mental disorders among suicide attempters. BMC Public Health 2018;18(1):477. https://doi.org/10.1186/s12889-018-5387-8.

Rakus T, Hubcikova K, Bruncvik L, Pechanova Z, Brunovsky M. Electrophysiological correlates of suicidality. Psychiatr Danub 2021;33(3):266–79. https://doi.org/10.24869/psyd.2021.266.
Randall JR, Sareen J, Chateau D, Bolton JM. Predicting Future suicide: clinician opinion versus a standardized assessment tool. Suicide Life Threat Behav 2019;49(4):941–51. https://doi.org/10.1111/sltb.12481.
Rechtschaffen A, Kales AD. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles: Brain Information Service/Brain Research Institute; 1968.
Rodenbeck A, Binder R, Geisler P, Danker-Hopfe H, Lund R, Raschke F, et al. A review of sleep EEG patterns. Part I: A compilation of amended rules for their visual recognition according to Rechtschaffen and Kales. Eine Übersicht über Schlaf-EEG-Muster. Teil I: Eine Zusammenstellung mit ergänzenden Regeln zu deren visueller Analyse. Somnologie 2006;10(4):159–75. https://doi.org/10.1111/j.1439-054X.2006.00101.x.
Roth B. The clinical and theoretical importance of EEG rhythms corresponding to states of lowered vigilance. Electroencephalogr Clin Neurophysiol 1961;13(3):395–9. https://doi.org/10.1016/0013-4694(61)90008-6.
Rudd MD. The suicidal mode: A cognitive-behavioral model of suicidality. Suicide Life Threat Behav 2000;30(1):18–33. https://doi.org/10.1111/j.1943-278X.2000.tb01062.x.
Rüesch A, Villar de Araujo T, Bankwitz A, Hörmann C, Adank A, Ip CT, et al. A recent suicide attempt and the heartbeat: Electrophysiological findings from a trans-diagnostic cohort of patients and healthy controls. J Psychiatr Res 2022;157:257–63. https://doi.org/10.1016/j.jpsychires.2022.11.020.
Sander C, Hensch T, Wittekind DA, Bottger D, Hegerl U. Assessment of Wakefulness and Brain Arousal Regulation in Psychiatric Research. Neuropsychobiology 2015;72(3–4):195–205. https://doi.org/10.1159/000439384.
Santamaria J, Chiappa KH. The EEG of drowsiness in normal adults. J. Clin. Neurophysiol. 1987;4(4):327–82. https://doi.org/10.1097/00004691-198710000-00002.
Schotte DE, Clum GA. Suicide ideation in a college population: A test of a model. J Consult Clin Psychol 1982;50(5):690–6. https://doi.org/10.1037/0022-006X.50.5.690.
Schotte DE, Clum GA. Problem-solving skills in suicidal psychiatric patients. J Consult Clin Psychol 1987;55(1):49–54. https://doi.org/10.1037/0022-006X.55.1.49.
Sharp R. The Hamilton rating scale for depression. Occup Med (Lond) 2015;65(4):340. https://doi.org/10.1093/occmed/kqv043.
Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22–33. quiz 34-57.
Soltaninejad A, Fathi-Ashtiani A, Ahmadi K, Mirsharafoddini HS, Nikmorad A, Pilevarzadeh M. Personality factors underlying suicidal behavior among military youth. Iran Red Crescent Med J 2014;16(4):e12686.
Stein DJ, Reed GM. Global mental health and psychiatric nosology: DSM-5, ICD-11, and RDoC. Braz J Psychiatry 2019;41:3–4. https://doi.org/10.1590/1516-4446-2018-4101.
Strauß B, Schumacher J. Hamilton Depression Skala [Hamilton depression rating scale]. In: Klinische Interviews und Ratingskalen [Clinical interviews and rating scales]. 1st ed., vol. 3. Hogrefe Verlag; 2004.
Sudol K, Mann JJ. Biomarkers of Suicide Attempt Behavior: Towards a Biological Model of Risk. Curr Psychiatry Rep 2017;19(6):31. https://doi.org/10.1007/s11920-017-0781-y.
Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite SR, Selby EA, Joiner Jr TE. The interpersonal theory of suicide. Psychol Rev 2010;117(2):575–600. https://doi.org/10.1037/a0018697.
Venigalla H, Mekala HM, Hassan M, Ahmed R, Zain H. An Update on Biomarkers in Psychiatric Disorders-Are we aware, Do we use in our clinical practice ? Ment Health Fam Med 2017;13:471–9.
Wenzel A, Beck AT. A cognitive model of suicidal behavior: Theory and treatment. Appl Prev Psychol 2008;12(4):189–201. https://doi.org/10.1016/j.appsy.2008.05.001.
WHO. ICD-10 : international statistical classification of diseases and related health problems : tenth revision, 2nd ed. World Health Organization; 2004. https://apps.who.int/iris/handle/10665/42980.
WHO. Suicide in the world: global health estimates. World Health Organization; 2019.
Wolfersdorf M, Etzersdorfer E. Suizid und Suizidprävention. *1*. Aufl. Stuttgart: Kohlhammer; 2011.