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An EEG signature of suicidal behavior in female patients with major depressive disorder? A non-replication

Noralie Krepel [a,b], Lars Benschop [c], Chris Baeken [c,d,e], Alexander T. Sack [a], Martijn Arns [a,b,f,*]

[a] Dept. of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands
[b] Research Institute Brainclinics, Brainclinics Foundation, Nijmegen, the Netherlands
[c] Ghent University, Department of Psychiatry and Medical Psychology, Ghent Experimental Psychiatry (GHEP) Lab, Ghent, Belgium
[d] Department of Psychiatry, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZBrussel), Laarbeeklaan 101, 1090, Brussels, Belgium
[e] Eindhoven University of Technology, Department of Electrical Engineering, Eindhoven, the Netherlands
[f] Amsterdam UMC, University of Amsterdam, Department of Psychiatry (Location AMC), Amsterdam Neuroscience, Amsterdam, the Netherlands

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ABSTRACT

Introduction: A recent study showed hypoactivity in the beta/gamma band in female suicide ideators and suicide attempters diagnosed with depression, relative to a low-risk group. The current study aimed to conceptually replicate these results.
Methods: In the iSPOT-D sub-sample (n = 402), suicide ideators and low-risk individuals were identified. Confining analyses to females only, differences between low-risk individuals and suicide ideators were tested for using the electroencephalogram (EEG) frequency bands SMR (Sensori-Motor-Rhythm; 12–15 Hz), beta (14.5–30 Hz), beta I (14.5–20 Hz), beta II (20–25 Hz), beta III (25–30 Hz), gamma I (31–49 Hz) using LORETA-software.
Results: None of the tested frequency bands showed to be significantly different between suicide ideators and low-risk individuals.
Conclusions: The current study could not conceptually replicate the earlier published results. Several reasons could explain this non-replication, among which possible electromyographic (EMG) contamination in the beta/gamma band in the original study.
Trial Registration: ClinicalTrials.gov identifier: NCT00693849.
URL: http://clinicaltrials.gov/ct2/show/NCT00693849.

1. Introduction

Recently, a study examining the resting state EEG signature of depressed individuals at multiple levels of suicide risks was published by several of us (Benschop et al., 2019). Benschop and colleagues, limiting the analysis to females only, demonstrated that suicide ideators and suicide attempters showed low frontal beta and gamma activation as compared to low-risk individuals, with quite similar topography for both ideator and attempter groups. Furthermore, higher occipital alpha was observed in ideators. Interestingly, research into the electroencephalogram (EEG) correlates of suicidal behavior is scarce. A recent report by Arikan and colleagues showed that suicide ideators exhibited higher gamma (Arikan, Gunver, Tarhan, & Metin, 2019), contrasting the results by Benschop and colleagues. It has also been found that lower gamma power was related to an increased response to paroxetine treatment in depression (Arikan, Metin, & Tarhan, 2018), whereas Whitton et al. (2018) found higher 18.5–21 Hz activity within the default mode network as well as higher 12–18 Hz connectivity between the default mode network and the frontoparietal network in individuals with depression, as compared to individuals who remitted from depression. Additionally, higher between-network connectivity was related to more frequent depressive episodes since the first depression onset (Whitton et al., 2018). Lee, Jang, & Chae (2017) found that individuals exhibiting suicidal ideation showed higher frontal theta power. Another study, albeit confined to polysomnography, showed higher alpha and beta (albeit the result for beta was trend level significant) power in individuals experiencing higher levels of suicidal ideation (Dolsen et al., 2017). All in all, the EEG correlates of suicidal ideation and behavior are still unclear. Given the clinical relevance of early and accurate identification of individuals experiencing symptoms of suicidal ideation or

* Corresponding author at: Research Institute Brainclinics, Brainclinics Foundation, Bijleveldsingel 34, 6524 AD, Nijmegen, the Netherlands.
E-mail address: martijn@brainclinics.com (M. Arns).

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behavior, more research is needed in this area.

The aim of the current study was to partially replicate the findings by Benschop et al. (2019), using data from the randomized, controlled, multicenter iSPOT-D study in 1008 MDD subjects (for additional information on this study and its parameters, please see: (Arns et al., 2016; Saveanu et al., 2015; Williams et al., 2011)). Since 'attempted suicide in the last 30 days' was an exclusion criterion for the iSPOT-D study (Williams et al., 2011), and thus no attempter group could be formed, the *a priori* defined hypothesis was that in female suicide ideators, relative to the low-risk group, beta/low gamma hypoactivation would be observed in the pre-frontal regions.

2. Methods and materials

The iSPOT-D study (registered at ClinicalTrials.gov (identifier: NCT00693849)) included 1008 patients diagnosed with Major Depressive Disorder (MDD). For the purpose of this study and replication, only the suicide items administered using the Mini-International Neuropsychiatric Interview (MINI-plus) were considered and only females were included (in line with Benschop et al. (2019)). Also, individuals reporting to have attempted to commit suicide in a lifetime but not in the last 30 days, and who also did not report any suicidal ideation, were excluded. This was done to solely focus on acute suicide risk and is in line with Benschop et al. (2019).

3. Statistics

In the current study, the EEG frequency bands as reported by Benschop et al. (2019) were prospectively tested in LORETA.

3.1. LORETA analyses

1) Analyses were performed using LORETA v20200106 in Windows 10, standalone version. LORETA tests statistical group differences based on nonparametric permutation tests for functional neuroimaging. The original bands that were found to be significantly different between low-risk individuals and ideators were SMR (12−15 Hz), beta (14.5−30 Hz), beta I (14.5−20 Hz), beta II (20−25 Hz), beta III (25−30 Hz), and gamma I (31−49 Hz) (Benschop et al., 2019). Thus, in the current study, these identical bands were investigated. Using LORETA, differences between suicide ideators and low-risk individuals in the iSPOT-D sample were examined. Significance level was set at $p < 0.01$, in line with other iSPOT-D studies (e.g., Arns et al. (2016)). Note: the original study also reports alpha hyperactivity in the occipital regions in suicide ideators. However, this finding was not found using LORETA software. To enhance comparability with the original study, it was decided to primarily focus on 14.5−48 Hz in the ROI analyses. In the first results Section (3.1) alpha (9−13 Hz, in line with Benschop et al. (2019)) will only be shortly elaborated on.
2) After this initial replication, a second exploratory analysis was performed. Based on the results presented in Benschop et al. (2019), a single target frequency band of 14.5−48 Hz was established (consisting of the frequencies showing most prominent differences between suicide ideators and low-risk individuals). Then, using this frequency band ('suicide-specific band') a Region of Interest (ROI) was created in LORETA. Note that this ROI was created based on voxels being significantly different between low-risk individuals and ideators in the original study. Thus, this is not a pre-existing ROI. This ROI was used to extract beta/low gamma current source density (CSD) for all patients, after which statistical differences between high-risk and low-risk individuals were examined. In SPSS 26 for Mac, a GLM Univariate using beta/low gamma activation as a dependent variable, suicide group as a between-subject variable, and age as a covariate was performed. This analysis was performed for both the original data as well as the iSPOT-D sample, in order to compare results and consistency between the samples. The *p*-value was set on 0.05 and 0.01 for the original and iSPOT-D sample, respectively, given the larger sample size and exploratory nature in iSPOT-D. This is in line with other iSPOT-D reports that employed a 0.01 threshold (e.g., Arns et al. (2016)).

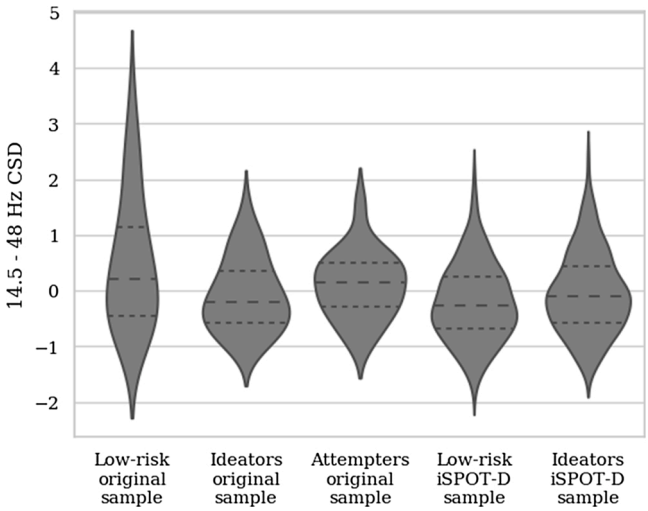

Fig. 1. This violin plot displays the CSD extracted from the ROI (14.5–48 Hz), separated by suicide group and sample group. The ROI is based on the original sample. Note that the 'Low-risk original sample' seems to have the largest spread. CSD = current source density.

4. Results

Excluding individuals with no acute suicide risk (consisting of individuals with past suicide attempts, but no current suicidal ideation), females with missing data, and males, the resulting sample size was n = 402. This sample consisted of 188 suicide ideators (age range (in years): 18–65, m = 37.2, SD = 13.3) and 214 low-risk individuals (age range (in years): 19–85, m = 37.7, SD = 12.5).

1) No significant differences were found between low-risk individuals and ideators for SMR ($p = .383$), beta ($p = .291$), beta I ($p = .339$), beta II ($p = .344$), beta III ($p = .201$), and gamma I ($p = .255$), thereby failing to replicate the earlier result as reported by Benschop et al. (2019). Alpha also did not show to be significantly different between ideators and low-risk individuals ($p = .143$).

4.1. ROI analyses

2) A ROI was developed based on the original sample ($n_{low\text{-}risk} = 23$ (29.5 %), $n_{ideators} = 36$ (46.2 %), $n_{attempters} = 19$ (24.4 %)) as used by Benschop et al. (2019), using the 14.5−48 Hz frequency range, consisting of the voxels showing to be significantly different between low-risk individuals and ideators at $p < .01$, one-tailed. In the original sample, a GLM Univariate analysis showed a significant main effect of suicide group ($F(2,74)=3.505$, $p = .035$). Significant differences were observed when contrasting ideators with low-risk individuals ($F(1,56)=5.904$, $p = .018$; $d=-.61$), but not when contrasting attempters with ideators ($F(1,52) = 2.079$, $p = .155$; $d = .28$), nor for attempters and low-risk individuals ($F(1,39) = 1.326$, $p = .257$; $d=-.44$), also see Fig. 1 below. Importantly, the direction of the results comparing low-risk to ideators and low-risk to attempters is identical (specifically, ideators and attempters show decreased activity compared to low-risk individuals) and the effect sizes are medium to large. This confirms that the established ROI and frequency band reflects the results as originally reported.

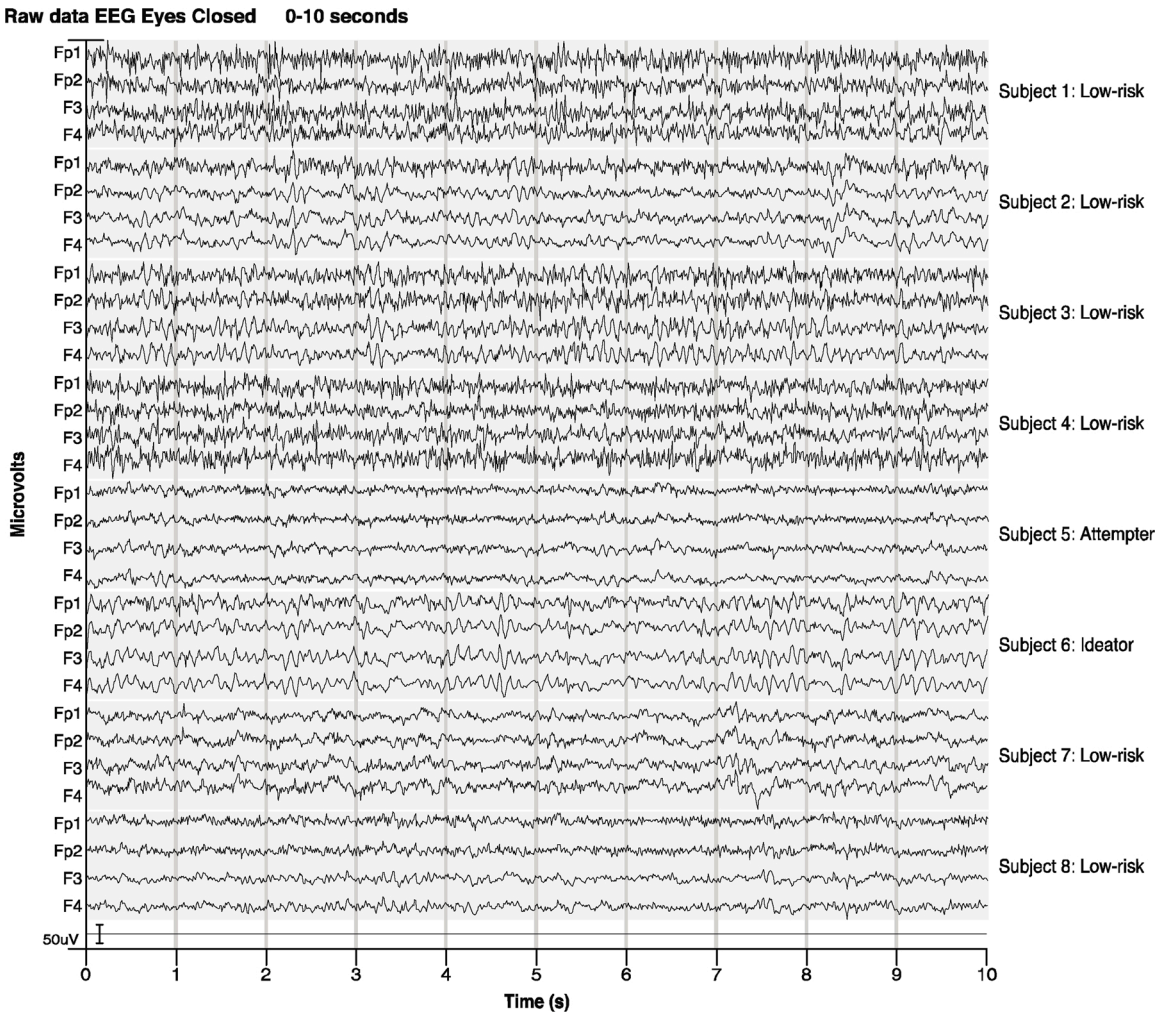

Fig. 2. Snapshot of the first ten seconds of the EC EEG for the eight people scoring highest on the ROI analyses, for the original sample only, ranked from scoring highest to lowest. Subject 1 scored highest and subject 8 scored lowest on the ROI analyses. Note that the four highest-scoring individuals all were part of the low-risk group.

Repeating this analysis on iSPOT-D, a GLM univariate showed a non-significant and opposite effect between ideators and low-risk individuals ($F(1,399) = 6.153$, $p = .014$; $d = .25$). This effect can be observed in Fig. 1.

5. Discussion

The current study aimed to partially replicate the results as reported by Benschop et al. (2019), which demonstrated a beta/gamma hypo-activation in female suicide ideators and attempters, as compared to low-risk individuals. Unfortunately, the current results did not confirm the results of the original study, meaning that no difference in the beta/low gamma band was found between suicide ideators and low-risk individuals. The current results were more in line with a recent report by Arikan et al. (2019), in which high gamma power at electrodes F4, Fz, C4, Cz, O2, F8, T5, and T6 was observed in individuals reporting higher levels of suicidal ideation. Another possibility is that gamma is not specifically related to suicidal ideation, but to a more general presentation of symptoms of depression. A recent report by Fitzgerald & Watson (2018) suggested that various gamma activity patterns in different brain areas may be related to depression. It also was suggested that gamma may even be able to discriminate between bipolar and unipolar depression (Fitzgerald & Watson, 2018). Additionally, although suicidal ideation and depression are heavily intertwined, suicidal ideation is not a symptom solely present in depression. For example, suicidal ideation has been reported in Obsessive-Compulsive Disorder (Pellegrini et al., 2020), Post-traumatic Stress Disorder (Krysinska & Lester, 2010), schizophrenia (Chapman et al., 2015), and Attention-Deficit/Hyperactivity Disorder (Furczyk & Thome, 2014; Taylor, Boden, & Rucklidge, 2014). Future studies should explore EEG signatures of suicidal ideation across different disorders to investigate if an EEG correlate is specific to a particular disorder, or whether this relation behaves transdiagnostically and is apparent in multiple disorders.

It is unclear why the current study did not confirm the earlier obtained results. One reason could be a lack of high-risk individuals (i.e., 'suicide attempters'), since this was an exclusion criterion for iSPOT-D, thereby decreasing the signaling contrast between groups. Another reason could be medication effects. In the original study, the original sample was not tapered of medication at the time of baseline QEEG assessment, whereas subjects in iSPOT-D were off medication at baseline. It has been reported that barbiturates and benzodiazepines augment beta activity, specifically in the 15–25 Hz range (Blume, 2006), yet medication effects on gamma have not been widely studied. Some animal studies also report NMDAR antagonist-induced gamma oscillations (Hiyoshi, Kambe, Karasawa, & Chaki, 2014; Jones et al., 2012; Phillips et al., 2012), but NMDAR antagonists (ketamine, among others) have not been reported in the original sample. A third reason for the current non-replication may be sample size. The original sample consisted of 78 females and dividing that group into three subgroups

resulted in relatively small samples of the subgroups. It is possible that individual contributions of the EEG within relatively small sample sizes introduced some noise which may have altered the signal-to-noise ratio in the samples. As can be observed in Fig. 1, it appears that the low-risk TMS sample has the widest spread (CSD for low-risk individuals: min=−1.01; max = 3.39; mean = .51, SD = 1.19), even relative to the large iSPOT-D groups (CSD for low-risk individuals: min=−1.75; max = 2.06; mean=−.21, SD = .69; CSD for ideators: min=−1.40; max = 2.35; mean=−0.04, SD = .72). All EEG data were collected using identical procedures, amplifiers, and automated artifact processing (also see Arns et al., 2016 for full details), reducing the likelihood that the current non-replication can be explained by differences in hardware or signal pre-processing. Post-hoc visual inspection of individuals from the low-risk group with 14.5−48 Hz CSD > 2.0 showed intermediate levels of frontal muscle tension (visualized in Fig. 2). Possibly, EMG contaminated the gamma activity (Whitham et al., 2007), yielding a quite strong signal in a relatively small sample (specifically, in the low-risk group), thus explaining the lower 'gamma' in the risk groups. In the original study, muscle artifacts were controlled for using a pre-processing pipeline and additional machine learning ICA artifact detection (MARA), thus the possible influences of muscle artifacts on the dataset would be expected to be minimal to none. Yet, individual contributions to the signal possibly may have skewed the results. Concluding, in the current study, no consistent differences between female suicide ideators and females with low suicide risk could be found in the EEG beta and gamma bands.

Author contributions

NK managed the literature search, performed the analyses and wrote the first draft of the manuscript. All other authors contributed, reviewed, and approved the final manuscript.

Potential conflicts of interest

The authors report no financial or other relationship relevant to the subject of this article.

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Disclosures

MA is unpaid research director of the Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation, and psychophysiology but does not own or receive any proceeds related to these patents.

Declaration of Competing Interest

The other authors report no conflict of interest.

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