Suicidal Thoughts, Behaviors, and Event-Related Potentials: A Meta-Analysis

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Abstract

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Suicide is a growing concern around the world. Estimates indicate that over 800,000 people die by suicide around the world annually (World Health Organization, 2014). In the United States (U.S.) alone, over 47,000 people die by suicide each year, making suicide the 10th leading cause of death (Centers for Disease Control, 2017). In contrast to trends in other western countries, suicide rates in the U.S. have been increasing over the last two decades (Hedegaard et al., 2018). This increase in the suicide rate has contributed to the trend that U.S. life expectancy has decreased every year since 2014 (Woolf & Schoomaker, 2019). Many scientists have forwarded that suicidal thoughts and behaviors (STBs) are partially the result of differences or abnormalities in neurobiological systems (Joiner et al., 2005; Mann, 2003; Van Heeringen & Mann, 2014). This has led to many studies investigating the brain regions that may be implicated in STBs, with most studies examining structural and functional brain differences between those with and without a history of STBs using magnetic resonance imaging (MRI). Though these approaches are promising, there is mixed evidence regarding the current state of this literature.

A recent qualitative review of the neuroimaging literature of STBs concluded that there is tentative, but converging evidence for two brain networks implicated in STBs (Schmaal et al., 2019). First, the authors forwarded that the ventral prefrontal cortex and many of its connections are involved in increasing negative and decreasing positive internal states, which can lead to suicidal ideation (SI). Second, they identified other regions, including the dorsomedial prefrontal cortex, the dorsolateral prefrontal cortex, and the inferior frontal gyrus, as a separate network that may be important for suicide attempts (SAs) due to their role in in planning, and cognitive control. The authors conclude that further studies investigating brain regions could aid in the development of novel treatments.

In contrast, a quantitative meta-analysis of neuroimaging studies using whole-brain analyses did not find a significant association between any brain region and SAs, and concluded there were not enough studies to analyze the relationship between SI and neural structure and function (Huang et al., 2019). Though these two reviews reached different conclusions about the state of the brain imaging literature of STBs, they both highlighted the need for larger sample sizes for future studies examining the relationship between brain regions and STBs. This is underscored by the meta-analysis conducted by Huang et al (2019), who found a median sample size of 45, a fact that may decrease the replicability of the literature examining the relationship between brain regions and STBs (Turner et al., 2018). Specifically, while small samples make it difficult to detect smaller true effects, small samples also increase the likelihood that significant effects are false positives (Button et al., 2013). However, the recommendation to increase sample sizes has proven to be difficult to implement in many areas of neuroscience, and neuroimaging is no exception. For example, a recent reanalysis of Button and colleague’s (2013) data showed that the statistical power for most neuroimaging studies included in their analysis fell below 0.5 (Nord et al., 2017). Though there are likely many factors contributing to low statistical power in the neuroimaging literature, including institutional incentives (Smaldino & McElreath, 2016), other factors include the high financial cost to conduct neuroimaging studies, and the relatively low base-rate of STBs (Fazel & Runeson, 2020). Thus, though brain imaging is a promising avenue for identifying biomarkers of STBs, barriers remain that have still to be sufficiently addressed.

Unfortunately, a meta-analysis conducted by Franklin and colleagues (2017) found that even the strongest predictors of death by suicide, suicide attempts, and suicidal ideation, are significant but weak predictors and may lack clinical utility. A series of more fine-grained meta-analyses supported the same conclusion: many risk factors, including previous suicidal thoughts and behaviors and biological markers, are significant, but weak, predictors of suicidal thoughts and behaviors (Chang et al., 2016; Ribeiro et al., 2016; Ribeiro, Huang, Fox, & Franklin, 2018; Witte, Gauthier, Huang, Ribeiro, & Franklin, 2018).

Since these meta-analyses were published, several solutions have been forwarded to address the field of suicidology’s lack of progress after over fifty years of research. These solutions include, but are not limited to, using machine learning (Ribeiro, Huang, Fox, Walsh, & Linthicum, 2019), using ecological momentary assessment (Kleiman & Nock, 2018), applying ideation-to-action theories of suicide (Klonsky et al., 2018), and abandoning prediction altogether (Klonsky, 2019). A final approach that has drawn increased attention is the potential use of event-related potentials as risk factors or biomarkers for suicidal thoughts and behaviors.

Event-related potentials (ERPs) are neural responses to specific events that are measured using an electroencephalogram (EEG; Luck, 2014). These waveforms are created by having participants complete multiple trials of a task and then averaging the EEG waveform across trials when the event of interest occurs. Though ERPs generally lack the ability to localize neural functions to regions in the brain, ERPs have excellent temporal resolution (e.g., over 1000 samples per second), which allow researchers to examine neural functions that occur before and during conscious awareness. Many ERPs have been discovered that serve different functions, such as emotion regulation, response inhibition, reward processing, reward anticipation, and error monitoring (Luck & Kappenman, 2011).

In a recent opinion piece, Gibb and Tsypes (2019) forwarded that ERPs may improve the prediction of suicidal thoughts and behaviors by including ERPs in machine learning algorithms. Though there have been studies examining ERPs and their ability to distinguish between different suicidal groups (i.e., those without ideation vs. those with ideation, and those with ideation vs. those who have attempted suicide), these studies have been limited by small sample sizes. For example, a recent study found that children with recent suicidal ideation had a significantly blunted reward positivity (RewP), an ERP that measures reward processing, compared to children that did not have recent suicidal ideation (Tsypes et al., 2019). However, this study only included 69 participants, 23 of which with recent suicidal ideation. Another study found that those who had attempted suicide had deficits in detecting the need for inhibitory control, as indexed by the N2 ERP, compared to those that had not attempted suicide (Albanese et al., 2019). Again, however, this study included 68 total participants, with 22 having a previous suicide attempt.

Though these studies found significant differences, research indicates that ERP studies are typically vastly underpowered to detect effect sizes typical in ERP research (Clayson et al., 2019). Thus, these underpowered studies are more likely to be false positives, with the true effect size either being much smaller than reported in these studies, or absent altogether. Knowing whether ERPs are significantly related to suicidal thoughts and behaviors has important implications for clinical practice and future research. Clinically, though ERPs are relatively inexpensive to measure compared to other neuroimaging approaches, EEG still has direct and indirect costs. Specifically, if clinicians were to use ERPs, they would still have to purchase the equipment and consumables needed to carry out ERP experiments, which can cost thousands of U.S. dollars. Moreover, the effectiveness of ERPs in predicting suicide risk may not justify the time spent collecting them, and that same time may be better spent implementing other suicide risk assessment and prevention procedures. Accurately estimating the effect size of the association between ERPs and suicidal thoughts and behaviors will also inform future research, as researchers may need to consider gathering larger samples to accurately estimate effects.

Thus, the purpose of this meta-analysis is to examine how strong the relationship is between ERPs, and three suicidal outcomes. Namely, the difference in ERPs between (1) those that do not experience suicidal ideation from those that do experience suicidal ideation, (2) those that experience suicidal ideation, but have not attempted suicide, from those that have attempted suicide, and (3) those with differing levels of suicide risk or suicidality.

# Method

## Inclusion and Exclusion Criteria

The aim of the present meta-analysis was to provide a broad overview of how different ERPs are between different suicidal groups. The following criteria were established to select relevant effect sizes.

**Language.**Only articles written in English were included.

**Event-related potential.** Only articles that had an effect size which included an event-related potential were included. Event-related potentials were defined as measures using EEG responses to specific, time-locked events mental processes. Given these criteria, studies that used cortical recordings, or stimulated the brain to produce neural activity, were excluded.

**Suicide-related outcome.** Studies were required to include some measure of suicidal thoughts, behaviors, or suicide risk/suicidality. Given this definition, studies that examined non-suicidal self-injury, or those with a history of non-suicidal self-injury, were excluded.

**Published in print or online by October 25th, 2019.** Our search results were limited to articles published in print or online by October 2019.

#### Literature Search

We conducted literature searches across PubMed, PsycInfo, Web of Science, and Proquest dissertations/theses to find relevant literature. Full search terms for each database will be made available on an online repository stored on the Open Science Framework (<http://www.osf.io>). To summarize here, though, search terms included different permutations related to ERPs and suicidal thoughts and behaviors, including: “event-related potential,” “event-related potentials,” “electroencephalography,” “EEG,” “evoked potential,” “evoked potentials,” “late positive potential,” “reward positivity,” “P3a,” “P3b,” “error-related negativity,” “suicide,” “suicidal,” “suicidal ideation,” “self-harm,” “self-injury,” “parasuicide,” “suicide ideation,” “suicidal ideation,” “suicide attempt,” “suicide plan,” “suicidality,” “suicide risk,” “attempter,” “attempters,” “ideators.” When this meta-analysis is complete, we will also examine the reference list of every article included in the final meta-analysis. In addition to these efforts, we will also make several attempts to gather existing grey literature. These efforts will consist of the following: (1) social media announcements on Twitter and Facebook, and (2) contacting researchers who are either a first or last author on at least two papers included in the meta-analysis.

**Data Extraction and Coding**

For each effect size, the following were also coded: mean age of the sample, suicide measure used, EEG reference used, scoring ERP procedure, type of ERP, and type of suicidal group and the type of comparison group. When the meta-analysis is complete, we will also code whether the sample was a clinical sample, and the proportion of males in the sample. For the results presented here, only one researcher coded and reviewed all studies. However, in the future, we will also include at least one additional Master’s level graduate student. We will also conduct reliability analyses for our codes, using agreement rate and Kappa for categorical variables, and Intercoder correlation and two-way random intraclass correlation for continuous variables. Using our search terms across all of our included databases produced 270 papers. After accounting for duplicates, we examined the abstracts of 195 papers and excluded studies that obviously did not meet inclusion criteria. After examining abstracts, 46 studies moved on to full-text review. In the end, 20 studies had at least one effect size that met inclusion criteria. Though many of these 20 studies has more than one effect size, the current meta-analysis only contains one effect size from each study.

**Effect Size**

Information was extracted from each study to calculate a Cohen’s *d*. Though we know Hedges *g* is preferred, some studies only included a correlation coefficient, and the authors are not aware of a way to calculate *g* using this information. Thus, the meta-analysis we present here uses Cohen’s *d*. Because there were relatively few effect sizes that were derived from a correlation coefficient, in the future we will consider dropping these studies and conducting our meta-analysis using Hedges’ *g*. Moreover, because the aim of this meta-analysis was to examine, in general, how strong are ERPs at differentiating different suicide groups, we converted all Cohen’s *d* effect sizes to |*d*|. This is because different ERPs may have different relations with suicidal outcomes, with some ERPs being blunted and others being larger. In the future, if we have enough effect sizes, we will also examine individual types of ERPs and their relation to suicidal outcomes. In these future analyses, we will not use |*d*|.

**Combining Effect Sizes**

For our meta-analysis, we used a random effects model. We chose this model given that we are combining many different ERPs that measure different neural functions. Thus, the assumptions made in a fixed effects meta-analysis are likely violated in this case. For our meta-analysis, used restricted maximum-maximum likelihood as our estimator of heterogeneity. We conducted all of our analyses in R (R Core Team, 2018) using the metafor package (Viechtbauer, 2010). In the future, when we have all effect sizes from each study, we will likely use the robumeta package due to the high dependency of our effect sizes. For the current analyses, all effect sizes are independent because they come from separate samples and thus, we did not need to address dependent effect sizes. To address outliers, we first conducted our meta-analysis using all effect sizes. Next, we visually inspected our forest plots for any potential outliers, removed outlier effect sizes, and then reran analyses. Here, we present our analyses without outliers. For sensitivity analyses (see Sensitivity Analyses), we will present our results if we had not removed outliers. To examine whether publication bias is present, we used two approaches: (1) we visually inspected the funnel plot for each outcome and (2) we used Egger’s test.

**Results**

**Suicidal Ideation**

After excluding one outlier effect size, our suicidal ideation meta-analysis consisted of five effect sizes. The difference in ERPs between those with suicidal ideation and those without was significant, with an average weighted *d* = 0.47 (95% CI: 0.14, .80). Our model also revealed significant heterogeneity (Q[5] = 34.49, *p* < .001, *I*2 = 92.08%). For a forest plot of our suicidal ideation results, see Figure 1. Regarding publication bias, visually inspecting the funnel plot (see Figure 2) was inconclusive given that we currently only have five studies included. However, if the trend continues, it appears there may be publication bias as there are few studies on the bottom-left side of the funnel. Egger’s test for funnel plot asymmetry did not find evidence of publication bias (*β* = .49, *p* = .624), but again due to so few effect sizes, this test may be underpowered. In the future, we would examine moderators of this relation since we found significant heterogeneity. Moderators may include the age of the sample, whether the sample was a clinical sample, and the proportion of the sample that was male.

**Suicide Attempt**

After excluding one outlier effect size, our suicidal attempt meta-analysis consisted of eight effect sizes. The difference in ERPs between those with a previous suicide attempt and those without a previous suicide attempt was significant, with an average weighted *d* = 0.54 (95% CI: 0.36, 0.71). Our model did not reveal significant heterogeneity in effect sizes (Q[7] = 12.02, *p* = .100, *I*2 < .01%). For a forest plot of our suicide attempt results, see Figure 3. Regarding publication bias, visually inspecting the funnel plot was again inconclusive due to so few studies included (see Figure 4). However, if the trend continues, then it appears there may be significant publication bias as our current funnel plot does not contain any studies in the bottom-left portion of the funnel. Egger’s test for funnel plot asymmetry found evidence of publication bias (*β* = 1.99, *p* = .047). Due to so few effect sizes, it remains to be seen whether this test will remain significant as our meta-analysis gathers more effect sizes.

**Suicide Risk/Suicidality**

Like our other two outcomes, we excluded one outlier for our suicide risk meta-analysis, leaving four studies for our meta-analysis examining the relation between ERPs and suicide risk. The differences in ERPs between those at higher suicide risk and those with lower suicide risk was significant, with an average weighted *d* = 0.39 (95% CI: 0.17, 0.61). Our model did not reveal significant heterogeneity in effect sizes (Q[3] = 1.58, *p* = .665, *I*2 < .01%). For a forest plot of our suicide risk results, see Figure 5. Regarding publication bias, we again had too few studies to draw conclusions (see Figure 6). Egger’s test for funnel plot asymmetry did not find evidence of publication bias (*β* = -0.37, *p* = .712). Again, it will be interesting to examine whether these results hold as we add more effect sizes.

**Sensitivity Analyses**

In our real meta-analysis, we will conduct several sensitivity analyses. First, reminder that when we conduct our real meta-analysis, we will use robust meta-analysis to handle our high effect size dependency. Thus, for one sensitivity analysis, we will handle dependent effect sizes by averaging dependent effect sizes and then using the random effects meta-analysis we used in this preliminary report. Another sensitivity analysis we will conduct is to use Duval and Tweedie’s Trim and Fill Method to examine what would happen if missing effect sizes were included in the analyses.

**Conclusions**

At this point, no conclusions can be drawn since we do not yet have all the effect sizes coded. So, we will speculate if our final results resemble those seen here. In summary, our results indicate that ERPs have a significant, but relatively small, relationship with various suicidal outcomes. All research to date has examined ERPs and their relationship to suicidal outcomes cross-sectionally, with no attempts at prediction. However, if ERPs have similar effect sizes longitudinally as those found cross-sectionally in the current meta-analysis, ERPs alone will not be an effect clinical tool in predicting suicidal thoughts and behaviors. However, it remains to be seen whether ERPs might be used in conjunction with other measures to create suicide risk algorithms that can accurately predict suicide. Our results also suggest that, at least for the relationship between suicide attempts and ERPs, there may be significant publication bias. Our results suggest that the modal study on ERPs and suicidal outcomes are likely vastly underpowered to estimate the expected effect size. Thus, future researchers should consider collaborating to obtain larger, more representative samples to detect effects.

*References marked by \* indicate studies included in meta-analysis before outliers removed.*

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*Figure 1.* Average weighted absolute difference *d* in ERPs between those with and those without suicidal ideation.



*Figure 2.* Funnel plot for suicidal ideation meta-analysis.



*Figure 3.* Average weighted absolute difference *d* in ERPs between those with and those without a previous suicide attempt.



*Figure 4.* Funnel plot for suicide attempt meta-analysis.



*Figure 5.* Average weighted absolute difference *d* in ERPs between those at lower risk for suicide, and those at higher risk for suicide.



*Figure 6.* Funnel plot for suicide risk/suicidality meta-analysis.