

Decreased Neural Response to Threat Differentiates Patients Who Have Attempted Suicide From Nonattempters With Current Ideation

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Abstract

Suicide prevention efforts have not slowed suicide rates, in part because of limited understanding of differences in risk for suicide ideation versus suicide attempts. Reduced fear of pain and death may be key to this distinction. In the present study we examine whether blunted neural response to threat of death, bodily harm, or illness, measured by the late positive potential (LPP), differentiates individuals who had previously attempted suicide from individuals who had never attempted suicide, controlling for current levels of suicidal ideation. We compared psychiatric outpatients with no history of suicide attempts ($n = 152$) and those with a history of suicide attempts ($n = 83$). Attempters exhibited a blunted threat-elicited LPP compared to patients with no history of attempts, regardless of current ideation. Findings suggest diminished neural response to threat can distinguish attempters from ideators and might be a target for future research on the transition from ideation to action.

Keywords

affective disorders, affective neuroscience, suicide attempts, suicidal ideation

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In 2014, the most recent year for which data are available, over 42,700 people died of suicide in the United States (Centers for Disease Control and Prevention, 2016), making it the 10th leading cause of death. Despite increases in research and prevention efforts in recent decades, there has been no evidence of a sustained decline in suicide rates (World Health Organization, 2015). One potential explanation for stalled prevention efforts is a limited understanding why some people with suicidal thoughts make suicide attempts and endanger their lives, whereas most do not (Glenn & Nock, 2014). Annually, approximately 9.4 million American adults report seriously considering suicide but less than 12% of these individuals will go on to act on those thoughts (Substance Abuse and Mental Health Services Administration, 2015). Past suicide attempts, which have been considered among the strongest

predictors of future suicidal behavior, appear to account for only a small number of future suicide attempts and deaths (Ribeiro et al., 2016). Furthermore, most consistently identified risk factors for suicide, such as gender, psychiatric disorders, and hopelessness, are powerful in indicating risk for suicide ideation, but are only weakly associated with suicide attempts among ideators (Kessler, Borges, & Walters, 1999; May & Klonsky, 2016). For example, a meta-analysis finds the presence of a depressive disorder is strongly associated with suicide ideation ($d = 0.85$). However, the relationship is almost

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negligible ($d = 0.24$) when examining attempts among ideators (May & Klonsky, 2016). Thus, although the field has a growing list of predictors of suicide ideation, our ability to calculate the risk of action among people thinking of suicide is quite limited.

Modern theories of suicide have recognized this critical gap in our knowledge and are positioned within an ideation-to-action framework (Klonsky & May, 2014). That is, they offer separate explanations for (a) the development of ideation and (b) the transition from ideation to attempt. The first of these theories was Thomas Joiner's interpersonal psychological theory (Joiner, 2007). This theory argues that exposure to painful and fearsome stimuli ultimately reduces innate fears of pain and death, making it easier for a suicidal individual to approach the task of inflicting lethal harm on himself or herself. Thus, this acquired capability is considered necessary to move from having suicidal thoughts to making suicidal actions. Building on this work, the three-step theory (Klonsky & May, 2015) takes a broader perspective, positing that there are three elements to the capacity to attempt suicide: practical (e.g., access to guns, familiarity with potentially lethal medications), dispositional (e.g., trait fearlessness, propensity toward risk taking), and acquired (e.g., nonsuicidal self-injury, combat training, working in an operating room). All three of these elements can contribute to an individual's capacity to act on his or her suicidal thoughts. Among adults with current ideation, these three domains of capacity differentiated those with a history of attempts from those without (Klonsky & May, 2015).

Across theoretical perspectives, reduced fear of pain and death is identified as a critical component of an individual's ability to act on his or her suicidal thoughts. Yet most of the research examining differences between ideators and attempters has measured fearlessness and pain tolerance using self-report methods. Although a number of studies have found that capacity (i.e., reduced fear of pain and death) is associated with attempts above and beyond ideation (Dhingra, Boduszek, & O'Connor, 2015; P. Smith, Cukrowicz, Poindexter, Hobson, & Cohen, 2010), results have been mixed (Bryan, Hernandez, Allison, & Clemans, 2013). There is a small body of work examining pain tolerance using behavioral measures such as the cold pressor task, thermal pain, electric shocks, or pressure algometers, predominantly among those with and without nonsuicidal self-injury (e.g., Franklin, Hessel, & Prinstein, 2011; Weinberg & Klonsky, 2012). As described in a recent review, this literature generally finds that those with a history of nonsuicidal self-injury have a higher pain threshold and tolerance than those without (Kirtley, O'Carroll, & O'Connor, 2016). However, behavioral measures of pain tolerance have yet to be used to compare suicide ideators to attempters.

Similarly, given the inherent difficulty in asking individuals to self-report their fearlessness about death, investigation of this construct with different methodologies is needed. In particular, objective measures of sensitivity to threats to life or bodily integrity may be useful in understanding capacity and, therefore, suicide risk. However, the modest body of research in threat reactivity in suicide attempters has turned up decidedly mixed results. Studies using behavioral, physiological, and neural indicators of threat reactivity have alternately found evidence for *no* differences in response to threatening or negative content in individuals who have attempted suicide compared to controls (Jollant et al., 2008; P. Smith et al., 2010) or evidence for increased threat response (Ballard et al., 2014; Becker, Strohbach, & Rinck, 1999; Cha, Najmi, Park, Finn, & Nock, 2010; Hazlett et al., 2016; Williams & Broadbent, 1986). In addition, a recent study specifically examining fearlessness about death found this construct was related to *reduced* facial electromyographic response to death-related images (Velkoff, Forrest, Dodd, & Smith, 2016). However, the majority of these studies have been conducted in small samples or have focused on a single diagnostic group, making it difficult to assess the generalizability of the results. Moreover, many of them have not directly compared ideators to attempters, making it difficult to determine whether the effects are specific to suicide attempt or are more general correlates of ideation. Therefore, in a large and heterogeneous sample of psychiatric outpatients, the present study aimed to identify abnormalities in neural response to threats of death, bodily harm, or illness associated specifically with suicide attempts, and not with suicidal ideation more broadly.

We focused our analyses on the threat-elicited late positive potential (LPP), a component of the event-related potential (ERP) that presents as a sustained positive-going deflection in the waveform beginning as early as 200 ms following stimulus onset (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Weinberg & Hajcak, 2011) and persists for the duration of picture presentation (Weinberg & Hajcak, 2010; Weinberg, Perlman, Kotov, & Hajcak, 2016). The LPP reflects neural reactivity to motivationally salient content (Grasso & Simons, 2011; Stockburger, Schmäzle, Fleisch, Bublitzky, & Schupp, 2009; Tacikowski & Nowicka, 2010) and appears to arise from the ongoing activation of, and communication between, multiple regions of the brain—including visual, parietal, and frontal cortices (Sabatinelli, Keil, Frank, & Lang, 2013; Sabatinelli, Lang, Keil, & Bradley, 2007), as well as subcortical structures like the ventral striatum and the amygdala (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012; Sabatinelli et al., 2013). The LPP has good internal consistency (Moser, Moran, & Jendrusina, 2012), is

stable over time and across developmental stages (Kujawa, Klein, & Proudfit, 2013), and is reliably enhanced following emotional relative to neutral images (Cuthbert et al., 2000; Weinberg & Hajcak, 2010, 2011). The LPP is particularly enhanced by those categories of emotional images most pertinent to survival, affiliation, and reproduction (Briggs & Martin, 2009; Weinberg & Hajcak, 2010). An enhanced LPP reflects sustained and ongoing elaboration of salient content (Dolcos & Cabeza, 2002; Weinberg & Hajcak, 2011), even in contexts in which engagement with this content is not adaptive (Weinberg & Hajcak, 2011).

In particular, the LPP elicited by images depicting infection, contamination, death, violence, or threat to self appears to reflect the rapid engagement of the brain's defensive motivation system (Bradley, Codispoti, Cuthbert, & Lang, 2001; Lang, Bradley, & Cuthbert, 1997). This defensive system—which involves the activation of sensory systems as well as central, autonomic, and motor responses in preparation for action—is thought to be a circuit critically involved in survival, and one that typically aids the organism in avoiding harm (Frijda, 1986; Lang & Bradley, 2010). Images depicting normative threatening content not only elicit a larger LPP in healthy participants, but also increased skin conductance responses and potentiated blink startle responses (e.g., Schupp et al., 2004), suggesting the threat-elicited LPP is capturing some portion of variance in defensive activation and increased mobilization of physiological resources in service of responding to threat.

Abnormalities in the magnitude of the LPP have also been observed in multiple groups characterized by maladaptive patterns of emotional reactivity. For instance, although threatening images elicit an enhanced LPP across participants, it is further enhanced in individuals who are highly threat-sensitive (e.g., specific phobic individuals viewing images of the object of their phobias; Flykt & Caldara, 2006; Leutgeb, Schäfer, & Schienle, 2009). In contrast, individuals who report high levels of trait *fearlessness* tend to show a reduced LPP to threatening stimuli (Verona, Sprague, & Sadeh, 2012; Weinberg, Venables, Hajcak, & Patrick, in prep), suggesting decreased sensitivity and attention to threatening content. Similarly, a blunted LPP has often been observed in individuals with depression (Foti, Olvet, Klein, & Hajcak, 2010; MacNamara, Kotov, & Hajcak, 2016; Proudfit, Bress, Foti, Kujawa, & Klein, 2015; Weinberg et al., 2016; Weinberg & Sandre, 2017), and in a recent report on a subset of the sample included in the present article, we found that greater suicidal *ideation* predicted a blunted LPP to emotional content across a sample of unipolar depressed and anxious patients (Weinberg et al., 2016). However, like most work in the area, we did not distinguish suicidal ideation

from a history of suicide attempts—thus, it is unclear if reduced neural response to threat relates broadly to ideation or more specifically to capacity to attempt suicide. Consistent with the capacity model of suicidal behaviors, we predicted that the LPP to threatening content (and not neutral or rewarding content) would be reduced in patients who had a history of suicide attempts, relative to individuals who had never attempted suicide. Thus, we expected that the threat-elicited LPP would specifically be reduced in relation to the capacity for suicidal action, operationalized in terms of past suicide attempts. We further predicted that reduced neural response to threat would be related to suicide attempts but not ideation.

Method

Participants

Participants in this study were recruited as a part of a larger, multimethod study intended to examine the associations between old and new means of categorizing internalizing diagnoses, symptom dimensions, and neural responses to threat and reward. Associations between diagnoses were expected to be at least moderate in size (correlation $r \geq .35$; Cohen, 1988). Given at least 20 participants with each diagnosis and an overall sample size of 300, we anticipated having very good power (.90) to detect such links. With 300 participants, the study was also designed to have .90 power to account for at least 13% of variance (a moderate effect) in neural responses to threat. Therefore, 318 patients were recruited from outpatient psychology and psychiatry clinics at Stony Brook University, local community mental health centers, and assisted-living facilities and community programs for the mentally ill, to gain a wide and representative range of internalizing psychopathology. All 318 participants were offered \$125 for their participation in a 5-hr protocol. All procedures were approved by Stony Brook University's Institutional Review Board and were carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki.

Of the 318 participants, 38 were excluded from the present analyses because they did not complete the viewing task, which was the target of this study, and 52 either did not complete the questionnaires used to assess suicidal ideation or suicide attempts or did not respond to the suicide attempt item (7 participants did not complete either the viewing task or the questionnaire assessing suicide attempts). The remaining 235 patients were included in the analyses that follow. Age and gender distributions are reported in Table 1; consistent with the population of the surrounding area, the

Table 1. Demographics, Principal Diagnoses, Current Symptoms, and Event-Related Potential Responses for the Two Patient Groups

Category	Variable	No suicide attempt (<i>n</i> = 152)	History of suicide attempt (<i>n</i> = 83)	<i>F</i> or χ^2	<i>p</i>
Demographics	Age, <i>M</i> (<i>SD</i>)	41.70 (13.64)	40.22 (11.81)	<i>F</i> (1, 233) = 0.69	.41
	Gender, <i>n</i> (% female)	87 (57)	42 (51)	χ^2 (1) = 0.95	.33
	Ethnicity, <i>n</i> (% Caucasian)	121 (79)	63 (78)	χ^2 (4) = 1.47	.83
	Employed, <i>n</i> (%)	64 (42)	24 (29)	χ^2 (1) = 4.46	.04
	On disability, <i>n</i> (%)	50 (33)	45 (54)	χ^2 (1) = 9.41	.003
Lifetime diagnosis, <i>n</i>	None	9	0		
	Bipolar I	22	29		
	MDD	85	38		
	Psychosis	10	22		
	Panic disorder	60	34		
	Social anxiety disorder	37	31		
	Specific phobia	50	31		
	OCD	16	18		
	PTSD	23	28		
IDAS scales, <i>M</i> (<i>SD</i>)	General depression	52.38 (15.48)	57.65 (16.54)	<i>F</i> (1, 233) = 5.90	.02
	Suicidal ideation	1.47 (0.64)	1.96 (1.10)	<i>F</i> (1, 233) = 18.63	<.001
	Well-being	16.81 (6.06)	16.40 (6.57)	<i>F</i> (1, 233) = 0.23	.63
	Ill temper	9.93 (4.95)	11.30 (5.41)	<i>F</i> (1, 233) = 3.88	.05
	Panic	13.81 (5.58)	16.10 (6.58)	<i>F</i> (1, 233) = 7.94	.005
	Social anxiety	12.97 (6.38)	15.64 (6.78)	<i>F</i> (1, 233) = 9.01	.003
	Traumatic intrusions	8.81 (4.29)	10.63 (5.02)	<i>F</i> (1, 233) = 8.54	.004
	Traumatic avoidance	10.37 (4.18)	11.86 (5.10)	<i>F</i> (1, 233) = 5.79	.02
LPP, <i>M</i> (<i>SD</i>)	LPP reward	3.99 (4.81)	2.98 (4.58)	<i>F</i> (1, 233) = 2.44	.12
	LPP neutral	0.08 (3.93)	-0.64 (3.77)	<i>F</i> (1, 233) = 1.82	.18
	LPP threat	6.04 (5.43)	3.49 (5.25)	<i>F</i> (1, 233) = 12.18	.001

Note: LPP = late positive potential; MDD = major depressive disorder; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder.

sample was primarily Caucasian (78.6%; 4.2% Hispanic, 9.5% African American, 1.3% Asian, and 4.2% Other).

Measures

Once in the lab, all participants were administered the fourth edition of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID; First, Spitzer, Gibbon, & Williams, 2002). The SCID is a well-validated semistructured interview for current and past *DSM-IV* Axis I diagnoses. The SCID was administered by five master's-level clinicians. Prior to the study, all diagnostic interviewers underwent an extensive training process, and regular meetings were held throughout the course of the study to ensure continued agreement and compliance. Lifetime diagnoses reported here are based on the SCID.

Current suicidal ideation, along with other symptoms of depression and anxiety, was assessed in all participants using an expanded Inventory of Depression and

Anxiety Symptoms (IDAS-II; Watson et al., 2012). The IDAS-II is a factor-analytically derived self-report inventory of empirically distinct dimensions of depression and anxiety symptoms. Each item assesses symptoms over the past two weeks on a 5-point Likert-type scale ranging from 1 (*not at all*) to 5 (*extremely*). The IDAS-II has demonstrated good internal consistency, test-retest reliability, and convergent and discriminant validity with diagnoses and self-report measures (Watson et al., 2007; Watson et al., 2012). Suicidal ideation is typically captured in the IDAS by six items ("I had thoughts of suicide," "I thought that the world would be better off without me," "I thought about my own death," "I thought about hurting myself," "I hurt myself purposely," and "I cut or burned myself on purpose"; $\alpha = .79$ in this sample). However, the latter two items assess self-injurious behaviors, rather than suicidal thoughts. These two items also had lower correlations with other items in the scale. To create a scale that captured suicidal ideation and not self-injurious behaviors, we used the

mean of the first four items indicated earlier ($\alpha = .83$ in this sample).

History of suicide attempts for all patients in the sample was assessed via an item on the Schedule for Nonadaptive and Adaptive Personality (SNAP; Clark, 1993). This item asks participants to endorse the statement "I have tried to commit suicide." In all, 83 participants (35.3%) reported having attempted suicide on the SNAP, and 152 reported no history of suicide attempts.

Task and materials

A total of 270 images were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005). Rewarding images included erotic images of heterosexual couples, as well as affiliative images (e.g., smiling families, people embracing, babies laughing). Threat images included images of contamination, infection, mutilation, death, and animal and human attack. Neutral images included images of objects (e.g., a lamp, a mushroom), as well as images of neutral human faces. Normative ratings (Lang et al., 2005) indicated that the 90 threatening pictures were less pleasant (valence $M = 2.44$, $SD = 0.69$) than the 90 neutral pictures ($M = 5.15$, $SD = 0.65$), which were less pleasant than the 90 rewarding pictures ($M = 7.13$, $SD = 0.62$; higher numbers indicate more pleasant ratings). Threatening ($M = 6.10$, $SD = 0.74$) and rewarding ($M = 5.91$, $SD = 0.85$) images were more emotionally arousing than neutral images ($M = 3.32$, $SD = 0.72$; higher numbers indicate higher arousal). Specific images used in the study are listed in the appendix.

All visual stimuli were presented on a Pentium D computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, CA). Prior to each trial, participants viewed a white fixation cross on a black background. Each picture was displayed in color at 48.26 cm, the full size of the monitor. Participants were seated approximately 60.96 cm from the screen and the images occupied about 40° of visual angle horizontally and vertically.

Procedure

Subsequent to verbal instructions indicating that they would be passively viewing pictures of varying emotional quality, participants were seated and electroencephalograph sensors were attached. All participants performed multiple tasks, completed multiple questionnaires, and underwent multiple interviews during the experiment; results from other tasks and interviews/questionnaires are reported elsewhere (e.g., MacNamara et al., 2016; Weinberg, Kotov, & Proudfit, 2015). This

article reports on all conditions and measures obtained in the course of the passive viewing task that was the target of this study. Results from this task in a subset ($n = 151$) of the participants included here are also reported in Weinberg et al. (2016); however, suicide attempts were not considered in that article.

The order of the tasks was counterbalanced across subjects. For the current study, participants viewed three blocks of images, with each block consisting of rewarding-only, threatening-only, or neutral-only images. The order of the blocks was random across subjects, and between each block, participants were given a short break. Within each block, the order of picture presentation was random for each participant, and each image was presented twice; blocks lasted approximately 5 min each. Each image was presented for 1,500 ms, with fixed 2-s intervals between image presentations. During all EEG tasks, participants were monitored via a closed-loop camera to ensure that they were looking at the images on the screen.

Electroencephalographic recording and data processing

Continuous EEG recordings were collected using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). In all, 34 electrode sites were used, including FCz and Iz, based on the 10/20 system, as well as 2 electrodes on the right and left mastoids. Electrooculogram generated from eye movements and eyeblinks was recorded using four facial electrodes: Horizontal eye movements (HEMs) were measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. Vertical eye movements (VEMs) and blinks were measured via two electrodes placed approximately 1 cm above and below the right eye. The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of 1× by a BioSemi ActiveTwo system (BioSemi, Amsterdam). The data were digitized at 24-bit resolution with a LSB value of 31.25 nV and a sampling rate of 1,024 Hz, using a low-pass fifth order sinc filter with -3 dB cutoff point at 208 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode, located between PO3 and POz, producing a monopolar (nondifferential) channel. CMS forms a feedback loop with a paired driven right leg (DRL) electrode. Offline, all data were referenced to the average of the left and right mastoids, and band-pass filtered from 0.01 to 30 Hz. Eye-blink and ocular corrections were conducted using VEM and HEM channels per a version of the original algorithm published in Gratton, Coles, and Donchin (1983).

A semiautomatic procedure was employed to detect and reject artifacts. The criteria applied were a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. These intervals were rejected from individual channels in each trial. Visual inspection of the data was then conducted to detect and reject any remaining artifacts (e.g., ocular artifacts that were not fully removed during ocular correction, or slow-wave activity that was not identified by the automatic parameters).

The EEG was segmented for each trial beginning 200 ms prior to picture onset and continuing for 1,700 ms (i.e., the entire duration of picture presentation). For each trial, a baseline of the average activity in a 200 ms window prior to picture onset was subtracted from every data point. ERPs were constructed by separately averaging epochs by picture content (rewarding, neutral, and threatening). Previous research has demonstrated that the LPP is maximal at centroparietal sites (Foti & Hajcak, 2008; Weinberg & Hajcak, 2011), and visual inspection of grand averages confirmed that this was also the case in the current sample; therefore, the LPP was scored as the average activity at three centroparietal sites (Pz, CP1, and CP2), between 400 and 1,000 ms (MacNamara, Ferri, & Hajcak, 2011; Weinberg & Hajcak, 2011).

All statistical analyses were conducted using SPSS General Linear Model software, with Greenhouse-Geisser correction applied to p values associated with multiple- df , repeated-measures comparisons when necessitated by violation of the assumption of sphericity. To evaluate group differences in neural response to rewarding and threatening images, a 3 (picture type: rewarding, neutral, threatening) \times 2 (group: no suicide attempt, suicide attempt) \times 2 (gender: male, female) repeated-measures mixed-model ANCOVA was conducted, with current suicidal ideation as a continuous predictor. This was followed by three one-way ANCOVAs comparing the groups on neural response to rewarding and threatening images, controlling for current suicidal ideation, gender, and neural response to neutral images. One-way ANOVAs were used to compare the groups on age and dimensional symptom scores on the IDAS. Groups were compared on demographic variables (gender, ethnicity, employment, disability payments) using chi-square tests.

Results

Participant characteristics

Demographic information and means for ERPs, alongside frequencies for lifetime diagnoses and means for current symptoms of anxiety and depression, are

reported in Table 1. The two patient groups did not differ in age, gender composition, or ethnic distribution. However, the group with a positive history of suicide attempts was more likely to be unemployed and more likely to collect disability insurance than the group who did not report a history of suicide attempts.

Group differences in neural response to rewarding, neutral, and threatening images

Picture type significantly influenced the magnitude of the LPP, $F(2, 462) = 45.76, p < .001, \eta_p^2 = .17$, such that rewarding ($M = 3.63, SD = 4.74$), $t(234) = 14.80, p < .001$, and threatening ($M = 5.14, SD = 5.49$), $t(234) = 17.09, p < .001$, pictures elicited a significantly larger LPP than neutral pictures ($M = -0.18, SD = 3.88$). The LPP elicited by threatening pictures was also significantly larger than that elicited by rewarding pictures, $t(234) = 543, p < .001$. Gender was not significantly associated with the magnitude of the LPP, $F(1, 231) = 0.13, p = .72, \eta_p^2 = .001$, nor did it interact with picture type to predict the magnitude of the LPP, $F(2, 462) = 1.59, p = .21, \eta_p^2 = .007$. Likewise, the LPP was not impacted overall by current suicidal ideation, $F(1, 231) = 3.60, p = .06, \eta_p^2 = .02$, and suicidal ideation did not interact with picture type to predict the LPP, $F(2, 462) = 1.58, p = .21, \eta_p^2 = .007$.

History of suicide attempts was significantly associated with the magnitude of the overall LPP (i.e., collapsing across picture types), $F(1, 231) = 3.95, p = .048, \eta_p^2 = .02$; however, this main effect was qualified by a significant interaction with picture type, $F(2, 462) = 3.71, p = .03, \eta_p^2 = .02$. To decompose this interaction, we examined group differences in neural response to threatening and rewarding pictures using one-way ANCOVAs, with gender, current suicidal ideation, and neural response to neutral images included as additional predictors. There were no significant group differences in the magnitude of the neural response to rewarding images, $F(1, 230) = 0.26, p = .61$; nor did gender, $F(1, 230) = 0.05, p = .82$, or suicidal ideation, $F(1, 230) = 1.98, p = .16$, significantly predict the reward-elicited LPP. The only significant group difference was in the magnitude of attempters and nonattempters' neural responses to threatening images, $F(1, 230) = 6.53, p = .01$; patients with a history of suicide attempts had a significantly smaller threat-elicited LPP ($M = 3.49, SD = 5.25$) than patients with no reported history of suicide attempts ($M = 6.04, SD = 5.43$). Again, neither gender, $F(1, 230) = 2.21, p = .14$, nor current suicidal ideation, $F(1, 230) = 3.55, p = .06$, significantly predicted the magnitude of the threat-elicited LPP.

Figure 1 displays grand average stimulus-locked ERPs at a pooling of Pz, CP1, and CP2, where the LPP was maximal across both groups (patients with and

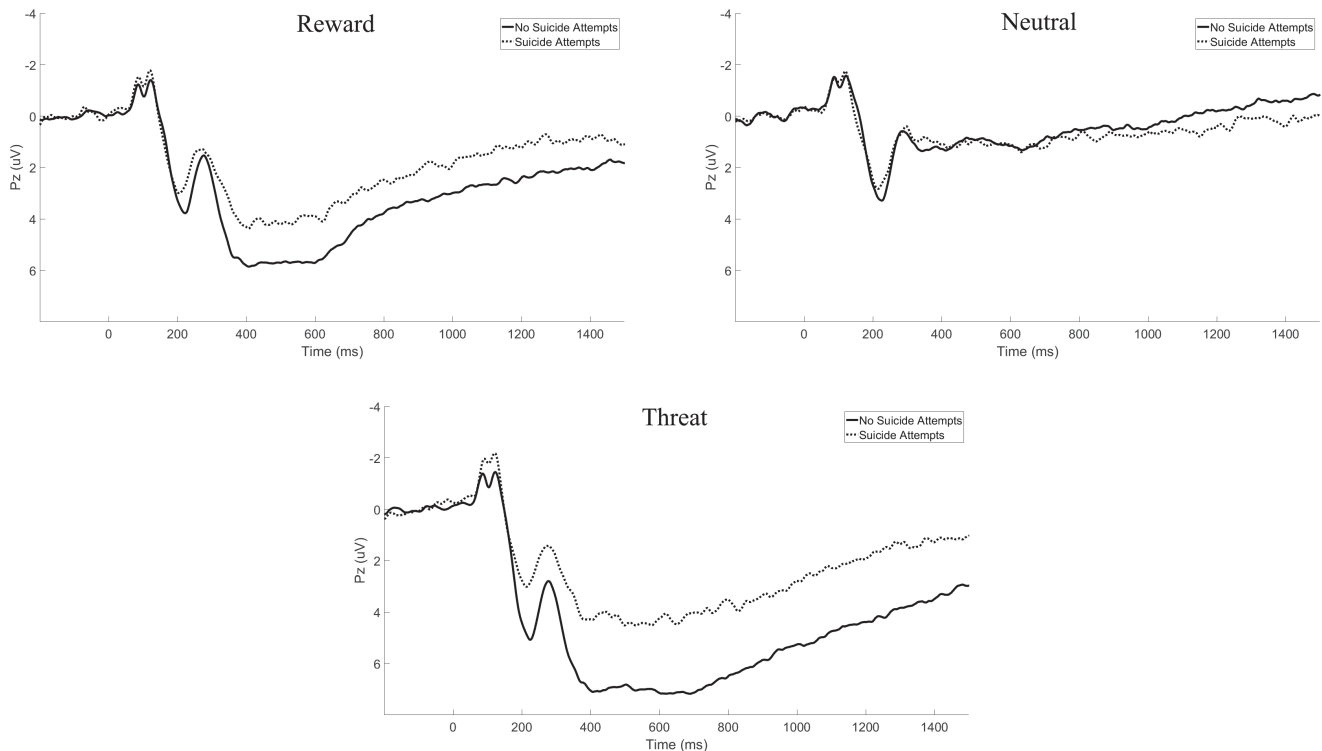


Fig. 1. Picture-locked event-related potential (ERP) waveforms at a pooling of electrode sites Pz, CP1, and CP2 for individuals with and without a history of suicide attempts. Per ERP convention, negative voltages are plotted up. A positive history of suicide attempts was associated with a decreased LPP to threatening images.

without a history of suicide attempt). Topographic maps depicting voltage differences (in μV) across the scalp for threatening minus neutral in the time window of the LPP are also presented in Figure 2.

Discussion

The present study examined the association between suicide attempts and neural response to threatening visual content in a large and heterogeneous sample of psychiatric outpatients. Although previous research has identified numerous risk factors associated with suicidality in general, it has been challenging to identify factors that distinguish those who contemplate suicide from those who act on suicidal thoughts. The goal of this study was therefore to identify patterns of neural response that would differentiate patients who had made a suicide attempt from those with suicide ideation only. The results of the study demonstrated that patients who had attempted suicide were characterized by a blunted LPP to threatening images relative to patients who reported no history of suicide attempts, regardless of levels of current suicidal ideation. This effect was specific to threatening content, and is consistent with theories suggesting that the capacity for suicide attempts is related to decreased reactivity to threat Joiner, 2007;

Klonsky & May, 2015). The evidence for a significant effect of history of suicide attempts, independent of current suicidal ideation, suggests that the blunted threat-elicited LPP is not merely a function of suicidal ideation, or more severe current impairment or distress, but may instead be a transdiagnostic marker that will be valuable in identifying individuals who have the capacity to attempt suicide.

There is abundant evidence that risk for suicide is subject to familial and genetic contributions (Baldessarini & Hennen, 2004; Brent & Mann, 2005; Joiner, Brown, & Wingate, 2005). Some of this shared familial risk may be explained by the heritable nature of many psychiatric disorders associated with suicide and suicide attempts (Greenwood et al., 2007; Kendler, Neale, Kessler, Heath, & Eaves, 1993); however, studies controlling for the presence of psychopathology have also found evidence for familial transmission of suicidal behaviors specifically (Mann, 2003). Genetically influenced threat insensitivity contributing to capacity may be one intermediate construct underlying the intergenerational transmission of suicidal behaviors. Indeed, capacity for suicide increasingly appears to include a stable or trait-like element. For instance, a longitudinal study of military personnel deployed to Iraq found that capacity scores remained stable from predeployment

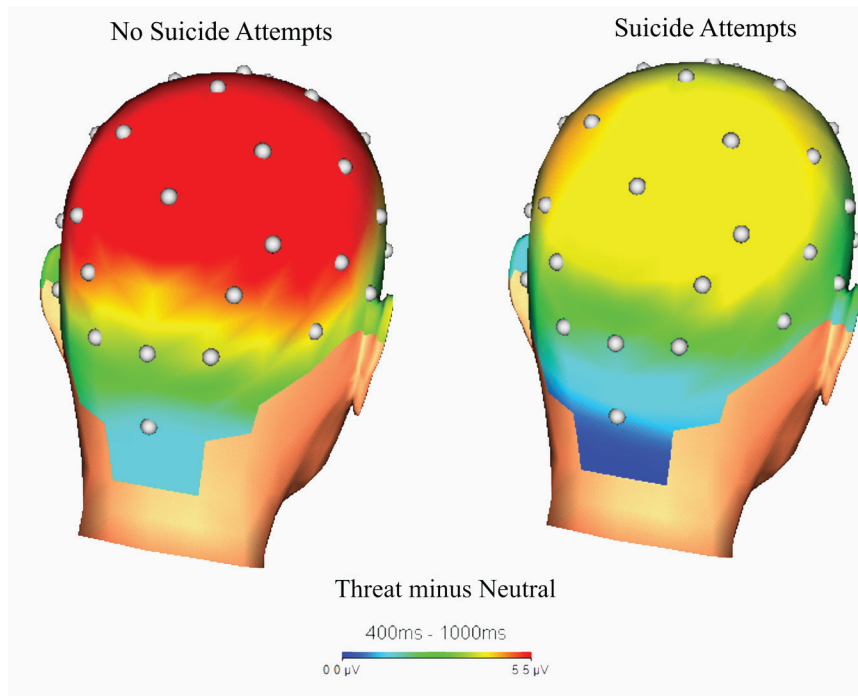


Fig. 2. Scalp topographies depicting neural response to threat minus neutral response to neutral images in the time-window of the late positive potential (LPP; 400 to 1,000 ms) for individuals with and without a history of suicide attempts.

to 2 years postdeployment, regardless of combat exposure (Bryan, Sinclair, & Heron, 2016). In addition, a recent twin study has found evidence of additive genetic effects influencing capacity for suicide (A. Smith et al., 2012).

The threat-elicited LPP may be a useful objective marker of trait-like and genetically influenced capacity. The LPP has trait-like properties, in that it has good internal consistency (Moser et al., 2012) and is stable over time and across developmental stages (Kujawa et al., 2013). And finally, the magnitude of the LPP, as well as emotional modulation of the LPP, is subject to genetic influence (Weinberg, Venables, Proudfit, & Patrick, 2015), suggesting the LPP may represent a heritable biomarker of patterns of reactivity to emotional content. Consistent with this, abnormalities in the magnitude of the LPP have been observed in unaffected individuals who are at risk for the development of psychopathology (Kujawa, Hajcak, Torpey, Kim, & Klein, 2012; Nelson, Perlman, Hajcak, Klein, & Kotov, 2015). Future studies investigating neural response in the family members of individuals who have attempted or died by suicide may also be useful in establishing whether this attenuated threat-elicited LPP represents a vulnerability marker for suicidal behaviors.

However, capacity to attempt suicide is also subject to environmental influences. The same twin study cited

earlier found nonshared environmental factors contributed to capacity (A. Smith et al., 2012), and capacity to act on suicidal thoughts can arise through practice or habituation. For example, engaging in more nonsuicidal self-injury predicts greater capacity the following year (Willoughby, Heffer, & Hamza, 2015) and playing more hours of violent video games is correlated with greater capacity, even when controlling for previous painful life events (Mitchell, Jahn, Guidry, & Cukrowicz, 2015). Exposure to threatening, dangerous, or provocative situations is also theorized to contribute to capacity. Among veterinary students, greater exposure to euthanasia is associated with increased fearlessness (Witte, Correia, & Angarano, 2013), whereas among physicians, greater exposure to provocative work experiences, such as performing surgeries or treating traumatic injuries, is associated with increased capacity (Fink-Miller, 2015). Similarly, only approximately 50% of the variance in the LPP is subject to genetic influence (Weinberg, Venables, et al., 2015), and there is evidence that the magnitude of the LPP is also sensitive to environmental effects (Kessel et al., in press).

The malleability of the LPP suggests it may be a useful tool in assessing the degree to which capacity is acquired, innate, or arises from an interaction of the two. Future prospective studies in settings where fearlessness is being specifically trained—for example, the

military, first responders, or surgical residency—would allow for the exploration of the origins of the blunted threat-elicited LPP and its relationship to suicidal behavior. It is possible that a blunted neural response to threat at baseline might predict who is drawn to these settings, as well as how people respond to these settings; these settings might also themselves lead to a blunted threat-elicited LPP. Longitudinal studies are needed to better explore the origins and consequences of this blunted threat-elicited LPP, as well as the ways in which these factors relate to suicide capacity. In addition, the use of divergent tools (e.g., self-report, pain tolerance trials, cognitive tasks, threat-potentiated startle, EEG) to measure capacity and fearlessness within a single study will further elucidate underlying mechanisms of this phenomenon.

Finally, in light of emerging evidence that the LPP to threatening images can predict individual differences in the response to acute life stressors (Kujawa et al., 2016), and given the role that stressful life events play in suicide attempts (Asarnow et al., 2008; King et al., 2001), the LPP may also be a useful predictor of who will be most susceptible to the effect of stress, thereby identifying individuals in most urgent need of intervention.

Limitations of the study suggest directions for future research. For instance, suicide attempts were assessed through a single yes/no self-report item on the SNAP. Although single-item measures of suicide attempts are commonly used in suicide research, they leave room for discrepancy between the researcher's and the participant's definition of a suicide attempt, which can result in misclassification (Hom, Joiner, & Bernert, 2016; Millner, Lee, & Nock, 2015). For example, a positive response to a single item could include aborted or interrupted attempts in addition to suicide attempts. However, recent work suggests there may be few differences between those with a history of suicide attempt versus interrupted/aborted attempts only (Burke, Hamilton, Ammerman, Stange, & Alloy, 2016), somewhat mitigating these concerns. An additional limitation of the single item measure is that it cannot provide information about the intent, lethality, recency, or frequency of suicide attempts—characteristics that may relate to response to threat. Future studies should collect more detailed information about past attempts to verify attempt status and to evaluate the extent to which characteristics of attempts are reflected in the magnitude of the neural response to threats. It is also important to note that this was a study of nonlethal suicide attempts, and thus the findings cannot necessarily be generalized to suicide decedents. A final limitation is the cross-sectional nature of the study. The directionality of the effect observed cannot be identified and thus, it is possible that past suicide attempts contributed to the LPP

differences observed, rather than the reverse. Hence the need for longitudinal studies to clearly delineate whether the attenuated threat-elicited LPP is a precursor to or results from suicide attempts.

Nonetheless, the present study was the first to examine the association between suicide attempts and neural response to threat across multiple diagnoses controlling for ideation. Results suggest that, regardless of current suicidal ideation, people who have attempted suicide exhibit a reduced neural response to threatening images. Thus, weakened reactivity to threatening stimuli may be a marker of risk specific to suicide attempts, separate from suicide ideation. Given the limited understanding of factors that differentiate ideators from attempters, the results of the present study suggest that it may be useful to incorporate biological markers of threat sensitivity into self-report and clinical assessment batteries to improve assessment of risk for suicidal behaviors. Future studies that use longitudinal and at-risk designs will be necessary to further substantiate these possibilities. Identification of risk markers that help predict who is at risk of transitioning from suicidal thoughts to suicide attempts are of vital importance.

Appendix

Specific Images Used in the Study

Rewarding Images: 5621, 8030, 8034, 8080, 8158, 8161, 8163, 8170, 8179, 8180, 8185, 8186, 8190, 8191, 8193, 8200, 8206, 8210, 8251, 8280, 8300, 8341, 8370, 8380, 8400, 8470, 8490, 8492, 8496, 8499, 1440, 1441, 1463, 1601, 1710, 1722, 1750, 1920, 2040, 2045, 2058, 2070, 2071, 2080, 2091, 2150, 2155, 2160, 2165, 2208, 2209, 2224, 2303, 2332, 2340, 2344, 2345, 2346, 2347, 2550, 4604, 4608, 4611, 4643, 4647, 4650, 4651, 4652, 4656, 4658, 4659, 4660, 4664, 4666, 4668, 4670, 4672, 4676, 4680, 4683, 4687, 4689, 4690, 4693, 4694, 4695, 4697, 4698, 4800, 4810.

Neutral Images: 7000, 7002, 7004, 7006, 7010, 7025, 7034, 7035, 7040, 7041, 7050, 7053, 7055, 7056, 7061, 7062, 7077, 7078, 7081, 7090, 7095, 7096, 7100, 7136, 7150, 7161, 7165, 7170, 7175, 7185, 2102, 2104, 2190, 2191, 2200, 2210, 2211, 2214, 2215, 2221, 2235, 2240, 2270, 2271, 2272, 2273, 2279, 2280, 2302, 2305, 2308, 2357, 2370, 2381, 2383, 2385, 2393, 2512, 2570, 7550, 5390, 5471, 5510, 5520, 5530, 5531, 5500, 5726, 5731, 5740, 5750, 7489, 7490, 7491, 7495, 7500, 7504, 7510, 7521, 7545, 7546, 7547, 7560, 7590, 7595, 7640, 7700, 7710, 9360, 9468.

Threatening Images: 1280, 2730, 2981, 7380, 9008, 9040, 9043, 9140, 9181, 9182, 9183, 9185, 9186, 9187, 9295, 9300, 9301, 9302, 9320, 9321, 9322, 9325, 9326, 9331, 9340, 9342, 9373, 9561, 9570, 9571, 9830, 1050, 1114,

1120, 1300, 1301, 1304, 1310, 1525, 1930, 2811, 3530, 6212, 6230, 6231, 6231, 6242, 6244, 6250, 6250, 6312, 6313, 6315, 6370, 6550, 6560, 6561, 6563, 6571, 6825, 9425, 3001, 3010, 3015, 3016, 3019, 3030, 3051, 3061, 3062, 3064, 3069, 3101, 3102, 3103, 3110, 3120, 3131, 3140, 3150, 3168, 3170, 3181, 3185, 3190, 3195, 3213, 3215, 3261, 3266, 3400.

Author Contributions

A. Weinberg and A. M. May are co-first authors. Testing and data collection were performed by A. Weinberg and many others, under the joint supervision of G. Hajcak and R. Kotov. A. Weinberg, A. M. May, and E. D. Klonsky developed the analytic concept for this article, and performed the data analysis and interpretation. A. Weinberg and A. M. May drafted the manuscript, and all authors provided critical revisions. All authors approved the final version of the manuscript for submission. We confirm that we have reported all measures and conditions from the passive viewing task that was the target of the reported analyses, as well as the rationale for data exclusion, and determination of sample size.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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