Psychological Medicine

cambridge.org/psm

Clinical, behavioral, and electrophysiological profiles along a continuum of suicide risk: evidence from an implicit association task

Steven J. Lamontagne, Jessica R. Gilbert, Paloma K. Zabala, Laura R. Waldman, Carlos A. Zarate Jr and Elizabeth D. Ballard

Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Original Article

Cite this article: Lamontagne SJ, Gilbert JR, Zabala PK, Waldman LR, Zarate Jr CA, Ballard ED (2024). Clinical, behavioral, and electrophysiological profiles along a continuum of suicide risk: evidence from an implicit association task. *Psychological Medicine* **54**, 1431–1440. https://doi.org/10.1017/S0033291723003331

Received: 10 March 2023
Revised: 23 August 2023
Accepted: 16 October 2023
First published online: 24 November 2023

Keywords:
dynamic causal modeling; gamma power; implicit association task; ketamine; magnetoencephalography; suicide

Corresponding author:
Elizabeth D. Ballard;
Email: Elizabeth.Ballard@nih.gov

Abstract

Background. An urgent need exists to identify neural correlates associated with differing levels of suicide risk and develop novel, rapid-acting therapeutics to modulate activity within these neural networks.

Methods. Electrophysiological correlates of suicide were evaluated using magnetoencephalography (MEG) in 75 adults with differing levels of suicide risk. During MEG scanning, participants completed a modified Life-Death Implicit Association Task. MEG data were source-localized in the gamma (30–58 Hz) frequency, a proxy measure of excitation-inhibition balance. Dynamic causal modeling was used to evaluate differences in connectivity estimates between risk groups. A proof-of-concept, open-label, pilot study of five high risk participants examined changes in gamma power after administration of ketamine (0.5 mg/kg), an NMDAR antagonist with rapid anti-suicide ideation effects.

Results. Implicit self-associations with death were stronger in the highest suicide risk group relative to all other groups, which did not differ from each other. Higher gamma power for self-death compared to self-life associations was found in the orbitofrontal cortex for the highest risk group and the insula and posterior cingulate cortex for the lowest risk group. Connectivity estimates between these regions differentiated the highest risk group from the full sample. Implicit associations with death were not affected by ketamine, but enhanced gamma power was found for self-death associations in the left insula post-ketamine compared to baseline.

Conclusions. Differential implicit cognitive processing of life and death appears to be linked to suicide risk, highlighting the need for objective measures of suicidal states. Pharmacotherapies that modulate gamma activity, particularly in the insula, may help mitigate risk.

Clinicaltrials.gov identifier: NCT02543983, NCT00397111.

Introduction

Suicide is a major public health challenge and a leading cause of death worldwide, including in the United States (Stone, Jones, & Mack, 2021). Suicide risk is typically characterized by lifetime history of suicide attempt, a known predictor for eventual death by suicide (Bostwick, Pabbati, Geske, & McKean, 2016; Horwitz, Czyz, & King, 2015). Unfortunately, fears about stigma, hospitalization, or other negative consequences often deter reliable reporting of suicidal thoughts and behaviors (STBs) (Smith et al., 2013). Patient reports nevertheless guide suicide prevention efforts, given the paucity of objective probes of suicidal states and a limited understanding of suicide-related biomarkers. Despite significant progress in this area, there is considerable heterogeneity in the characterization of suicide risk across clinical trials and neuroimaging studies. Moreover, the neurobiology of suicide can be conflated with neural signatures associated with co-occurring psychiatric disorders (e.g. mood disorders), thereby impeding the pursuit of suicide-specific biomarkers; this suggests that the neural underpinnings of suicide should be examined in groups with differing degrees of risk, including non-suicidal comparators with and without a history of psychiatric diagnoses.

Distinct brain regions and networks have been implicated in STBs. Aberrant prefrontal cortex (PFC) connectivity is particularly relevant in this context, as impairments within the ventral PFC (default mode network [DMN]) and dorsal PFC (central executive network [CEN]) are linked to suicide ideation and attempt, respectively (Schmaal et al., 2020). Although these parameters are impaired in a wide range of psychopathologies, their relevance in facilitating processes linked to suicide (e.g. cognitive control and flexibility, decision-making, planning) warrants careful consideration. In particular, a combination of CEN and DMN impairments could precipitate an imminent suicide crisis via diminished top-down inhibition of behavior, thereby contributing to the transition from SI to potentially lethal action. These systems can

become dysregulated under conditions of acute stress (e.g. death of a loved one, job loss) (Hermans et al., 2011; Hermans, Henckens, Joëls, & Fernández, 2014; Qin, Hermans, Van Marle, Luo, & Fernández, 2009), underscoring the importance of external environmental events in initiating the disruptions linked to SI and attempts. Critically, the right fronto-insular cortex mediates switching between the CEN and DMN (Sridharan, Levitin, & Menon, 2008), suggesting that this region might facilitate the transition from suicide ideation to attempt (Schmaal et al., 2020). The posterior cingulate cortex (PCC), a central node of the DMN, has also been linked to suicide, particularly in relation to self-referential processing (Northoff & Bermpohl, 2004) and mental imagery (Motoyama & Hishitani, 2016). It remains unclear whether the PCC differentially integrates self-referential stimuli, particularly in the context of suicide-related cues, depending on suicide risk. To that end, dissociable activation patterns in the PCC would offer insight into promising biomarkers for suicide.

Recent studies have examined differences in implicit cognitions – particularly automatic associations of self with death or suicide – as useful behavioral markers of suicide risk. The Life/Death Implicit Association Task (LD-IAT), a brief computer task that captures implicit associations of life and death with the self, differentiates suicide attempters from non-attempters. Specifically, suicide attempters were found to hold stronger implicit associations between the self and death compared to psychiatrically distressed individuals who had not attempted suicide (Nock et al., 2010). These findings have been replicated in diverse populations, including inpatient and emergency department samples (Barnes et al., 2017; Glenn et al., 2017a; Randall, Rowe, Dong, Nock, & Colman, 2013); however, considerable heterogeneity exists regarding the characterization of suicide risk across studies. Indeed, low-risk control groups – typically defined by an absence of *recent* suicide attempts – often comprise individuals with a *lifetime* history of one or multiple attempts and/or individuals in current psychiatric distress (Barnes et al., 2017; Nock et al., 2010; Tello, Harika-Germaneau, Serra, Jaafari, & Chatard, 2020). Such variability in risk characterization might contribute to disparate findings in the literature (for a systematic review, see Moreno, Guitérrez-Rojas, & Porras-Segovia, 2022), as well as replication challenges replicating the methodology from Nock et al. (2010), a more recent study found no differences in D-scores between a high-risk group (those with an attempt in the past week) and a control group (those without an attempt in the past week), but 62% of the control group had a lifetime history of attempts (Tello et al., 2020). When restricting analyses to those in the control group with no prior suicide attempts, they found lower D-scores (denoting a self-life bias) compared to those with prior attempts (Tello et al., 2020). This underscores potential nuances between various risk profiles, as well as the need to parse these groups in future replication efforts. Nevertheless, the LD-IAT overcomes the limitations of existing methods that rely on introspection and instead evaluates a transdiagnostic dimension – implicit self-identification with death – that can improve our understanding of suicide risk. In this context, the LD-IAT can be conceptualized within the Social Processes domain of the Research Domain Criteria (RDoC), specifically self-knowledge of one's current cognitive or emotional internal states (i.e. the 'Perception and Understanding' construct). For an in-depth discussion of suicide within the RDoC framework and a corresponding meta-analysis, see Glenn, Cha, Kleiman, and Nock (2017b) and Glenn et al. (2018), respectively.

Conventional resting-state approaches offer important insight into functional connectivity parameters in suicide risk (see Schmaal et al., 2020); however, these methods fail to capture transient fluctuations in neural responses to specific stimuli. In contrast, task-based activity can reveal neural correlates that subserve suicide-related cognitive processing. In this context, the LD-IAT offers a novel way to evaluate real-time neural processes associated with suicidal thoughts. A recent study from our laboratory was the first to use a functional magnetic resonance imaging (fMRI) version of the LD-IAT to evaluate differential neural activation patterns between self-life and self-death contrasts (Ballard et al., 2019). In a sample of healthy volunteers (HVs), greater activation for self-death compared to self-life trials was found in regions associated with emotional processing, specifically the insula and right ventrolateral PFC (Ballard et al., 2019). The insula might also be relevant in discriminating between conceptualizations of death *v.* life with the self (Ballard et al., 2019). To this end, a magnetoencephalography (MEG) study found enhanced insular gamma power for self-death compared to self-life trials in HVs (Ballard, Gilbert, Fields, Nugent, & Zarate, 2020). A pilot study with four participants experiencing a suicide crisis revealed dissociable connectivity patterns between those individuals and HVs (Ballard et al., 2020), suggesting that distinct neural activation patterns in the LD-IAT might differentiate participants with differing suicide risk profiles, although this has not been investigated in large samples.

The current study sought to examine clinical, behavioral, and electrophysiological correlates of suicide in individuals with differing levels of suicide risk: (1) those with recent suicide crises within the past two weeks and/or lifetime suicidal ideation with intent; (2) those with a history of attempt, but no STBs in the past year; (3) those with anxiety or mood symptoms but no suicide history; and (4) those without psychiatric or suicide history. All participants completed the LD-IAT during MEG scanning in order to measure group differences in implicit associations between the self and life or death as well as underlying neural responses to each categorization. To delineate markers of neural activity based on suicide risk stratification, group differences in gamma power between self-life and self-death trials were investigated, specifically examining distinct source localization and connectivity patterns (dynamic causal modeling [DCM]) based on trial type. Gamma power was the frequency of interest because it is a putative surrogate marker of excitation-inhibition balance (Buzsáki & Wang, 2012) and has been considered a biomarker for both suicide ideation (e.g. anterior insular gamma power (Gilbert, Ballard, Galiano, Nugent, & Zarate, 2020) and attempt (Arikan, Gunver, Tarhan, & Metin, 2019).

The primary goal of this study was to identify biomarkers associated with differing levels of suicide risk – specifically, the degree to which people self-identify with life- and death-related stimuli depending on risk. Prior studies found that subanesthetic-dose ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist with rapid antidepressant and anti-SI effects (Wilkinson et al., 2018) reduced implicit suicide-related associations in psychiatric samples (Price et al., 2014; Price, Nock, Charney, & Mathew, 2009). Studies have yet to assess biomarkers associated with treatment response in this context. To evaluate the relevance of the identified biomarkers, an additional open-label pilot study was conducted to examine the electrophysiological effects of ketamine on implicit self-associations with life and death in a small subgroup of six participants experiencing a suicide crisis (defined as a suicide attempt or ideation with intent in the prior two

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press

weeks). Clinical (self-report), behavioral (implicit cognitions), and neural (gamma power) correlates of suicide were measured before and after ketamine administration to assess whether ketamine effectively reduces implicit self-identification with death. As a proof-of-concept, the goal of the pilot study was to examine: (1) whether ketamine modulates gamma power in critical regions associated with the categorization of death with self, and (2) associations between post-treatment electrophysiological activity and clinical outcomes. Collectively, findings from this study could help isolate relevant biological targets in suicide prevention as well as inform future directions for interventional suicide studies.

Methods and materials

Participants

Seventy-five adults ($N = 47$ female; $M_{age} = 38.32$, range 19–65) were recruited through the suicide-focused Neurobiology of Suicide Protocol ($N = 65$; NCT02543983) (Ballard et al., 2020) or an imaging research protocol ($N = 10$; NCT00397111). Participants with active or prior STBs were subdivided into one of two experimental groups based on scores on the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011), regardless of psychiatric diagnosis: High Risk (HR), defined as having had a suicide attempt in the past two weeks and/or lifetime suicidal ideation with intent ($n = 15$) or Moderate Risk (MoR), defined as history of suicide attempt but no suicidal behavior or ideation with intent in the past year ($n = 18$). Participants with no lifetime history of STBs were subdivided into one of two control groups: Low Risk (LR), defined as having anxiety or mood symptoms but no suicide history ($n = 19$) or Minimal Risk (MinR), defined as an absence of psychiatric or suicide history ($n = 23$). Six participants from the HR group consented into a pilot study investigating the effects of subanesthetic-dose ketamine (0.5 mg/kg) on correlates of suicide risk and completed clinical measures and the LD-IAT during MEG one to three days before and after ketamine infusion; inclusion criteria are provided in the Supplement.

All participants provided written informed consent, and the study was approved by the Combined Neuroscience Institutional Review Board at the NIH in Bethesda, MD.

Clinical measures

Participants completed the following clinician-rated measures of depression and anxiety severity: the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), and the Hamilton Anxiety Rating Scale (HAM-A; Maier, Buller, Philipp, & Heuser, 1988). Participants also completed the following self-report measures: the Beck Hopelessness Scale (BHS; Beck, Weissman, Lester, & Trexler, 1974), the Barratt Impulsiveness Scale (BIS; Patton, Stanford, & Barratt, 1995), and the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). To assess the severity of suicide ideation, participants completed the 21-item clinician-rated Scale for Suicide Ideation (SSI; Beck, Kovacs, & Weissman, 1979), which measures both past and current ideation. The mean of the first five items of the SSI was used to evaluate current suicide ideation (Ballard et al., 2015).

Life/death implicit association task (LD-IAT)

During MEG scanning, participants completed a modified version of the LD-IAT (Nock et al., 2010), as described previously (Ballard et al., 2019, 2020). Briefly, the LD-IAT is a computer task that assesses the strength of implicit associations between oneself and death (see online Supplemental Fig. S1). Using a button box response, participants categorized target words as belonging to either life or death (e.g. 'live' or 'die') and the self ('me') or other ('not me'). The task was presented in eight blocks: four blocks of single category stimuli (training blocks) and four critical blocks (categorization of life/death with me/not me). Categories were presented on the top left and right sides of the screen (counterbalanced across blocks and participants). Target stimuli were presented centrally for 1.5s with an inter-trial interval of 1.5–2.5s. Response latencies were recorded for each trial, and the relative strength of self-death word pairings (i.e. associations between death-related target words and 'me') was indexed using a *D* score (the difference in mean reaction time (RT) between self-death and self-life trials divided by the standard deviation of all trials). Positive *D* scores denote a stronger self-death implicit association (i.e. faster RT on death/me word pairings), whereas negative *D* scores denote a stronger self-life implicit association (i.e. faster RT on life/me word pairings). As per standard IAT scoring procedures, RTs under 400 ms were eliminated. Participants were excluded from analyses if they had a >30% error rate across all critical blocks or a 40% error rate in one critical block.

MEG acquisition, preprocessing, and source localization

A detailed description of all MEG and DCM experimental procedures is provided in the Supplement.

Data analysis

Ten MinR participants did not complete clinical ratings because they were recruited from a separate research protocol for healthy volunteers. One MinR participant did not complete the BDI-II, BHS, or SHAPS. All remaining clinical measures were completed by the full sample of participants. Furthermore, two MinR, one MoR, and one LR participant were excluded from LD-IAT analyses due to a >30% error rate across critical blocks (final LD-IAT sample sizes: $n = 15$ HR, $n = 17$ MoR, $n = 18$ LR, $n = 21$ MinR). For the open-label ketamine pilot study, one participant did not complete the LD-IAT; thus, final sample sizes were $N = 6$ for clinical measures and $N = 5$ for *D* score and gamma power analyses. Detailed descriptions of each data analysis method are provided in the online Supplement.

Results

Clinical measures

Group differences emerged for depression severity, as indexed by the BDI-II [$F_{(3,60)} = 15.35$, $p < 0.001$, $\eta^2 = 0.43$] (Fig. 1a) and MADRS [$F_{(3,61)} = 28.47$, $p < 0.001$, $\eta^2 = 0.58$] (Fig. 1b). BDI-II and MADRS scores were higher for the HR group *v.* both the MoR ($ps < 0.01$) and MinR ($ps < 0.001$) groups. The HR and LR groups did not differ on BDI-II scores ($p = 0.36$), but the HR group had higher MADRS scores than the LR group ($p = 0.01$). Group differences in hopelessness also emerged, as indexed by the BHS [$F_{(3,60)} = 13.20$, $p < 0.001$, $\eta^2 = 0.40$] (Fig. 1c), with the HR group having higher scores than all other groups ($ps < 0.01$). No group differences emerged for impulsivity, as indexed by the BIS [$F_{(3,60)} = 0.98$, $p = 0.41$, $\eta^2 = 0.05$] (Fig. 1d). Anhedonia and anxiety scores, as indexed by the SHAPS

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press

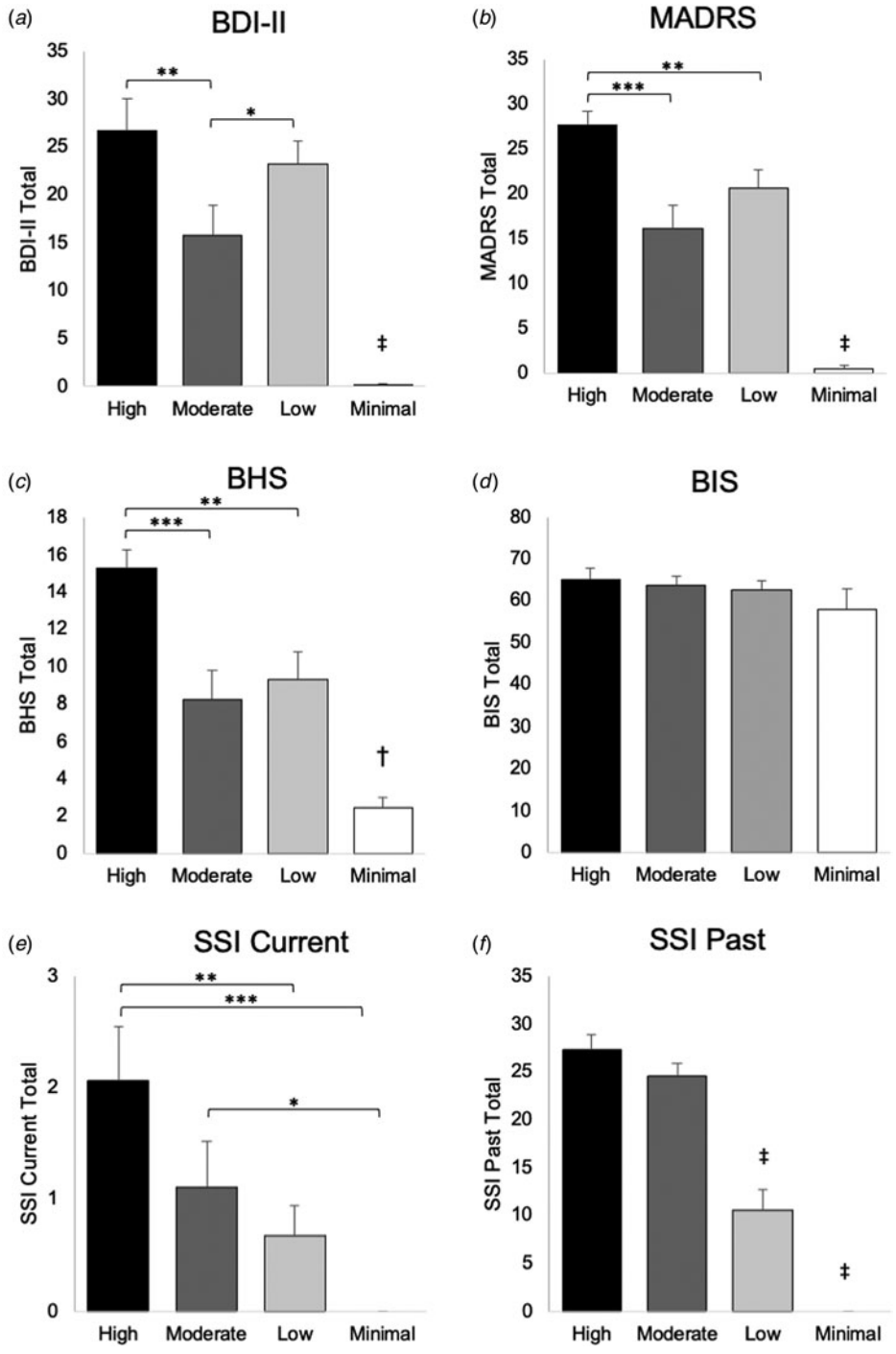

Figure 1. Mean (±S.E.M.) scores on clinical measures across risk groups. (a) Beck Depression Inventory-II (BDI-II); (b) Montgomery-Åsberg Depression Rating Scale (MADRS); (c) Beck Hopelessness Scale (BHS); (d) Barratt Impulsiveness Scale (BIS); (e, f) Scale for Suicide Ideation (SSI). Asterisks denote statistical significance, (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$. Daggers denote significant differences compared to all other groups, (†) $p < 0.01$, (‡) $p < 0.001$.

$[F_{(3,60)} = 7.82,\ p < 0.001,\ \eta^2 = 0.28]$ and HAM-A $[F_{(3,60)} = 22.49,\ p < 0.001,\ \eta^2 = 0.53]$, respectively, did not differ between the HR, MoR, and LR groups ($ps > 0.07$) (data not shown). With the exception of the BIS, scores on each of these measures were significantly lower for the MinR group compared to all other groups ($ps < 0.01$).

As expected, group differences emerged for suicide ideation, as indexed by current $[F_{(3,61)} = 5.24,\ p < 0.01,\ \eta^2 = 0.21]$ (Fig. 1e) and past $[F_{(3,61)} = 39.09,\ p < 0.001,\ \eta^2 = 0.72]$ (Fig. 1f) SSI scores. Both current and past SSI scores were significantly higher for the HR group than for the LR and MinR groups ($ps < 0.01$). For the MoR group, current and past SSI scores were significantly higher compared to the MinR group ($ps < 0.05$), but only past SSI scores were higher compared to the LR group ($p < 0.001$). No differences were observed between the HR and MoR groups on past SSI scores ($p = 0.28$), but current SSI scores were marginally higher for the HR group ($p = 0.06$).

LD-IAT D-score

LD-IAT D-scores within each group were: HR: −0.54 to 0.99, MoR: −1.13 to 0.21, LR: −1.26 to 0.36, MinR: −1.30 to 0.46 (Fig. 2). Group differences emerged $[F_{(3,67)} = 5.02,\ p = 0.003,\ \eta^2 = 0.18]$, such that *D* scores for the HR group were significantly higher than for the MoR ($p = 0.002$), LR ($p < 0.001$), and MinR ($p = 0.006$) groups. No differences emerged between the MoR, LR, or MinR groups ($ps > 0.43$). As a secondary analysis, a

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press

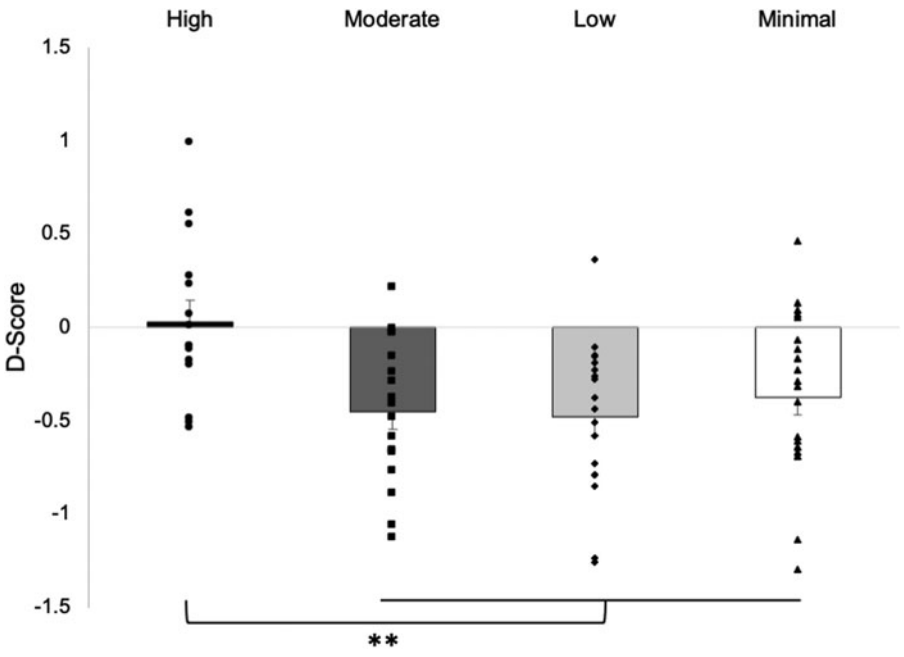

Figure 2. Mean (±SEM) D-scores on the Life-Death Implicit Association Task (LD-IAT) across risk groups. Positive values reflect a self-death bias whereas negative values reflect a self-life bias. Asterisks denote statistical significance, (**) $p < 0.01$.

one-sample t test revealed that D scores for the HR group did not differ from zero [$t(14) = 0.29$, $p = 0.78$], suggesting that this group did not show an implicit bias toward life or death. In contrast, D scores were significantly lower than zero, denoting a self-life bias, for the MoR, LR, and MinR groups ($ps < 0.001$; Cohen's $ds >$ 1.11). Additional secondary analyses are provided in the Supplement.

Group differences in gamma power for self-life and self-death trials

A significant (cluster-level $p < 0.05$) main effect of condition was observed within the gamma frequency in the PCC (see online Supplemental Fig. S2). Across the entire sample, gamma power in the PCC was higher for self-death compared to self-life trials.

The linear mixed effects model also revealed a group-by-condition interaction (uncorrected $p < 0.05$) (Fig. 3), with group differences in gamma power within the PCC, right insular cortex, and orbitofrontal cortex (OBF). Extracting gamma power estimates in these regions showed higher gamma power for self-death compared to self-life trials in the OBF for the HR group (uncorrected $p < 0.01$) and in the insula and PCC for the MinR group (uncorrected $ps < 0.05$). For the MoR group, higher gamma power for self-life compared to self-death trials was found in the PCC ($p < 0.01$). No differences in gamma power between self-life and self-death trials emerged for the LR group

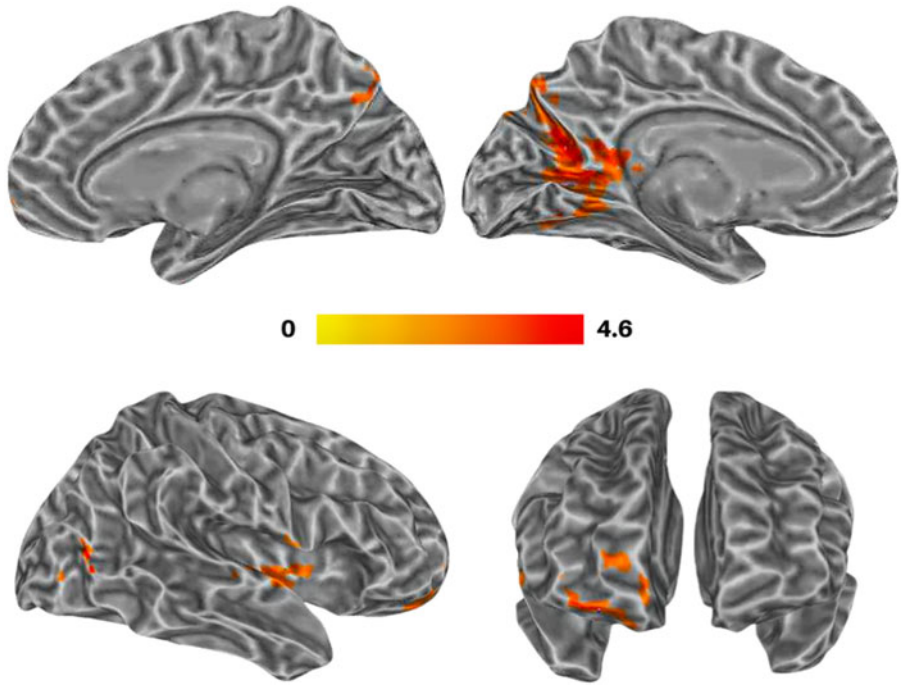

Figure 3. Group-by-condition interaction and gamma power. A significant group-by-condition interaction was identified in the gamma frequency in the PCC as well as the right insula and orbitofrontal cortex (OBF). Extracting gamma power estimates in these regions showed enhanced gamma power for self-death compared to self-life word pairings in the insula and PCC for the minimal risk (MinR) group and the OBF for the high risk (HR) group. The moderate risk (MoR) group had enhanced gamma power for self-life compared to self-death word pairings in the PCC.

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press

(*p*s > 0.05). Additional secondary analyses are provided in the Supplement.

Dynamic causal modeling (DCM) parametric empirical Bayesian (PEB) analyses

The canonical microcircuit (CMC) model and model architecture are described in the Supplement (see online Supplemental Fig. S3). Two plausible models were constructed to evaluate message-passing between the early visual cortex (EV), PCC, insula, and OBF using DCM. Bayesian model selection yielded the strongest evidence for model 2, which included fully reciprocated forward and backward connections between the EV and PCC, PCC and OBF, OBF and insula, insula and EV, and lateral connections between the PCC and insula. Model fits were computed for model 2 by correlating the estimated modeled event-related potential (ERP) responses to the data. Model fits were compared between the HR group and the sample average to ensure the HR group did not have a biased fit. Model 2 consistently recapitulated ERP responses in both groups: HR: $M = 0.693$, S.E. = 0.102; sample average: $M = 0.676$, S.E. = 0.028.

PEB analysis revealed parameters mediating differences between the HR group and the full sample, as well modulation by trial type (self-life *v.* self-death) (see online Supplemental Table S1 for a full list of parameters). Significant parameters (i.e. Posterior probability > 0.95) included forward connections from the EV to the PCC across trial types (Fig. 4a, b). Compared with the sample average, the HR group showed reduced connectivity for modulations carried by superficial pyramidal cells (SPs) to spiny stellate cells (SSs) and increased connectivity for those carried by SPs to deep pyramidal cells (DPs). Modulations based on trial type were also identified on the forward connections from the EV to the insula (Fig. 4c, d) and backward connections from the OBF to the PCC (Fig. 4e, f). In both the HR group and the sample average, increased connectivity was found for self-death compared with self-life trials for both SP to SS and SP to DP connections.

Association between LD-IAT D-scores and clinical measures/ gamma power

Correlation analyses between D-scores and clinical measures (see online Supplemental Table S2) and gamma power (see online Supplemental Table S3) are provided in the Supplement.

Effects of ketamine on suicide risk: preliminary evidence from an open-label study

A main effect of session was trending ($p = 0.08$), such that insular gamma power across trial types was higher post-ketamine

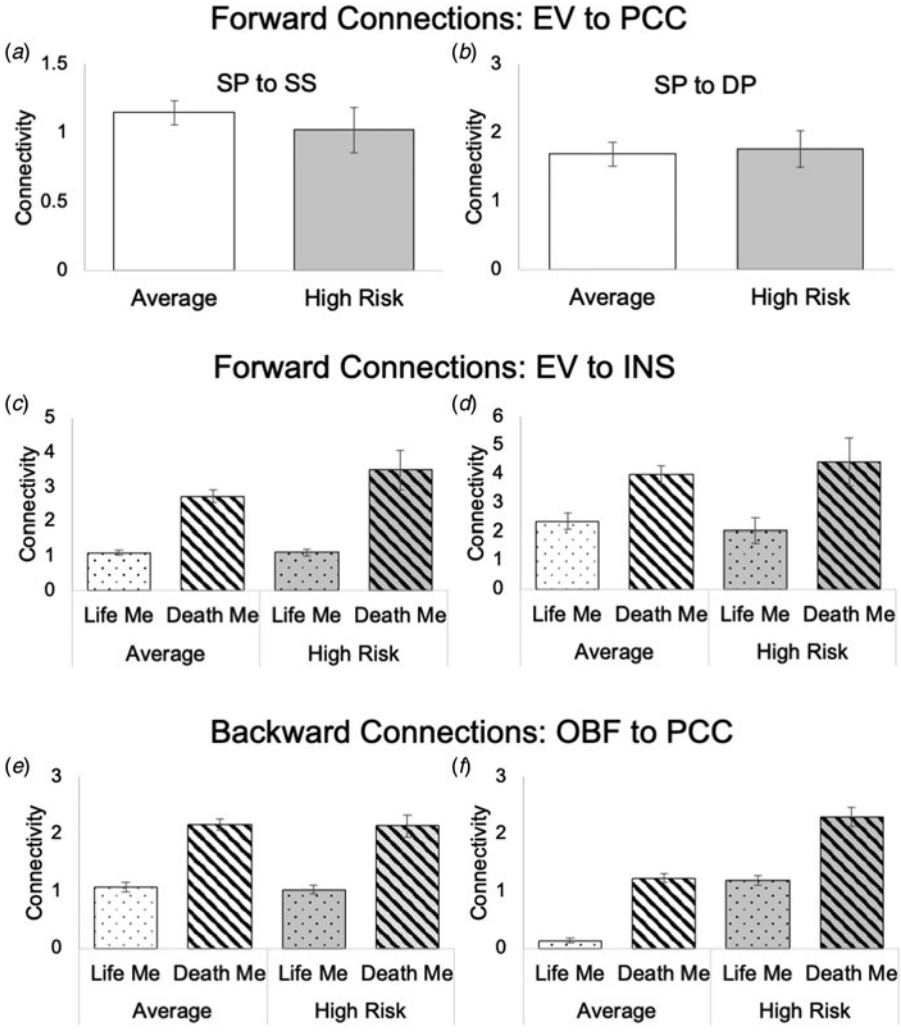

Figure 4. Parametric Empirical Bayesian (PEB) analysis. (a, b) Across trial types, modulations were identified on the forward connections from early visual cortex (EV) to posterior cingulate cortex (PCC). Compared with the sample average, the high risk (HR) group showed reduced connectivity for modulations carried by superficial pyramidal cells (SPs) to spiny stellates (SSs) and increased connectivity for those carried by SPs to deep pyramidal cells (DPs). Modulations based on trial type were also identified on the (c, d) forward connections from the EV to the insula (INS) and (e, f) backward connections from the orbitofrontal cortex (OBF) to the PCC. In both the sample average and HR group, increased connectivity was found for self-death compared with self-life trials for both SP to SS and SP to DP connections.

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press

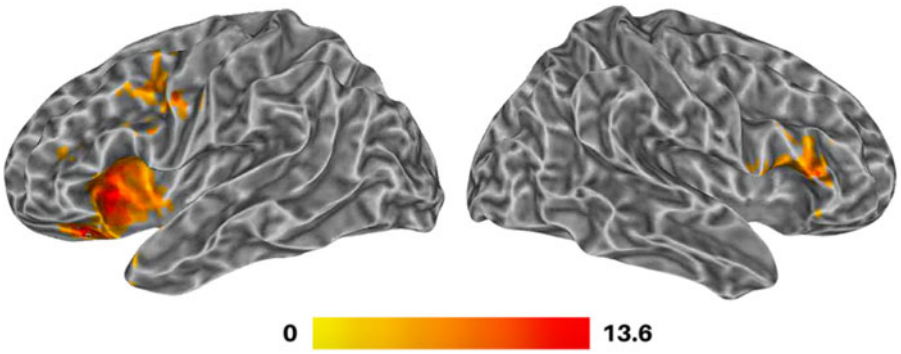

Figure 5. Group-by-condition interaction and gamma power after ketamine administration. A significant group-by-condition interaction was identified in the insula in the gamma frequency. Extracting gamma power estimates in this region showed enhanced gamma power for self-death word pairings after ketamine treatment. No effects of ketamine on gamma power for self-life word pairings emerged.

compared to baseline. As shown in Fig. 5, a session-by-condition interaction emerged (uncorrected $p < 0.05$). At baseline, gamma power estimates in the left insula were significantly lower for self-death compared to self-life trials ($p < 0.05$). Indeed, 100% of participants (5/5) had higher self-life compared to self-death gamma power in this region (mean difference: 1.02, S.E.M. ± 0.33). Relative to baseline, post-ketamine gamma power for self-death trials was higher in the left insula ($p < 0.001$). After ketamine administration, 80% (4/5) of participants had higher self-death compared to self-life gamma power in this region (mean difference: 1.02, SEM ± 0.50), resembling the effects observed in the insula for the MinR group. Ketamine had no effect on gamma power for self-life trials ($p = 0.83$).

Our secondary analysis using Bayes Factor (BF) statistics corroborated these results. For the main effect of session, the BFs supported inconclusive results of ketamine treatment across trial types (i.e. BF = 1.58). However, there was an extremely large BF supporting the alternative hypothesis of differences in gamma power before and after ketamine treatment for self-death trials (i.e. BF = 31.40). In other words, the alternative hypothesis was 31 times more probable than the null hypothesis for self-death trials. In contrast, the BFs yielded inconclusive results for self-life trials (i.e. BF = 0.41), suggesting equal support for the null and alternative hypotheses. These findings further support a specific effect of ketamine treatment on insular gamma power for self-associations with death rather than life. All additional effects from the pilot study are described in the Supplement (see online Supplemental Tables S4 and S5).

Discussion

The current study offers novel insights into clinical, behavioral, and electrophysiological correlates of differing suicide risk profiles, advancing efforts to identify biomarkers of suicide. Clinically, those at highest risk of suicide ideation (the HR group) were differentiated from all other levels of risk, showing a greater severity of self-reported hopelessness, clinician-rated depression, and current suicide ideation. Behaviorally, these individuals showed a significantly greater self-death bias on the LD-IAT compared to all other groups despite similar self-reported depression, anxiety, anhedonia, and impulsivity scores relative to the LR and MoR groups. D-scores did not differ between the MoR, LR, and MinR groups, even though the MinR group had significantly lower scores on all clinical measures. In conjunction with group differences in clinical profiles, these behavioral findings suggest that the LD-IAT captures suicide risk independently of the subjective or clinical characterizations of mood disturbances conventionally used to evaluate risk (Nock et al., 2022). Electrophysiologically, risk groups were differentiated based on region-specific contrasts in gamma power for self-life and self-death trials, particularly in the PCC, OBF, and insular cortex. Connectivity estimates also differentiated the HR group from all groups, particularly with respect to forward connections from the EV to the PCC. These findings contribute to a growing body of research that aims to identify behavioral and biological markers of suicide risk that will help refine suicide prevention strategies.

Echoing the original findings by Nock and colleagues (Nock et al., 2010), the LD-IAT differentiated those with a recent suicide attempt or ideation with intent (the HR group) from those with a distal suicide attempt and no recent STBs (the MoR group). In contrast to existing literature, the latter group did not differ from those with no lifetime STBs but a psychiatric history (the LR group). This suggests that implicit self-identification with death uniquely characterizes those at more imminent suicide risk relative to those with less proximal attempts or those with a history of psychiatric distress but no STBs.

Consistent with previous findings (Ballard et al., 2020), region-specific differences in gamma activity emerged based on suicide risk. As hypothesized, higher gamma power was observed in the left PCC for self-death compared to self-life trials across risk groups, complementing studies showing enhanced left PCC activity in response to death-related visual stimuli (Kim et al., 2017), as well as negative imagery generation (Motoyama & Hishitani, 2016). In the HR group, OBF gamma power was greater for self-death compared to self-life trials, implicating the recruitment of higher-order cognitive processes for death-oriented word pairings. The OBF biases attention to emotionally salient events (Hartikainen, Ogawa, & Knight, 2012), and suicide attempters (particularly those with a recent attempt) showed attentional biases toward suicide-related stimuli in a Stroop task (Cha, Najmi, Park, Finn, & Nock, 2010). This is particularly relevant given that amplified gamma power is typically found in response to attended *v.* unattended visual stimuli (Jensen, Kaiser, & Lachaux, 2007). Finally, greater gamma power in the right insular cortex was found for self-death compared to self-life contrasts in the lowest risk group, corroborating recent findings from an analogous HV group (Ballard et al., 2020). This is also consistent with recent fMRI findings showing greater anterior insular activation for self-death *v.* self-life pairings in HVs (Ballard et al., 2019). Importantly, the insula has previously been implicated in both SI and attempts, as well as non-suicidal self-injury (for reviews, see Domínguez-Baleón, Gutiérrez-Mondragón, Campos-González, & Rentería, 2018; Lengvenyte, Conejero, Courtet, & Olié, 2021). These effects were only observed in our HV sample (i.e. MinR), suggesting that implicit self-associations with death uniquely

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press

activate insular gamma oscillatory responses in those with no current or prior STBs. In HVs, insular activation has been linked to the anticipation and avoidance of aversive visual stimuli (Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Perlis et al., 2008; Sarinopoulos et al., 2010; Simmons, Strigo, Matthews, Paulus, & Stein, 2006), particularly the right insular cortex (Simmons, Matthews, Stein, & Paulus, 2004). Indeed, HVs showed increased activity in regions of the salience network in response to statements that associate the self with mortality (Quirin et al., 2012). Relatedly, insular activity in response to death-related judgments was positively associated with dispositional death anxiety (Shi & Han, 2013), which might characterize the MinR sample more than the others. In contrast, the HR, MoR, and LR groups showed no self-life *v.* self-death contrast in insular gamma power. It remains unknown whether this reflects relative differences in death anxiety and/or aversion processing in these groups. However, suicide attempters show increased tolerance for aversive sensations and diminished aversive threat processing (DeVille, Kuplicki, Stewart, Paulus, & Khalsa, 2020), suggesting this explanation could be plausible. This does not contradict the prior OBF findings but, instead, implicates blunted insular-mediated aversion responses to self-death word pairings, despite enhanced OBF-mediated attentional biases to these word pairings. Very few studies have directly examined the insula's role in STBs, necessitating further research into the reason for the differentiation observed here.

DCM analyses revealed dissociable connectivity patterns between the HR group and the full sample. Across trial types, the HR group showed reduced forward connectivity from EVs to the PCC for modulations carried by SPs to SSs. This resembles findings from Ballard et al. (2020) showing reduced forward connectivity from the EV to the anterior insula (SPs to SSs) among those experiencing a suicide crisis compared to HVs. These findings suggest that heightened suicide risk is linked to aberrant connectivity patterns from thalamic inputs to regions associated with the processing of self-relevant, emotionally salient information. Furthermore, increased connectivity was found across our sample for self-death compared with self-life trials in forward connections from the EV to the insula, suggesting a role for forward connections to the salience network in self-referential processing with death. Similarly, prior studies found increased forward connectivity from the EV to the amygdala for self-death compared with self-life trials across participants (Ballard et al., 2020). Interestingly, increased connectivity was also found for self-death compared with self-life trials in the backward connections from the OBF to the PCC, implicating CEN-DMN connectivity in self-death categorizations. Dissociable CEN-DMN gamma connectivity patterns were previously found between suicide ideators and attempters independent of depression severity (Dai et al., 2022), suggesting this inter-network connectivity might be a critical biomarker underpinning the progression from suicide ideation to attempt. Future studies could use a longitudinal design to investigate whether disruptions to these interconnections predict either the development of STBs or deaths by suicide. Intervention studies might also examine the effects of drugs, like ketamine, that modulate these parameters within the gamma frequency (see Nugent et al., 2019), which could help identify the relevance of these biomarkers in the context of suicide risk.

Notably, our preliminary findings suggest that ketamine could reconcile neural differences between those with the highest and lowest risk for suicide by modulating insular gamma activity. Post-ketamine, insular gamma power for self-death (but not self-life) trials was enhanced in the HR group, mirroring the effects observed in the insula of the MinR group. Indeed, baseline (pre-treatment) gamma power was lower for self-death compared to self-life trials in 100% of HR participants, but the inverse was found post-ketamine administration (80% of participants showed greater self-death insular gamma power). This might represent a normalization of insular gamma responses to self-death associations after ketamine treatment. Of note, ketamine had no behavioral effects despite improving self-reported hopelessness and depression rating scale scores. Although the sample size for the pilot study was very small and uncontrolled, these findings point to promising new directions for suicide research, with insular gamma power as a potentially critical biomarker of suicide-related cognitive processes.

The current findings should be considered in the context of several limitations. First, the cross-sectional design limits the scope of broader interpretations, namely whether implicit associations about death represent predispositions (i.e. antecedents to STBs) or whether they manifest in response to STBs. Second, the study did not differentiate attempters from non-attempters based on severity or frequency of suicide ideation. Indeed, the HR and MoR groups did not significantly differ on current or past SSI scores (although current SSI was marginally higher in the HR group). Third, research on gamma oscillations in suicide, particularly in the context of implicit cognitions, is in its infancy. Accordingly, we conducted a whole-brain analysis on the MEG data and our interpretations of the results are largely speculative. Fourth, results of the open-label ketamine pilot study, while promising, should be interpreted with caution; more work is needed to replicate these effects in larger samples using appropriate suicide control and placebo groups. While participants were selected on the basis of suicide risk and not psychiatric diagnosis, there were key exclusion criteria (active substance dependence and psychosis) that are also important risk factors for suicide. Therefore, future studies should examine this biomarker across the full range of psychiatric symptomatology associated with suicide risk. Finally, some participants in the HR group had made a recent suicide attempt (within the prior two-week period). Although participants were excluded if they sustained injury that precluded participation in study procedures, it is possible that their recovery from injury affected study outcomes. Future studies might consider including a control group of individuals hospitalized for non-suicidal accident-related injuries (e.g. Orbach et al., 1996) to account for the residual effects of injury on these primary outcomes.

Taken together, the current study found evidence of subjective, behavioral, and electrophysiological signatures that differentiate various suicide risk profiles. Continued efforts to uncover biomarkers of suicide will promote the development of optimal strategies, including biological interventions, to mitigate suicide risk.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003331

Acknowledgements. The authors thank the 7SE research unit and staff for their support. Ioline Henter provided invaluable editorial assistance.

Funding statement. Funding for this work was provided by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIAMH002857; NCT02543983, NCT00397111).

Competing interests. Dr Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on

a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (*R*,*S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Arikan, M. K., Gunver, M. G., Tarhan, N., & Metin, B. (2019). High-Gamma: A biological marker for suicide attempt in patients with depression. *Journal of Affective Disorders*, *254*, 1–6. https://doi.org/10.1016/j.jad.2019.05.007

Ballard, E. D., Gilbert, J. R., Fields, J. S., Nugent, A. C., & Zarate Jr, C. A. (2020). Network changes in insula and amygdala connectivity accompany implicit suicidal associations. *Frontiers in Psychiatry*, *11*, 1–8. https://doi.org/10.3389/fpsyt.2020.577628

Ballard, E. D., Luckenbaugh, D. A., Richards, E. M., Walls, T. L., Brutsché, N. E., Ameli, R., … Zarate Jr, C. A. (2015). Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. *Journal of Psychiatric Research*, *68*, 68–73. https://doi.org/10.1016/j.jpsychires.2015.06.003

Ballard, E. D., Reed, J. L., Szczepanik, J., Evans, J. W., Yarrington, J. S., Dickstein, D. P., … Zarate Jr, C. A. (2019). Functional imaging of the implicit association of the self with life and death. *Suicide and Life-Threatening Behavior*, *49*(6), 1600–1608. https://doi.org/10.1111/sltb.12543

Barnes, S. M., Bahraini, N. H., Forster, J. E., Stearns-Yoder, K. A., Hostetter, T. A., Smith, G., … Nock, M. K. (2017). Moving beyond self-report: Implicit associations about death/life prospectively predict suicidal behavior among veterans. *Suicide and Life-Threatening Behavior*, *47*(1), 67–77. https://doi.org/10.1111/sltb.12265

Beck, A. T., Kovacs, M., & Weissman, A. (1979). Assessment of suicidal intention: The scale for suicide ideation. *Journal of Consulting and Clinical Psychology*, *47*(2), 343–352. https://doi.org/10.1037/0022-006X.47.2.343

Beck, A. T., Steer, R. A., & Brown, G. (1996). *Beck depression inventory–II*. San Antonio, TX: The Psychological Corporation. https://doi.org/10.1037/t00742-000

Beck, A. T., Weissman, A., Lester, D., & Trexler, L. (1974). The measurement of pessimism: The hopelessness scale. *Journal of Consulting and Clinical Psychology*, *42*(6), 861–865. https://doi.org/10.1037/h0037562

Bostwick, J. M., Pabbati, C., Geske, J. R., & McKean, A. J. (2016). Suicide attempt as a risk factor for completed suicide: Even more lethal than we knew. *American Journal of Psychiatry*, *173*(11), 1094–1100. https://doi.org/10.1176/appi.ajp.2016.15070854

Buzsáki, G., & Wang, X. J. (2012). Mechanisms of gamma oscillations. *Annual Review of Neuroscience*, *35*, 203–225. https://doi.org/10.1146/annurev-neuro-062111-150444

Cha, C. B., Najmi, S., Park, J. M., Finn, C. T., & Nock, M. K. (2010). Attentional bias toward suicide-related stimuli predicts suicidal behavior. *Journal of Abnormal Psychology*, *119*(3), 616–622. https://doi.org/10.1037/a0019710

Dai, Z., Shao, J., Zhou, H., Chen, Z., Zhang, S., Wang, H., … Lu, Q. (2022). Disrupted fronto-parietal network and default-mode network gamma interactions distinguishing suicidal ideation and suicide attempt in depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *113*, 1–9. https://doi.org/10.1016/j.pnpbp.2021.110475

DeVille, D. C., Kuplicki, R., Stewart, J. L., Paulus, M. P., & Khalsa, S. S. (2020). Diminished responses to bodily threat and blunted interoception in suicide attempters. *Elife*, *9*, e51593. https://doi.org/10.7554/eLife.51593

Domínguez-Baleón, C., Gutiérrez-Mondragón, L. F., Campos-González, A. I., & Rentería, M. E. (2018). Neuroimaging studies of suicidal behavior and non-suicidal self-injury in psychiatric patients: A systematic review. *Frontiers in Psychiatry*, *9*, 500. https://doi.org/10.3389/fpsyt.2018.00500

Gilbert, J. R., Ballard, E. D., Galiano, C. S., Nugent, A. C., & Zarate Jr, C. A. (2020). Magnetoencephalographic correlates of suicidal ideation in major depression. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(3), 354–363. https://doi.org/10.1016/j.bpsc.2019.11.011

Glenn, C. R., Cha, C. B., Kleiman, E. M., & Nock, M. K. (2017b). Understanding suicide risk within the Research Domain Criteria (RDoC) framework: Insights, challenges, and future research considerations. *Clinical Psychological Science*, *5*(3), 568–592. https://doi.org/10.1177/2167702616686854

Glenn, C. R., Kleiman, E. M., Cha, C. B., Deming, C. A., Franklin, J. C., & Nock, M. K. (2018). Understanding suicide risk within the Research Domain Criteria (RDoC) framework: A meta-analytic review. *Depression and Anxiety*, *35*(1), 65–88. https://doi.org/10.1002/da.22686

Glenn, C. R., Kleiman, E. M., Coppersmith, D. D., Santee, A. C., Esposito, E. C., Cha, C. B., … Auerbach, R. P. (2017a). Implicit identification with death predicts change in suicide ideation during psychiatric treatment in adolescents. *Journal of Child Psychology and Psychiatry*, *58*(12), 1319–1329. https://doi.org/10.1111/jcpp.12769

Hartikainen, K. M., Ogawa, K. H., & Knight, R. T. (2012). Orbitofrontal cortex biases attention to emotional events. *Journal of Clinical and Experimental Neuropsychology*, *34*(6), 588–597. https://doi.org/10.1080/13803395.2012.666231

Hermans, E. J., Henckens, M. J., Joëls, M., & Fernández, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends in Neurosciences*, *37*(6), 304–314. https://doi.org/10.1016/j.tins.2014.03.006

Hermans, E. J., Van Marle, H. J., Ossewaarde, L., Henckens, M. J., Qin, S., Van Kesteren, M. T., … Fernández, G. (2011). Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. *Science (New York, N.Y.)*, *334*(6059), 1151–1153. https://doi.org/10.1126/science.1209603

Horwitz, A. G., Czyz, E. K., & King, C. A. (2015). Predicting future suicide attempts among adolescent and emerging adult psychiatric emergency patients. *Journal of Clinical Child & Adolescent Psychology*, *44*(5), 751–761. https://doi.org/10.1080/15374416.2014.910789

Jensen, O., Kaiser, J., & Lachaux, J. P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences*, *30*(7), 317–324. https://doi.org/10.1016/j.tins.2007.05.001

Kim, Y. J., Park, H. J., Jahng, G. H., Lee, S. M., Kang, W. S., Kim, S. K., … Park, J. K. (2017). A pilot study of differential brain activation to suicidal means and DNA methylation of CACNA1C gene in suicidal attempt patients. *Psychiatry Research*, *255*, 42–48. https://doi.org/10.1016/j.psychres.2017.03.058

Lengvenyte, A., Conejero, I., Courtet, P., & Olié, E. (2021). Biological bases of suicidal behaviours: A narrative review. *European Journal of Neuroscience*, *53*(1), 330–351. https://doi.org/10.1111/ejn.14635

Maier, W., Buller, R., Philipp, M., & Heuser, I. (1988). The Hamilton Anxiety Scale: Reliability, validity and sensitivity to change in anxiety and depressive disorders. *Journal of Affective Disorders*, *14*(1), 61–68. https://doi.org/10.1016/0165-0327(88)90072-9

Montgomery, S. A., & Åsberg, M. A. R. I. E. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382–389. https://doi.org/10.1192/bjp.134.4.382

Moreno, M., Guitérrez-Rojas, L., & Porras-Segovia, A. (2022). Implicit cognition tests for the assessment of suicide risk: A systematic review. *Current Psychiatry Reports*, *24*, 141–159. https://doi.org/10.1007/s11920-022-01316-5

Motoyama, H., & Hishitani, S. (2016). The brain mechanism that reduces the vividness of negative imagery. *Consciousness and Cognition*, *39*, 59–69. https://doi.org/10.1016/j.concog.2015.11.006

Nitschke, J. B., Sarinopoulos, I., Mackiewicz, K. L., Schaefer, H. S., & Davidson, R. J. (2006). Functional neuroanatomy of aversion and its anticipation. *Neuroimage*, *29*(1), 106–116. https://doi.org/10.1016/j.neuroimage.2005.06.068

Nock, M. K., Millner, A. J., Ross, E. L., Kennedy, C. J., Al-Suwaidi, M., Barak-Corren, Y., … Kessler, R. C. (2022). Prediction of suicide attempts using clinician assessment, patient self-report, and electronic health records. *JAMA Network Open*, *5*(1), e2144373–e2144373. https://doi.org/10.1001/jamanetworkopen.2021.44373

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press

Nock, M. K., Park, J. M., Finn, C. T., Deliberto, T. L., Dour, H. J., & Banaji, M. R. (2010). Measuring the suicidal mind: Implicit cognition predicts suicidal behavior. *Psychological Science*, *21*(4), 511–517. https://doi.org/10.1177/0956797610364762

Northoff, G., & Bermpohl, F. (2004). Cortical midline structures and the self. *Trends in Cognitive Sciences*, *8*(3), 102–107. https://doi.org/10.1016/j.tics.2004.01.004

Nugent, A. C., Ballard, E. D., Gould, T. D., Park, L. T., Moaddel, R., Brutsche, N. E., & Zarate Jr, C. A. (2019). Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects. *Molecular Psychiatry*, *24*(7), 1040–1052. https://doi.org/10.1038/s41380-018-0028-2

Orbach, I., Stein, D., Palgi, Y., Asherov, J., Har-Even, D., & Elizur, A. (1996). Perception of physical pain in accident and suicide attempt patients: Self-preservation vs self-destruction. *Journal of Psychiatric Research*, *30*(4), 307–320. https://doi.org/10.1016/0022-3956(96)00008-8

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768–774. https://doi.org/10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1

Perlis, R. H., Holt, D. J., Smoller, J. W., Blood, A. J., Lee, S., Kim, B. W., … Breiter, H. C. (2008). Association of a polymorphism near CREB1 with differential aversion processing in the insula of healthy participants. *Archives of General Psychiatry*, *65*(8), 882–892. https://doi.org/10.1001/archgenpsychiatry.2008.3

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., … Mann, J. J. (2011). The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American Journal of Psychiatry*, *168*(12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704

Price, R. B., Iosifescu, D. V., Murrough, J. W., Chang, L. C., Al Jurdi, R. K., Iqbal, S. Z., … Mathew, S. J. (2014). Effects of ketamine on explicit and implicit suicidal cognition: A randomized controlled trial in treatment-resistant depression. *Depression and Anxiety*, *31*(4), 335–343. https://doi.org/10.1002/da.22253

Price, R. B., Nock, M. K., Charney, D. S., & Mathew, S. J. (2009). Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biological Psychiatry*, *66*(5), 522–526. https://doi.org/10.1016/j.biopsych.2009.04.029

Qin, S., Hermans, E. J., Van Marle, H. J., Luo, J., & Fernández, G. (2009). Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex. *Biological Psychiatry*, *66*(1), 25–32. https://doi.org/10.1016/j.biopsych.2009.03.006

Quirin, M., Loktyushin, A., Arndt, J., Küstermann, E., Lo, Y. Y., Kuhl, J., & Eggert, L. (2012). Existential neuroscience: A functional magnetic resonance imaging investigation of neural responses to reminders of one's mortality. *Social Cognitive and Affective Neuroscience*, *7*(2), 193–198. https://doi.org/10.1093/scan/nsq106

Randall, J. R., Rowe, B. H., Dong, K. A., Nock, M. K., & Colman, I. (2013). Assessment of self-harm risk using implicit thoughts. *Psychological Assessment*, *25*(3), 714–721. https://doi.org/10.1037/a0032391

Sarinopoulos, I., Grupe, D. W., Mackiewicz, K. L., Herrington, J. D., Lor, M., Steege, E. E., & Nitschke, J. B. (2010). Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. *Cerebral Cortex*, *20*(4), 929–940. https://doi.org/10.1093/cercor/bhp155

Schmaal, L., van Harmelen, A. L., Chatzi, V., Lippard, E. T., Toenders, Y. J., Averill, L. A., … Blumberg, H. P. (2020). Imaging suicidal thoughts and behaviors: A comprehensive review of 2 decades of neuroimaging studies. *Molecular Psychiatry*, *25*(2), 408–427. https://doi.org/10.1038/s41380-019-0587-x

Shi, Z., & Han, S. (2013). Transient and sustained neural responses to death-related linguistic cues. *Social Cognitive and Affective Neuroscience*, *8*(5), 573–578. https://doi.org/10.1093/scan/nss034

Simmons, A., Matthews, S. C., Stein, M. B., & Paulus, M. P. (2004). Anticipation of emotionally aversive visual stimuli activates right insula. *Neuroreport*, *15*(14), 2261–2265. https://doi.org/10.1097/00001756-200410050-00024

Simmons, A., Strigo, I., Matthews, S. C., Paulus, M. P., & Stein, M. B. (2006). Anticipation of aversive visual stimuli is associated with increased insula activation in anxiety-prone subjects. *Biological Psychiatry*, *60*(4), 402–409. https://doi.org/10.1016/j.biopsych.2006.04.038

Smith, E. G., Kim, H. M., Ganoczy, D., Stano, C., Pfeiffer, P. N., & Valenstein, M. (2013). Suicide risk assessment received prior to suicide death by Veterans Health Administration patients with a history of depression. *The Journal of Clinical Psychiatry*, *74*(3), 226–232. https://doi.org/10.4088/JCP.12m07853

Snaith, R. P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. *The British Journal of Psychiatry*, *167*(1), 99–103. https://doi.org/10.1192/bjp.167.1.99

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569–12574. https://doi.org/10.1073/pnas.0800005105

Stone, D. M., Jones, C. M., & Mack, K. A. (2021). Changes in suicide rates – United States, 2018–2019. *Morbidity and Mortality Weekly Report*, *70*(8), 261–268. https://doi.org/10.15585/mmwr.mm7008a1

Tello, N., Harika-Germaneau, G., Serra, W., Jaafari, N., & Chatard, A. (2020). Forecasting a fatal decision: Direct replication of the predictive validity of the suicide–implicit association test. *Psychological Science*, *31*(1), 65–74. https://doi.org/10.1177/0956797619893062

Wilkinson, S. T., Ballard, E. D., Bloch, M. H., Mathew, S. J., Murrough, J. W., Feder, A., … Sanacora, G. (2018). The effect of a single dose of intravenous ketamine on suicidal ideation: A systematic review and individual participant data meta-analysis. *American Journal of Psychiatry*, *175*(2), 150–158. https://doi.org/10.1176/appi.ajp.2017.17040472

https://doi.org/10.1017/S0033291723003331 Published online by Cambridge University Press