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Functional Imaging of the Implicit Association of the Self with Life and Death

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Abstract

Objective: A critical need exists to identify objective markers of suicidal ideation. One potential suicide risk marker is the Suicide Implicit Association Task (S-IAT), a behavioral task that uses differential reaction times to compare the implicit association between the self and death to the implicit association between the self and life. Individuals with a stronger association between the self and death on the S-IAT are more likely to attempt suicide in the future. To better understand the neural underpinnings of the implicit association between self and either life or death, an fMRI version of the S-IAT was adapted and piloted in healthy volunteers.

Method: An fMRI version of the S-IAT was administered to 28 healthy volunteers (ages 18–65, 14F/14M).

Results: Behavioral results were comparable to those seen in non-scanner versions of the task. The task was associated with patterns of neural activation in areas relevant to emotional processing, specifically the insula and right ventrolateral prefrontal cortex.

Conclusions: Performance on the S-IAT fMRI task may reflect scores obtained outside of the scanner. In future evaluations, this task could help assess whether individuals at increased risk of suicide display a different pattern of neural activation in response to self/death and self/life stimuli.

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Conflict of Interest
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 dehydro 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.

Keywords

Suicide; Neuroimaging; implicit association; depression

Introduction

Suicide remains a leading cause of death worldwide and is difficult to predict. Suicide risk assessment often relies on self-report, which is subject to many biases, including the individual's potential desire to minimize suicide risk in order to avoid stigma, hospitalization, or restrictions, as well as rapid fluctuations in suicidal thoughts themselves (Kleiman *et al.*, 2017). As a result, a tremendous need remains to identify potential suicide risk factors that do not depend on self-report. The Suicide Implicit Association Task (S-IAT) is one potential tool for assessing suicide risk that relies on response time to specific stimuli rather than direct assessment of suicidal thoughts and behaviors. In the task, the implicit association between an individual's self and death (self-death condition) is assessed and compared with the implicit association between that individual's self and life (self-life condition). The S-IAT has been associated with past suicide attempts as well as risk for suicide re-attempt above and beyond other suicide risk factors, including suicidal thoughts and clinician assessment (Nock *et al.*, 2010). Since the initial publication of the S-IAT in 2010, these results have been replicated in large-scale studies (Glenn *et al.*, 2017), and the task has been used to predict later suicide attempts and self-harm in emergency department (Randall *et al.*, 2013) and veteran samples (Barnes *et al.*, 2017). The S-IAT has also been shown to predict suicidal ideation over the course of psychiatric hospitalization (Ellis *et al.*, 2016).

Adapting the S-IAT for use with functional magnetic resonance imaging (fMRI) represents an opportunity to understand the underlying neurobiological mechanisms of the self-life/self-death relationship. The neuroimaging literature on suicide risk is relatively limited (Cox Lippard *et al.*, 2014); the tasks often used in conjunction with fMRI are similar to those used in the psychiatric literature for mood disorders and include measures of response inhibition (Pan *et al.*, 2011), decision making (Jollant *et al.*, 2010), and response to emotional faces (Jollant *et al.*, 2008; Pan *et al.*, 2013). It may be beneficial to more specifically probe cognitive biases underlying the suicidal state, as recent evaluations have suggested that suicidal indivduals have altered neural responses to life and death words (Just *et al.*, 2017). It is possible that illuminating the neural correlates of how individuals consider the self in relation to life or death can be used to better understand suicidal cognition.

The present study sought to evaluate whether an fMRI S-IAT task could be a useful paradigm for understanding neural correlates of implicit suicide risk. In this context, the S-IAT fMRI task was administered to a sample of healthy volunteers undergoing fMRI. The utility of the task was evaluated in two areas: 1) whether the behavioral results from the fMRI version of the task mirrored previous results of the task conducted outside of the scanner; and 2) whether the task could elucidate different patterns of activation in the self-death versus self-life conditions. We sought to pilot the task in a healthy volunteer sample in the hopes that the task could eventually be used in future clinical samples of individuals reporting suicidal thoughts or behavior to improve our understanding of the cognitive processes underlying suicide risk.

Methods and Materials

Participants

Healthy volunteers (ages 18–65 (14F/14M)) were recruited via community and internet advertising. All participants provided written informed consent (NCT00397111) and the study protocol was approved by the NIH combined Neuroscience Institutional Review Board. Exclusion criteria included any psychiatric diagnosis, including lifetime substance dependence, as assessed by the Structured Clinical Interview for DSM-IV–Non-Patient version (First *et al.*, 2002), as well as any first-degree relatives with a psychiatric diagnosis. Participants were physically healthy as determined by medical and psychiatric history, laboratory testing, drug screening, and physical examination.

Behavioral Task

The IAT is a computerized task that measures reaction time to a series of stimuli in an effort to understand implicit associations (Greenwald et al., 2003). The S-IAT fMRI task used in this study was adapted from the behavioral task developed by Nock and colleagues, which specified target concepts relating to life or death and associated attributes relating to the self or other (Nock *et al.*, 2010). Briefly, words defining the categories of interest (categorization words) are presented on the left and right sides at the top of the screen, and target words to be classified appear in the center of the screen. The participant is instructed to press a left or right button to classify the target word according to the categorization words. Two preliminary training blocks precede two "critical blocks" during which participants first categorize words related to either life or death (target discrimination) followed by me or not-me (attribute discrimination). In the "critical blocks", participants are then asked to categorize the words as death or me (death-me) compared with life or not-me (life-not me), or death or not me (death-not me) compared with life or me (life-me). Across blocks and subjects, screen side and order of pairings are then counterbalanced. The overall task structure is presented in Supplemental Figure S1[1].

In the adapted fMRI version of the S-IAT used here, the task comprised two runs of about eight minutes each. A run consisted of four blocks: two blocks of single category stimuli and two critical blocks, as noted previously. A fixation cross was presented between stimuli. Each stimulus was presented for two seconds, with an inter-trial fixation interval of two to five seconds (average=three seconds). Words used in the analysis were taken from previous publications by Nock and colleagues (Nock *et al.*, 2010). To increase the number of trials in each block to achieve a more reliable blood-oxygen-level dependent (BOLD) signal, two additional words were added to each category; the full list of words is presented in Supplementary Table S1. All target words were presented in randomized order. The task

[1]Please note that the term "Suicide IAT" is being used to describe a version of the task that uses words associated with death, such as "funeral" or "lifeless". However, other versions of this task focus on suicide method, such as "gunshot" or "overdose", and these are also sometimes titled "Suicide IAT" (Glenn *et al.*, 2017).

used a mixed event-related and block design, although only results from the blocks are presented here, in line with the initial aims of this pilot analysis.

Image acquisition

The images were collected on a 3T Signa HDx scanner (General Electric Healthcare, Milwaukee, WI) with an eight-channel phased-array head coil and echo-planar imaging (EPI) sequence (echo time (TE)=30 ms; repetition time (TR)=2000 ms; axial slices=33; voxel dimensions=3.75*3.75*3.5mm; flip angle=60 degrees; 224 timepoints per run). To allow for steady-state tissue magnetization, five volumes were discarded from the beginning of each EPI acquisition. An MPRAGE T1 weighted structural sequence was used for co-registration (TE=3.228 ms; TR=8 ms; flip angle=12 degrees, slice thickness=1.2 mm).

Study Procedures

Participants were oriented to the task using a behavioral version of the IAT outside the scanner that used flowers (i.e. “daisy”,”sunflower”), insects (“ant”,”caterpillar”), good (“peace”,”joy”), and bad (“pain”,”terrible”) as the primary categories. Before the scan, all participants completed a series of self-report rating scales, specifically the Behavioral Activation/Behavioral Inhibition Scale (BIS/BAS) (Carver and White), the Barratt Impulsiveness Scale (BIS) (Barratt, 1965), the State-Trait Anxiety Inventory (STAI) (Spielberger, 1970), and the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974). To evaluate the potential mood effects of the S-IAT, mood ratings before and after the task were assessed using the Visual Analogue Scale (VAS) (Price *et al.*, 1983). Participants were asked to rate their levels of happiness, sadness, anxiety, and anger.

Behavioral Analysis

For all analyses, and consistent with standard IAT scoring procedures, response time latencies under 400 ms were eliminated. Scores were disqualified if there was a greater than 30% error over all critical blocks or 40% in one critical block. Only one participant had scores disqualified due to accuracy and was excluded from the entire analysis. Again, critical blocks were the conditions in which target discriminations (death/life) and attribute discriminations (me/not me) were presented simultaneously. The primary behavioral outcome from the S-IAT is a D-score; positive D-scores represent a stronger association between self and death (as indicated by a faster response time when “death” and “me” words are paired together compared to when “life” and “me” words are paired together), and negative D-scores represent a stronger relationship between self and life. The D-score from the S-IAT fMRI task was calculated by subtracting the reaction time in the self-death trials from the reaction time in the self-life trials and dividing by the standard deviation of all critical trials.

Statistical Analyses

Mood ratings before and after scanning were assessed using paired *t*-tests. D-scores from the behavioral analysis were correlated with self-report rating scales using Pearson correlations. IBM SPSS version 24 was used for behavioral statistical analyses and significance was considered at $p<.05$, two-tailed.

Imaging Analysis

BOLD data were pre-processed and analyzed using AFNI (Cox, 1996). Processing was conducted using the afni_proc.py script and involved despiking, slice timing correction, and realigning to the third volume. Data were aligned to the high-resolution structural scan with an affine transform using the AFNI LPC cost-function, normalized to Talairach (Talairach and Tournoux, 1988) space using nonlinear warping and smoothed to 6 mm full width at half max. Outlying time points and time points with motion greater than 0.3 mm were censored, and any subjects with greater than 15% censored data points were excluded from the imaging analysis.

Individual subject analysis included regressors for each stimulus type (life, death, self, or other word to be categorized), block type (death/life; me/not me; critical blocks death-me/life-not-me and death-not me/life-me), and the instructions screens. A general linear test was then used to contrast BOLD activity during the self-death and self-life critical blocks for each subject. For the group analysis, a one-sample *t*-test was conducted using 3dttest++ in AFNI to analyze the mean activation across participants for this self-death versus self-life contrast.

One-sample *t*-tests were also used to examine mean activation during the self-death and self-life blocks separately, each compared to fixation. Follow-up analyses included constructing a general linear model to compare the self-death versus self-life contrasts with participants' corresponding D-scores as a covariate. To determine significant areas of activation and control for multiple comparisons in all analyses, we used 3dClustSim (with the ACF method), which calculated a cluster size threshold of at least 32 voxels for a family-wise error (FWE)-corrected $p<0.05$ for a significant cluster (cluster-defining voxel threshold of $p<0.01$).

Results

Thirty-one subjects enrolled in the study. One participant did not complete the study because of anxiety related to MRI scanning, and one participant was excluded due to technical difficulties during scanning; thus, 29 participants completed the scan. As noted above, one participant was excluded from analyses due to an error rate of 55% across trials, resulting in 28 participants included in the behavioral analysis. One participant had excessive motion in the scanner and so fMRI data were excluded, resulting in 27 participants in the imaging analysis.

Participant demographics are presented in Supplemental Table S2. Results from the mood ratings are presented in Supplementary Figure S2. For the 26 participants who completed the scans and all mood ratings, no significant differences in levels of happiness, sadness, or anger were observed after the S-IAT fMRI task ($p>0.05$). A significant reduction in anxiety was noted ($t(25)=2.83$, $p=0.009$).

Behavioral Analysis

D-Scores on the S-IAT ranged from −.98 to 0.04 (mean=−.48, SD=.31), with two individuals (7%) receiving a score of 0.04, suggesting a slight association between themselves and death. No other associations between self-ratings and D-scores were stastistically significant, although there was a trend between D-score and trait anxiety (Supplemental Table S3).

Imaging Analysis

When examining the contrast between the self-death and self-life blocks across participants, greater activity was observed during the self-death blocks in five clusters (see Table 1); no regions with greater activity were identified during the self-life blocks. Significant clusters were identified in the bilateral anterior insula, right ventrolateral prefrontal cortex (VLPFC)/ lateral orbital cortex, right precuneus/angular gyrus, and right middle temporal cortex (Figure 1).

Brain activity during the self-death and self-life blocks was investigated separately (Supplemental Figure S3). In the self-death condition, subjects showed significant clusters of activation, most notably in the bilateral insula, middle occipital cortex, medial PFC, and parahippocampal gyri (Supplementary Table S4). In contrast, in the self-life condition, subjects primarily demonstrated significant regions of deactivation, most notably in many regions of the central executive network (CEN), including the bilateral dorsolateral prefrontal cortex (DLPFC), parietal cortex, and dorsal anterior cingulate cortex (dACC). Deactivation was also observed in the bilateral insula and posterior cingulate cortex. Both conditions induced activation in bilateral parahippocampal gyri, medial frontal gyri, and right middle occipital cortex. Full results are listed in Supplementary Table S5. In the analysis with D-score as a covariate, no significant results were found for the association between the self-death versus self-life activation and behavioral D-scores.

Discussion

The present study—which is among the first to adapt the S-IAT behavioral task to probe the neural mechanisms of implicit associations between the self and life or death—administered an fMRI version of the S-IAT to a group of healthy volunteers. Behavioral scores were comparable to other investigations of the S-IAT conducted outside of the scanner (Nock *et al.*, 2010), suggesting that the S-IAT fMRI task could be evaluated in future studies as a potential marker of implicit suicide risk. Imaging results demonstrated differential activation in the self-death condition of the task compared to the self-life condition, specifically the finding of increased activation in the insula and right VLPFC. The differential activation between these two conditions in the bilateral insula suggests that the salience network may play a role in discriminating the relevance of either death- or life-related words to the self. How participants with increased suicide risk factors may respond to the same stimuli remains unknown.

Specifically, the behavioral results obtained suggest that the task may mirror typical S-IAT administration as conducted outside the scanner. A previous analysis of the S-IAT conducted in a sample of undergraduate students found that scores for approximately 8% suggested a self-death association (Harrison *et al.*, 2014), which is comparable to the range of scores found in our sample (7%). The average adjusted score of that sample (−.47) was also comparable to the mean of the current sample (−.45). In our analysis, D-scores were not significantly correlated with levels of depression, impulsivity, or inhibition, although there was a trend with state-level anxiety that aligns with the literature on the relationship between suicide attempts and anxiety (Sareen *et al.*, 2005). Lastly, and similar to previous analyses, completion of the S-IAT was not associated with increased levels of sadness or anger or with decreased levels of happiness (Cha *et al.*, 2016). Although the task was associated with decreased anxiety, it is important to note that the S-IAT was conducted at the end of the scanning session, which might have affected these results.

Interestingly, the imaging findings from the S-IAT fMRI task noted significant differences in the self-death versus self-life conditions. Compared directly, the self-death condition was associated with increased activation relative to the self-life condition in the anterior insula, a key component of the salience network (SN), which is involved in affective and interoceptive processing (Menon, 2011). The insula was also implicated in another evaluation of death-related—as compared to life-related—words in a sample of undergraduate and graduate students, where bilateral insula activation was found when judging words for their relavence to death versus life (Shi and Han, 2013). The lack of an association between the neuroimaging findings and D-scores suggests that further work is needed to determine whether the differences in brain activity observed here in the self-death versus self-life conditions are directly related to behavioral differences in reaction time, particularly in samples with greater D-score variability.

A major limitation of the analysis is that only healthy volunteers were used. Future analyses should examine whether differing levels of suicide risk affect response to this task. Also, while the task structure was developed to parallel the behavioral version of the S-IAT, it does not necessarily follow that the fMRI version will have the same association with past or future suicide attempts. Given that participants are in a scanner during the S-IAT and are responding to an expanded word list, a different relationship may exist between the task and clinical outcomes. In addition, it should again be noted that the words chosen for this task were related to death, as compared to other versions of the task that are method-specific (e.g. hanging, overdose) or related to non-suicidal self-injury (Glenn *et al.*, 2017). Therefore, further analyses may be needed to distinguish specific patterns of response on the S-IAT with conceptualizations of death and self more generally, or suicide attempt methods more specifically. Finally, the design of the task was mixed event-related and block design, although only results from the blocks are presented here to correspond with the S-IAT literature conducted outside the scanner. Further analyses of the individual word comparisons, preferably in samples of patients across a continuum of suicide risk, are needed to determine whether a differential neural response would be observed at the word level.

In summary, although suicide risk is difficult to assess and predict, our results suggest that the neural correlates of the relationship between self and death/self and life can be evaluated using tasks such as S-IAT. Here, an fMRI version of the S-IAT was piloted in a sample of healthy volunteers with comparable behavioral results to those seen in non-scanner versions of the task. The task was also associated with patterns of neural activation in areas relevant to emotional processing. While it is unlikely that a neuroimaging paradigm will replace patient reports or even brief behavioral measures of implicit suicide risk, such tasks can be used to better understand the neural underpinnings of how people consider the self in relation to both death and life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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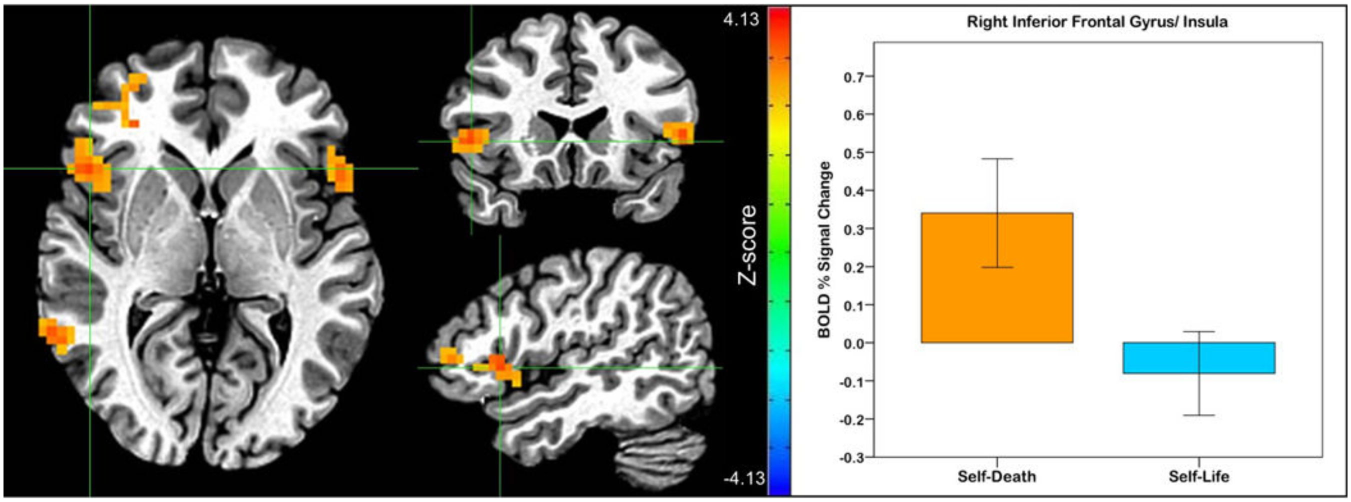

Figure 1:

Areas of greater activation during the self-death versus self-life blocks. Crosshairs are centered at the peak activation of the right inferior frontal/insula cluster: [−47 −17 3] (scale: Z-score; left=right). Graph represents extracted values of functional magnetic resonance imaging (fMRI) activation during the self-death and self-life blocks in the right inferior frontal gyrus/insula cluster (error bars = +/− 1 standard error).

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Table 1:

Clusters with Greater Activation during the Self-Death than Self-Life Blocks

REGION	X	Y	Z	# VOXELS	CLUSTER P-VALUE
Right inferior frontal gyrus/insula	47	17	3	54	< 0.003
Right Ventrolateral prefrontal cortex/lateral orbital cortex	30	34	−1	37	< 0.03
Right precuneus/angular gyrus	40	−71	35	34	< 0.04
Right middle temporal gyrus	61	−47	3	32	< 0.05
Left inferior frontal gyrus/insula	−51	13	7	32	< 0.05