



From motivation, decision-making to action: An fMRI study on suicidal behavior in patients with major depressive disorder

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ABSTRACT

Objective: We explored the neural mechanisms underlying disadvantageous risk decision making in un-medicated major depressive disorder patients who had recent suicide attempts.

Methods: 53 patients with major depressive disorder (MDD), including 23 with a history of suicide attempts (SA) and 30 without (NS), and 30 healthy controls (HCs) completed pertinent psychometric assessments, and the dynamic decision making balloon analogue risk task (BART) under fMRI. We also built a 4-parameter Bayesian computational modeling for decision making analyses.

Results: Several distinct findings emerged. First, SA patients had no depression intensity difference but higher pain avoidance in psychometrics, and more risk aversion in the BART when compared to the NS patients, with computational modeling confirming such reduced risk-taking propensity. Second, SA patients showed smaller left insular cortex activation than NS patients during the high risk, decisional phase of BART, and the modulation correlated with pain avoidance in both SA and NS groups. Third, during feedback phase of loss trials of the BART, SA patients had greater activation in the left dorsolateral prefrontal cortex (dlPFC) than NS patients.

Conclusion: Taken together, we present novel findings and propose interpretations that the differential insula activation likely relates to high uncertainty-aversion in SA patients, contrary to the typical view that they are impulsive and risk prone. The differential left dlPFC activation likely suggests hypersensitivity to loss, contributing to conservative decision-making at large, and extreme choices such as suicide when value estimations are compromised and emotionally overwhelmed. The interactive interpretation places a renewed focus on psychological pain avoidance as a robust motivator for suicidal behavior.

1. Introduction

Suicide is one of the leading causes of mortality globally (World Health Organization, 2019) and most people who die by suicide have a mental illness, with the largest number affected by major depressive disorder (MDD) (Cavanagh et al., 2003). Understanding and predicting suicidal behavior is an important and potentially lifesaving endeavor.

However, suicidality is associated with many risk factors such as mood disorders, hopelessness, stressful life events, interpersonal problems and poor social support, etc (Serafini et al., 2012; Franklin et al., 2017; Turecki et al., 2019). Of these, depression symptom severity, including suicidal ideation are not strong predictors of suicidal behavior in MDD patients (Campos et al., 2016; Mann et al., 1999; Montemmarano et al., 2018). Although suicidal ideation is common among MDD patients, the

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vast majority do not attempt suicide. Suicidality itself has thus been described by some as an independent clinical syndrome (Bostwick and Pankratz, 2000; Pompili, 2010). Prediction of suicidal behavior is known to be notoriously difficult, despite extensive studies using a myriad of epidemiological, psychological, neuropsychiatric, and risk decision making information, among others.

By studying those who have a history of attempted suicide and through psychological autopsies, a number of models on suicide motivation and psychological mechanisms have been advanced to guide pertinent psychological assessments and research (Barzilay and Apter, 2014). Among these, increasing theoretical and research attention has been paid to psychological pain avoidance, a notion of “psychache” originated by Shneidman, as a model to understand suicide motivation (Shneidman, 1993; Ducasse et al., 2018; Olie et al., 2010; Reisch et al., 2010). For example, Li and colleagues (Li et al., 2014; Xie et al., 2014) developed the Three-Dimensional Psychological Pain Scale (TDPPS) to assess psychological pain from three dimensions: cognitive pain arousal, emotional painful feelings, and motivational pain avoidance. Of the three, pain avoidance was the strongest predictor of suicidal behavior. Given that the evolution of suicidality has been conceived to be a dynamic process of transitions from motivation to volition, and finally action (O'Connor and Kirtley, 2018), suicide could be regarded as a profound decision, motivated by a need to avoid intolerable psychological pain, carried to action via a multifactorial process involving impaired decision making, impulsivity, and psychiatric symptoms, among others.

From a decision-making perspective, maladaptive choices and faulty estimations of future rewards – in this case the value of life, have been found to predispose those who are vulnerable to suicidal behavior (Dombrowski et al., 2013). A meta-analysis further highlighted that impaired decision-making play a key role in identifying suicide attempters (SAs) from suicide ideators (Klonsky et al., 2017). Specially, SAs display a persistent propensity for risk-taking to maximize potential short-term gains (Hegedüs et al., 2018; Jollant et al., 2008; Richard-Devantoy et al., 2014), but a reduced willingness to risk future loss when compared to healthy controls (HCs) and depressed patients controls (Baek et al., 2017). These findings suggest that uncertainty aversion and deficient estimation of long-term, value-based outcomes may be characteristic of SAs. Hence, faced with stress, or intolerable psychological pain, SAs may be more likely to make rash choices to eliminate uncertainty and the risk of future psychological pain through suicide.

In line with these theoretical frameworks and experimental findings, functional neuroimaging studies have found unique neural circuit patterns that distinguish SAs from others in terms of altered activation within regions important for affective and executive controls (Jollant et al., 2011; Li et al., 2019). For examples, when viewing emotional faces, SAs with MDD exhibited increased activation in the lateral orbitofrontal cortex (OFC) and decreased activation in the anterior cingulate cortex (ACC) (Jollant et al., 2008; Olié et al., 2015). When performing a decision making test involving uncertainty and rewards like Iowa Gambling Task (IGT), disadvantageous decision-making in suicide attempters has been linked to reduced contrast in the left lateral OFC (Jollant et al., 2010). Furthermore, when assessed by delayed discounting tasks - which also involve uncertainty in the time horizon and amount of rewards - SAs who engaged in serious, more planned suicide had more pronounced deactivation of the dorsolateral PFC (dlPFC) than those who had more impulsive, less serious attempts when responding to an increasing value of immediate choices, suggesting a lack of modulation in subjective valuations with changing contexts in the former, with generally impaired decision making in both (Vanyukov et al., 2016).

Thus, patients with MDD who attempt suicide may have specific abnormalities in neural processing involving reward-related estimations, leading to faulty evaluation and decision making involving future rewards or value of life. Also, this may be accompanied by tendency to favor short-term rewards, or more immediate relief from overwhelming

uncertainties or psychological pain, leading to suicidal motivation and potential action (Jollant et al., 2011). To test these hypotheses further, and more rigorously, the aim of the present study is to examine suicide-related psychological and neuroimaging features in un-medicated MDD patients with and without a history of suicide attempt, using the Balloon Analogue Risk Task (BART) to assess risk decision making under the conditions of uncertainty and changing reward contexts. The BART provides a realistic and dynamic, sequential decision-making paradigm in which participants are unaware of outcome probabilities, which also assesses unique, non-overlapping decision making processes from that of IGT (Buelow and Blaine, 2015). We hypothesize that risk decision making involved in BART will be able to differentiate patients with MDD who have a history of suicide from those who do not, and shed light on related specific neural mechanisms involved in risk taking, emotional responses, and cognitive processing. Furthermore, we hypothesize that these differential neural activations will interact and correspond to the emerging psychological pain avoidance findings that are important in understanding and predicting suicidal behaviours. To the best of our knowledge, no prior study has used the BART to investigate the connection with psychological pain avoidance and distinction between suicidal attempters and non-attempters in MDD patients.

2. Methods

2.1. Participants

Between December 2015 and September 2018, 53 patients with MDD, including 23 with a history of suicidal attempts (SA group) and 30 with no suicide attempts (NS group), were recruited from the mental health outpatient clinic at Second Xiangya Hospital, Changsha city, China.

All MDD patients were recruited during an acute episode of mental health crisis, prior to any treatment or receiving any antidepressant therapy in the preceding 6 months. They were diagnosed by psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV). The inclusion criteria for MDD patients were: age 16–45 years; right-handedness; no organic brain disorder, mental retardation, severe head trauma, or history of substance abuse [based on chart reviews and the Semi-structured Clinical Interview for DSM-IV Axis I Disorders (SCID I)]; no prior electroconvulsive therapy; and a Beck Depression Inventory-I (BDI-I) score ≥ 19 (Beck et al., 1961). Assessments of suicide ideation utilized the Beck Scale for Suicide Ideation. Assessments of suicide attempts - defined as a self-destructive act, intended and aimed to ending one's life, and a suicide attempt history was verified by 2 study psychiatrists based on the interview, medical records, and information from the family, friends and the treatment team guided by the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). Participants with significant discrepancies between these sources, or primarily personality disordered were excluded; no participant had experienced significant head injuries related to the suicide attempt. All patients in both SA and NS groups have had suicide ideations. The methods of suicide were carefully assessed: the means were diverse, generally carefully planned, non-impulsive and not personality disorder driven “suicide-related behavior”, with relatively moderate to high lethality [wrist cutting ($n = 11$), jumping from heights or into river ($n = 8$), overdoses ($n = 7$), and hanging ($n = 3$), and immolation ($n = 1$). N represents suicide events. Some subjects attempted suicide more than once].

Thirty healthy controls (HCs) were recruited from local communities and colleges with the following inclusion criteria: age 16–45 years; right-handedness; has no history of meeting diagnostic criteria for any psychiatric/mood disorder according to a SCID Interview for DSM-IV-TR Axis I Disorders Non-patient Edition; no organic brain disorder, mental retardation, severe head trauma, or history of substance abuse; no suicidal history; and a BDI-I total score < 10 . All participants provided

informed written consent after receiving a study description. The study was approved by the Institutional Ethical Board of the Second Hospital of Xiangya, Central South University.

2.2. Questionnaires

Seven psychometric instruments were used to measure clinical and psychological information.

Depression severity was measured with Beck Depression Inventory (BDI, Beck et al., 1961). Scores on BDI range between 0 and 63, with higher score reflecting more depression symptoms. The respondents' hopelessness severity was assessed with the Beck Hopelessness Scale (BHS, Beck et al., 1974), which including three subscales: feelings about the future, loss of motivation, and future expectations. Total BHS scores range from 0 to 20, with higher scores reflecting more hopelessness. Suicide ideation in the past week and the at the worst time was assessed by Beck Scale for Suicide Ideation (BSI, Beck and Steer, 1991). BSI consists of 19 items with each rating from 0 to 2, with higher values indicating higher ideation. Participants' levels of psychological pain were measured with the 17-item Three-Dimensional Psychological Pain Scale (TDPPS, Li et al., 2014), which was comprised of pain arousal, painful feelings, and pain avoidance subscales. The higher score reflects higher degree of psychological pain. The severity of anhedonia was assessed by Temporal Experience of Pleasure Scale (TEPS, Gard et al., 2006), which was comprised of anticipation and consumption anhedonia subscales, and the lower score reflecting more severe anhedonia symptom. The State-Trait Anxiety Inventory (STAI, Spielberger and Gorsuch, 1983) includes two 20-item subscales measuring state and trait anxiety respectively, with higher score reflecting higher level of anxiety. The 30-item Barratt Impulsiveness Scale (BIS-11, Barratt, 1959) has been widely used to assess impulsiveness, which involves three dimensions namely attentional, motor and non-planning impulsiveness, and the

higher score indicate the higher impulsiveness.

2.3. Balloon analogue risk task (BART)

The BART, which requires sequential decision-making in uncertain conditions (De Groot and Thuriq, 2018; Lejuez et al., 2002), has been shown to have good re-test reliability in behavior performance and brain activation (Buelow and Barnhart, 2018; Li et al., 2020), as well as high ecological validity (Schonberg et al., 2011; White et al., 2008). As shown in Fig. 1, a modified 20-min version of the BART (Rao et al., 2008) was administered on a screen during fMRI. Participants were instructed to press button 1 to inflate or 2 to discontinue inflation. If the balloon inflated successfully, a reward corresponding to the balloon size was added to the total wager; if it exploded, the cumulative wager for that trial was deducted from the total account. If participants chose to discontinue inflation, the rewards earned for that trial was added to the total account. Although the balloon could explode at any size, the reward and risk of explosion increased as it got larger (see Fig. 2a/b). The maximum number of times a single balloon could be inflated was 12. Information on the number of trials under different balloon size preceding discontinuing was collected.

In addition, five behavioral indicators related to risk decision making were analyzed: 1) mean number of pumps of win-balloons (PW); 2) mean number of pumps of win-balloons immediately following a pop (PW_PP); 3) mean number of pumps of win-balloons immediately following a win (PW_PW); 4) number of pop-balloons (NP); 5) and the number of win-balloons (NW).

2.4. Bayesian computational modeling

To optimize analyses of available risk decision making information at individual and group levels, computational models were built to map

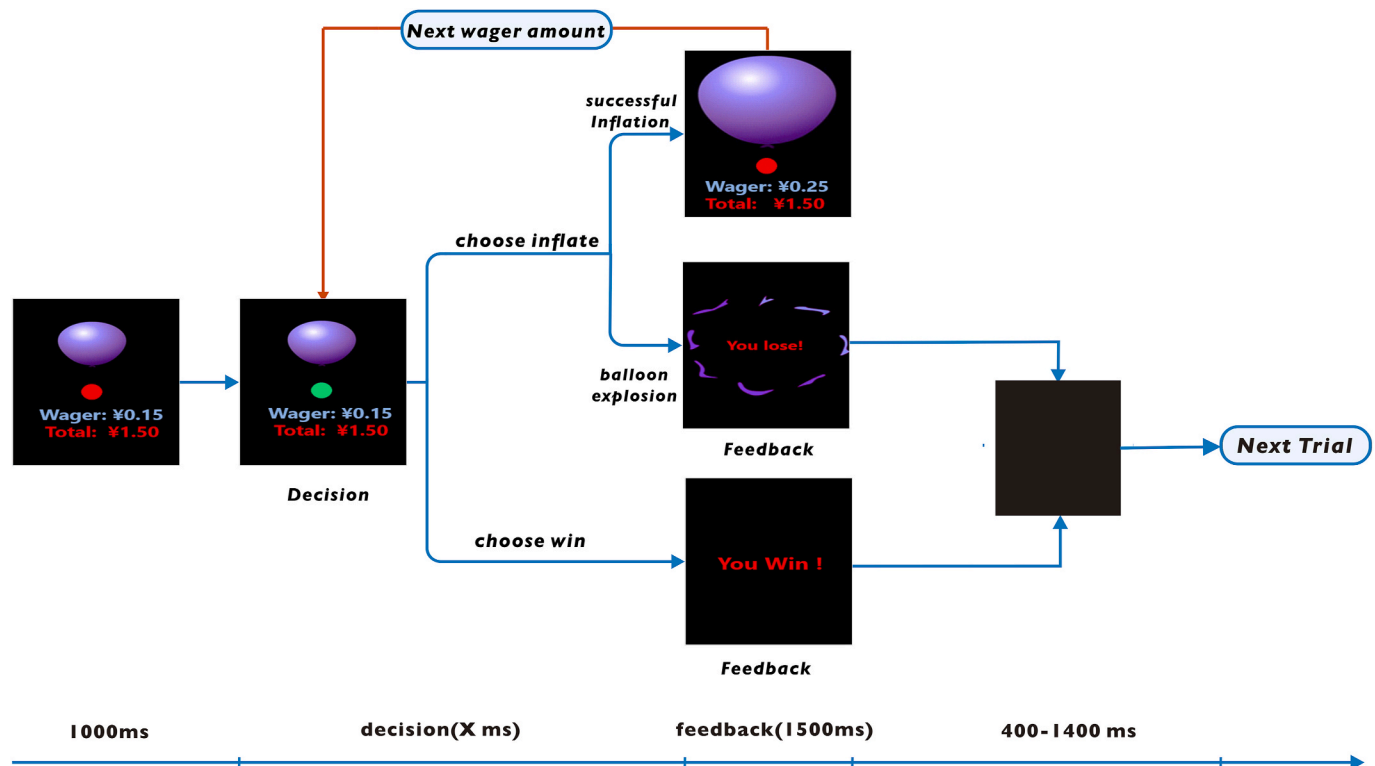


Fig. 1. Overview of BART. Participants chose to inflate the balloon or stop inflation at each turn. If the balloon inflated successfully, a reward corresponding to the balloon size was granted according to the total wager. If the balloon exploded, the cumulative wager amount was deducted from the participant's account. The choice to discontinue inflation led to a cash withdrawal in such trials. Following a win-outcome or a loss-outcome, the screen was blank, after which a new balloon appeared, and the inflation process repeated.

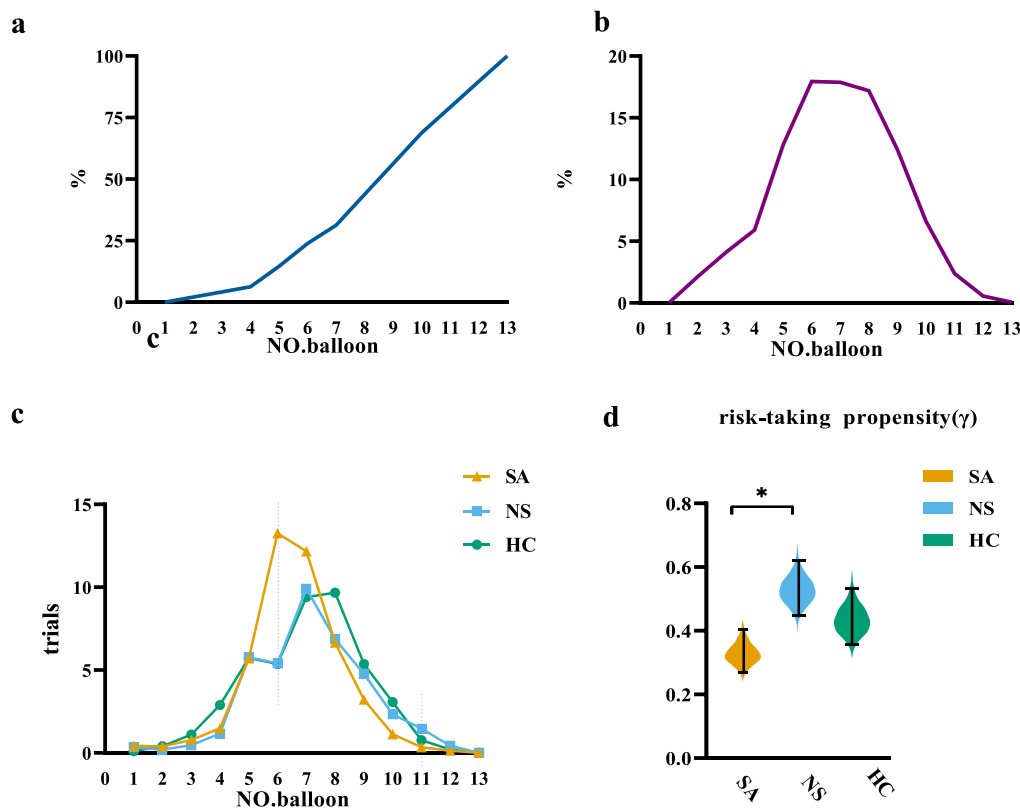


Fig. 2. The original explosion probability of balloon in BART, the actual mean number before discontinuing inflation balloon and modeled risk-taking propensity in three groups. (a) The original explosion probability of balloon. (b) The explosion probability of balloon as independent event for each size. (c) The actual mean number before discontinuing inflation balloon in three groups. (d) Posterior distributions of the risk-taking propensity parameter with the computational model of BART. Tick marks on bottom and top of each graph indicate 95% highest density intervals (HDIs).

observed behaviors in BART, to cognitive processes of interest. These processes are hypothesized to underlie the learning and sequential choices and decisions made by the participants. Construction of the parameters for the model aimed to examine propensity for risk taking, prior belief, and learning process. A 4-parameter model was chosen to best reflect the complexities in BART, capturing the cognitive learning processes involved in decisions under uncertainty (Wallsten et al., 2005, details in supplemental materials). The four parameters were: ϕ (participant's initial belief that pumping will not lead to explosion); η (updating coefficient of the participant's belief based on observation); γ (risk-taking propensity); τ (inverse temperature determining how deterministic or random a choice is). The modeling was conducted with hBayesDM tools (Ahn et al., 2017) in the R platform (version 3.6.2). A total of 2000 samples were drawn after burn-in of 1000 samples for 4 chains (= 2000 \times 4 chains = a total of 8,000 samples; with = 4000 burn-in).

2.5. Imaging data acquisition

fMRI scans were acquired on a Siemens 3T scanner (Skyra, Siemens, Erlangen, Germany) with a 32-channel, high-resolution, transmit/receive brain volume coil. Series of 600 contiguous functional scans were acquired with a single-shot gradient echo-echo planar (EPI) imaging sequence [repetition time/echo time (TR/TE) = 2000/30 ms; field of view (FoV) = 220 mm; matrix = 64 \times 64; slice thickness = 4 mm; in-plane resolution = 3.44 \times 3.44 mm; 36 axial slices]. Individual high-resolution coplanar anatomical images were acquired during the same session (three-dimensional magnetization prepared rapid gradient echo sequence; TR = 1900 ms, TE = 3.01 ms; FA = 9°; FoV = 256 mm; matrix size = 256 \times 256; voxel size = 1 mm³; 176 sagittal slices).

2.6. Imaging analyses

2.6.1. Preprocessing

Data were preprocessed and analyzed in Statistical Parametric Mapping software (SPM12; Functional Imaging Laboratory, London, UK). We realigned individual data, applied movement thresholds (translation \leq 2 mm, rotation \leq 2°), and corrected for acquisition time (reference, middle slice). Data were co-registered with a standard EPI template (resampled, 3-mm³ voxels) and smoothed with a Gaussian kernel (6-mm full-width at half-maximum). A high-pass filter (cutoff, 128 s) was applied to temporal fMRI signals to remove low-frequency noise trends.

2.6.2. Task modeling

An event-related design was employed for fMRI data analysis. The first-level fixed-effect model was constructed for the following conditions: a choice to inflate in the decision-making phase, a win outcome, a loss outcome. Movement parameters were set as covariates. Additionally, balloon-explosion probabilities (z-transformed) were included as parametric modulators of choice to inflate. Contrast images were calculated for each participant. A second-level random-effects model was used for between-group comparisons, and three-group conjunction maps (uncorrected $p < 0.01$, cluster size > 10 /group) were used as masks. A significance threshold of $p < 0.05$ with small-volume family-wise-error (FWE) correction yielded no surviving activation areas, likely due to the small numbers of loss events in all three groups (17.96 \pm 6.30). Thus, a threshold of uncorrected $p < 0.001$ was applied.

2.7. Statistical analysis

Categorical data (e.g. gender) were compared with a Chi-squared test. One-way analyses of variance (ANOVAs) was used to assess normally distributed data (e.g. group differences in demographics, psychometric test scores, and task performance, with Bonferroni post hoc tests. Non-normally distributed data were compared using the Mann-Whitney *U* test (e.g. illness duration), and the Kruskal-Wallis test (e.g. differences in trial discontinuation across balloon options). Peak BOLD signal changes were extracted from regions showing a significant group difference for post hoc analysis. Relationships between brain activation and behavioral detected were examined with Pearson correlations. Analyses were conducted in SPSS 25.0 (SPSS Inc., Chicago, IL) with a significance criterion of $p < 0.05$.

For behavior computational modeling, the highest density interval (HDI) of the posterior distribution was used to make decisions for group comparisons. If the HDI excluded 0 in the planned comparisons, the comparison was considered significant.

3. Results

3.1. Demographic and clinical characteristics

The three groups did not differ in demographics data, and the two MDD groups were similar with respect to illness duration and proportion of first/recurrent episodes (Table 1). Significant group effects were observed for all questionnaires ($12.47 < F < 188.47$, ANOVA $p < 0.01$). Relative to HC, the SA and NS groups had higher clinical symptom levels ($p > 0.05$); the SA group scored higher than the NS group on the BSI, TDPPS total score, and TDPPS-pain avoidance (PA) subscale ($p < 0.05$), whereas the two MDD groups did not differ in their BDI, TDPPS-pain arousal subscale, TDPPS-painful feelings subscale, TEPS, STAI, and BIS scores. Of note, gender and age did not independently affect the main clinical results. A representative sub-analysis of gender effect in the SA group is presented in Table S1. Sub-analyses of the demographic and clinical characteristics among three groups controlling for age are presented in Table S2.

3.2. Behavior and computational modeling

As summarized in Table 1, we found main effects of group on PW, PW_PP, and NW, but not PW_PW or NP. The mean numbers of trials before discontinuing are shown according to balloon size for each group in Fig. 2c. Kruskal-Wallis tests indicated that the SA group had more discontinued trials at the sixth ($H = 9.24$, $p = 0.01$) and eleventh balloon ($H = 6.94$, $p = 0.03$) than the other two groups. In line with this, computational modeling showed that the SA group displayed a higher prior belief of success (φ) than the NS group (95% HDI: 0.013, 0.0469) and the HCs group (95% HDI: 0.0043, 0.0411); and a lower risk-taking propensity (γ) than the NS group (95% HDI: -0.3088 , -0.0918 ; Fig. 2d). Risk-taking propensity for both MDD groups correlated with TDPPS-PA subscale scores ($r = -0.43$, $p < 0.001$). No differences were observed among groups on updating coefficient η and inverse temperature τ .

3.3. Neuroimaging

Consistent with prior BART studies, in our results, HCs showed significant activations related to increasing explosion risk in the insula, bilateral thalamus, and middle frontal gyrus during parametrically modulated inflation events (voxel-wise $p_{\text{uncorrected}} < 0.001$, Table S3). In contrast, both MDD groups showed widespread cortical-subcortical activations that were inversely associated with explosion risk, including in the regions activated in the HCs (voxel-wise $p_{\text{uncorrected}} < 0.001$, Table S3). During the feedback phase of loss trials, significant activations were observed in the HCs in the middle frontal gyrus, medial frontal gyrus, insula, anterior cingulate gyrus, precuneus, lingual gyrus,

Table 1

Demographic, clinical, psychological and behavior characteristics of patients and healthy participants.

Parameter	SA (N = 23)	NS (N = 30)	HC (N = 30)	$\chi^2/F/Z$	<i>p</i>	Cohen's <i>d</i> (SA vs NS)
Gender, no. males/females	8/15	12/18	19/11	5.18	0.08	–
Age, years	21.39 ± 5.51	23.36 ± 4.37	20.60 ± 3.75	2.81	0.07	–
Schooling, years	11.83 ± 4.06	12.46 ± 4.71	12.60 ± 2.12	0.31	0.74	–
Duration of illness, months	28.22 ± 41.67	17.05 ± 28.23	–	1.25	0.21	–
first episode/non-first episode	16/7	26/4	–	2.32	0.13	–
BDI score	35.19 ± 8.59	33.21 ± 7.87	3.73 ± 3.32	188.47	<0.01	–
BHS score	13.04 ± 2.27	13.83 ± 3.71	1.69 ± 1.19	187.75	<0.01	–
BSI_C score	16.87 ± 8.99	6.77 ± 6.71	–	48.08	<0.01 ^a	1.30
BSI_W score	25.65 ± 7.68	15.15 ± 10.32	0.43 ± 0.32	76.39	<0.01 ^a	1.13
TDPPS total score	65.61 ± 12.19	58.89 ± 10.15	26.10 ± 7.56	125.49	<0.01 ^a	0.59
Pain arousal	28.22 ± 6.03	27.14 ± 5.14	11.20 ± 3.64	105.03	<0.01	–
Painful feelings	22.91 ± 5.47	22.75 ± 5.23	11.77 ± 4.24	46.90	<0.01	–
Pain avoidance	14.48 ± 8.74	9.00 ± 6.40	3.13 ± 0.51	23.61	<0.01 ^a	0.71
TEPS score total score	63.57 ± 19.96	63.43 ± 15.55	84.50 ± 9.78	18.25	<0.01	–
Anticipation	33.74 ± 14.29	34.25 ± 9.69	45.60 ± 5.56	12.47	<0.01	–
Consumption	30.30 ± 9.24	29.18 ± 7.09	38.90 ± 5.98	14.89	<0.01	–
STAI score S_AI	59.48 ± 10.62	59.18 ± 11.54	30.47 ± 5.29	88.77	<0.01	–
T_AI	64.35 ± 7.79	63.79 ± 7.90	33.97 ± 6.23	160.85	<0.01	–
BIS score	73.65 ± 13.58	75.06 ± 8.99	59.30 ± 8.93	19.32	<0.01	–
BART trial type PW	5.83 ± 0.81	6.60 ± 1.01	6.43 ± 1.32	3.49	0.02 ^{a,b}	0.84
PW_PP	5.58 ± 0.86	6.37 ± 1.26	6.34 ± 1.43	3.25	0.03	–
PW_PW	6.48 ± 1.24	6.81 ± 1.14	6.50 ± 1.34	2.75	0.05	–
NP	17.96 ± 6.29	19.27 ± 7.06	18.00 ± 5.83	1.55	0.20	–
NW	44.74 ± 9.7	37.67 ± 10.29	43.93 ± 14.05	3.11	0.03 ^{a,b}	0.71

SA: major depressive disorder with suicide attempts; NS: major depressive disorder without suicide attempts; HC: healthy controls.

BDI: Beck Depression Inventory; BSI_C: Beck Scale for Suicide Ideation at the current time; BSI_W: Beck Scale for Suicide Ideation at the worst time; TDPPS: Three-dimensional Psychological Pain Scale; TEPS: The Temporal Experience of Pleasure Scale; BHS: Beck Hopelessness Scale; STAI: State-trait Anxiety Inventory; SAI: State anxiety inventory; TAI: Trait Anxiety Inventory; BIS: Barratt Impulsiveness Scale; PW: mean pump times of win-balloons; PW_PP: mean pump times of win-balloons immediately following a pop; PW_PW: mean pump

times of win-balloons immediately following a win; **NP**: the number of pop-balloons; **NW**: the number of win-balloons.

^a Post-hoc between SA group and NS group, $p < 0.05$;

^b Post-hoc between SA and NS group after controlling for current suicidal ideation.

caudate, putamen, and hippocampus/thalamus regions. The MDD groups showed similarly distributed activations, including the left middle frontal lobe, bilateral insula, and several limbic regions (voxel-wise $p_{\text{uncorrected}} < 0.001$, Table S4). In addition, activations in three groups during the feedback phase of won trials are presented in Table S5.

As shown in Fig. 3, in the decision-making phase with parametric modulators accounting for explosion probability, significant group differences emerged in the left insular cortex, and right temporal gyrus/insula cortex. Compared with the NS group, the SA group exhibited significantly blunted activation in the left insular cortex ($\text{small volume corrected } p_{\text{FWE-corrected}} = 0.03$). Also, parametric modulation of explosion probability on insula activation in the decision-making phase for both MDD groups correlated with TDPPS total scores ($r = -0.31$, $p = 0.03$) and TDPPS-PA subscale scores ($r = -0.36$, $p < 0.01$).

In the feedback phase of loss trials, significant group differences emerged in the dlPFC (Fig. 4), with the SA group showing greater activity than the NS group in the left dlPFC. The behavioral index PW correlated inversely with percent signal change in the dlPFC ($r = -0.27$, $p < 0.05$). No significantly different activations in success event/win outcome conditions emerged among the three groups.

4. Discussion

In this fMRI study, compared to the NS patients, SAs reported greater suicide ideation and pain avoidance, as well as lower risk taking reflected through higher number of win-balloons and lower pumps of win-balloons quantities, which were corroborated by computational modelling findings of SAs having a lower risk propensity, despite an

initial higher belief to win. Correspondingly, parametric fMRI analyses showed that, relative to the NS group, the SA group had decreased left insular cortex activation during the decision-making phase where there was increasing probability of balloon explosion, but increased dlPFC activation in the feedback phase of loss trials. Correlation analyses suggest that these neural abnormalities may underlie increased suicide risks.

4.1. Pain avoidance motivation, uncertainty aversion, and conservative decision-making

Our findings of the SA group having higher TDPPS total and pain avoidant scores than the NS group fit with Shneidman’s well-accepted psychache theory that emphasizes ending intolerable, and perceived-to-be otherwise unavoidable, psychological pain is a suicide driver (Shneidman, 1993; Olie et al., 2010; Reisch et al., 2010). Although psychological pain may be a core factor for suicidality, distinct components of psychological pain may have different impacts on suicide acts (Conejero et al., 2018; Li et al., 2014). Our results suggest that psychache escape may be a critical factor for suicidal acts, while intense perception of emotional pain may contribute to the escape motive (Li et al., 2014). This finding is particularly remarkable as our SA and NS groups had no differences in term of depression severity, and hopelessness – two of the most studied and established predictors of suicidal ideation, attempt, and death (Ribeiro et al., 2018), therefore reducing confounding effects of these important clinical factors (along with no differences in anxiety), and accentuating the key role of psychological pain avoidance in suicidality (Verrocchio et al., 2016). Increasing evidence has implicated MDD symptoms of emotional dysregulation and emotional pain in generation of suicidal ideation, but not specifically to suicide attempts (Molaie et al., 2019; Sisti et al., 2020).

Similarly, there were no differences between the SA and NS groups in terms of levels of impulsivity, but they were both more impulsive than the HCs. This finding is on the surface counter-intuitive, as impulsivity is often conceived and reported to be a risk factor for suicidal behavior.

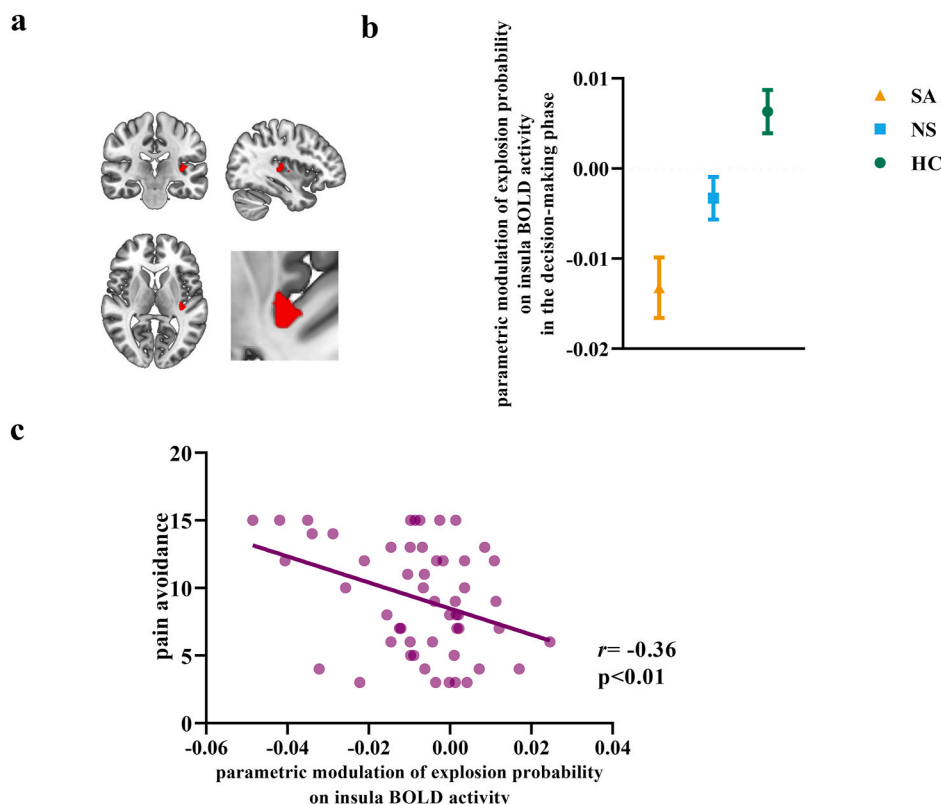


Fig. 3. Group difference in neural activation during the decision-making stage. (a) In the decision-making phase with parametric modulators accounting for balloon explosion probability, a significant group difference was in the left insular cortex (cluster size $k = 5$, peak voxel = MNI -36, -24, 6; $p = 0.031$, FWE small volume corrected). $Z = 6$. (b) Post hoc tests revealed that when compared with the NS group, the SA group exhibited significantly blunted activation in the left insular cortex. (c) Parametric modulation of explosion probability on insula BOLD activity in the decision-making phase was significantly correlated with TDPPSpain avoidance subscore in the two MDD subgroups. Error bars represent 1 SEM.

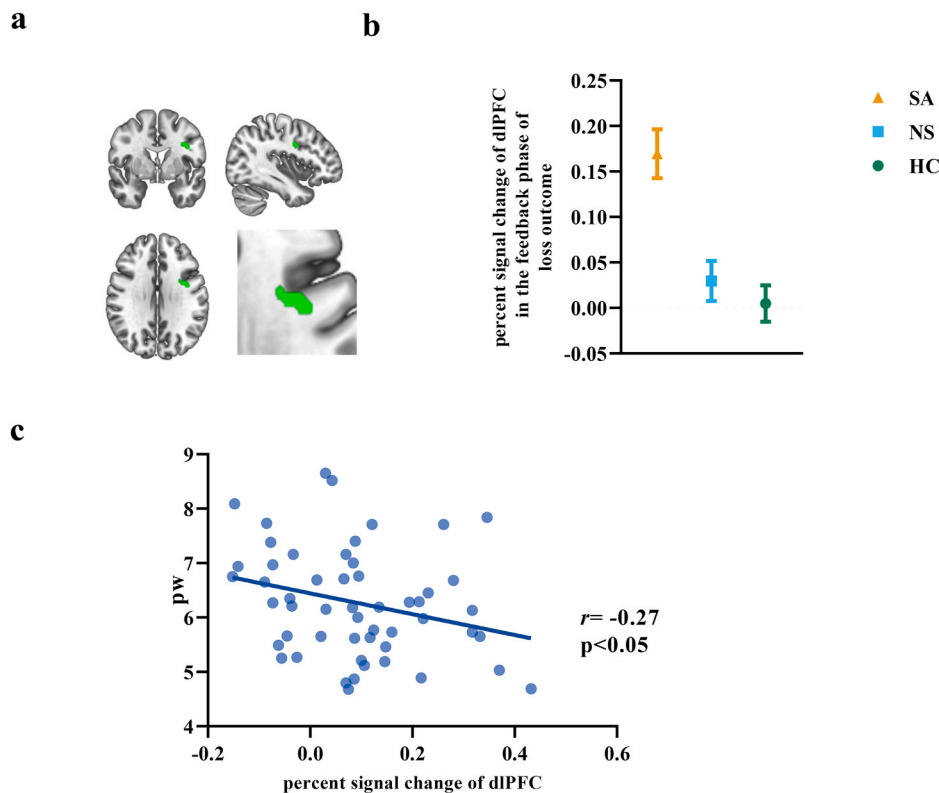


Fig. 4. Group difference in neural activation during the negative feedback stage. (a) In the feedback phase of loss trials, a significant group difference was in the left dorsolateral frontal cortex (cluster size $k = 20$, peak voxel = MNI -39, -3, 30; $p < 0.001$, uncorrected). (b) Post hoc tests revealed that when compared with the NS group, the SA group exhibited significantly higher activation in the left dorsolateral frontal cortex. (c) Percent signal change of dlPFC in the feedback phase of loss trials was correlated with the mean number of pumps of win-balloons (PW) in the two MDD groups. Error bars represent 1 SEM.

However, increasing research has shown that the relationship between impulsivity and attempted suicide is a complex and non-direct one, and impulsivity itself does not necessarily predict suicide attempt, but perhaps relevant in certain contexts and in combination with other risk factors. Suicidal acts can be goal-oriented, carefully planned decisions, but impulsivity may be an important element in turning the ideation and planning into action (Chaudhury et al., 2016; Witte et al., 2008). Degree of planning and levels of lethality in suicide attempts also interact with impulsivity (Chaudhury et al., 2016; Dombrovski et al., 2011). Furthermore, depressive patients with both well-planned or poorly planned attempts, have less impulsivity and display greater delay discounting behavior than patients with suicide ideation and no attempts, supporting the notion that suicide risk may be determined by evaluation of value differences among options rather than by trait impulsivity alone, especially in a dynamic and uncertain environment (Dombrovski et al., 2013; Dombrovski and Hallquist, 2017; Vanyukov et al., 2016). Some research has also argued that well-planned suicide attempts and impulsive suicide attempts might represent distinct phenotypes (Oquendo, 2015; Simon et al., 2001). Given the complex nature of impulsivity, it may be fruitful to study mechanisms of suicidality independent of impulsivity, and focus on other aspects of decision making related to uncertainty (Van den Bos, 2009). Our current study provides a good opportunity to illustrate this.

Our findings from the BART tasks showed that the SA group had a higher level of risk-aversion, lower risk-taking propensity, and was more conservative in decision-making than the NS group when facing possible loss are consistent with a small but meaningful literature on this subject (Baek et al., 2017). Employing a similar monetary decision-making task, Baek et al. demonstrated that suicide attempters had a heightened aversion to both risk and loss, compared with healthy subjects and patients without suicide attempts. The authors hypothesized that risk and loss aversion may induce a negative bias in estimates of future values, contributing to suicidal behavior. Our results reproduce this finding, as well as linking risk aversion to avoiding intolerable psychological pain.

It should also be noted that our finding of heightened risk aversion in

the SA group is inconsistent with a larger body of literature that showed suicide attempters were more risk prone in decision-making. There are a number of possible explanations for this difference. One explanation rests on the difference in study population. For example, higher risk propensity is often observed in adolescent suicide attempters and less so on adults (Ackerman et al., 2014). A second explanation is related to study paradigms and instruments. Most related studies on suicide attempters relied on the IGT or similar reversal learning instruments, which require extensive adaptive learning from positive and negative feedbacks, in-depth cognitive and affective processes that may not be feasible for some participants, and make it very difficult to pinpoint specific decision deficits or biases in the participants. Moreover, different task paradigms assess different aspects of decision making, often with varying sensitivity, and researches have shown that IGT and BART have limited correlations (Xu et al., 2013). Lastly, and perhaps most nuanced and important, it has been reported that suicide attempters with carefully planned and high lethality attempts displayed more risk aversion in the short term, and were able to wait for longer term rewards than those with low lethality and more impulsive attempts (Dombrovski et al., 2011), suggesting finer distinction on risk decision among the suicide attempters, and our SA group shares similar characteristics as the carefully planned suicide attempters. In sum, our finding affirms that risk and loss aversions are important entities involved in suicide behavior in patients with MDD, and these risk decision making characteristics may also be more specifically uncovered by BART, a relatively novel tool for suicide studies.

It is also counterintuitive, as increased risk aversion is typically conceptualized as a protective mechanism against suicide. The explanation may in essence lie in what subjective advantage do risk and loss aversions bring to the suicide attempt patients who attempt suicide, and what reward is perceived to be valuable enough for them to abandon this aversion. In our study, such aversion is accompanied by the participants correspondingly opting for shorter-term, more immediate gains. Although objectively these choices resulted in poorer future rewards and outcome, and the risk evaluation and estimation were

deemed poor; we hypothesize that, from the perspective of the suicide attempters, the short-term gains may well meet their more urgent and immediate need to avoid intolerable psychological pain, and the escape of pain is considered a worthwhile gain frame in this risk decision process. Interestingly, in a longitudinal study with a large cohort of adolescents, [Hadlaczky et al. \(2018\)](#) reported that suicide attempters had lower loss aversion, and concluded that loss aversion might be a protective factor against suicidal behavior. We believe this discrepancy from our results is understandable based on the facts that their study was a large, epidemiological, non-clinical sample of adolescents, where any person with a suicide history, regardless of psychiatric diagnoses, and likely still less mature in their risk and loss appraisal ability, was included in the analyses. In addition, the loss aversion measurement they used is based on questionnaire with the relatively knowable probability, which is not the same as our BART. Future suicide studies involving risk and loss aversion across age and diagnostic groups involving different paradigms will help to improve the knowledge in this area.

4.2. Neural alterations related to decision-making and negative feedback processing

Decision-making can be parsed into three neurocognitive processes: assessing options and forming preferences, execution, and outcome evaluation ([Ernst and Paulus, 2005](#)). The BART produces increasing tension and engagement, mimicking naturalistic risk-taking and allowing the detection of all three neurocognitive process abnormalities ([Buelow and Barnhart, 2018](#); [Schonberg et al., 2011](#)). Consistent with the literature, our fMRI results in the HCs group showed increasing insular activation in relation to increasing explosion risk level during decision-making ([Li et al., 2020](#); [Tikász et al., 2019](#)). In contrast, our SAs group had decreased activations in the left insula when compared to the NS group. Also, the lowered insular activation correlated with psychological pain avoidance in TDPPS-PA subscores.

The present insula findings add new evidence regarding a potential key role the insula may play in dynamic decision-making in the context of uncertainty. The insular cortex has been implicated in the processing of interoceptive awareness and the integration of visceral information with cognitive and emotional processes, providing on-going adjustments accordingly ([Craig, 2009](#); [Uddin et al., 2017](#)). According to the somatic marker hypothesis—which proposes that visceral and emotional information guides rapid decision-making involving risk, uncertainty, or social interactions—the insula is also a key region in decision-making circuitry ([Bechara et al., 1994](#); [Damasio, 1996](#)). It was also reported that the unique sensory processing patterns of depressed individuals were crucial factors in determining unfavorable outcomes ([Serafini et al., 2017](#)). Indeed, neuroimaging studies with gambling tasks show robust insular activation during decision-making with uncertain outcomes ([Clark et al., 2014](#); [Von Siebenthal et al., 2017](#)), and growing evidence suggests that the insula may also be an important mediator of the transition from suicidal thoughts to actions ([Schmaal et al., 2019](#)), though the directionality of insula activation/deactivation in relation to such transition remains unclear ([Minzenberg et al., 2015](#); [Olié et al., 2017](#)).

Our findings in our SA group of an inverse correlation between parametric modulation of balloon explosion probability and activation on the insula cortex, and the intensity of one's motivation to avoid psychological pain raises the possibility that a higher pain avoidance motivation may modulate insula activation during decision-making with uncertain outcomes. SA patients may not have adequate or adaptive risk evaluation information via the insula, favoring disadvantageous choices. Of note, [Baek et al. \(2017\)](#) also found that neural activity of the left insula in depressed patients with suicide attempts significantly decreased as the subjective values of probabilistic loss (akin to our balloon explosion probability) increased. Also of interest, another research group found lower activation in the posterior insula in

depressive patients with suicide attempts facing social exclusion; although there was no direct study of their decision making, the authors hypothesized it may be related to their level of tolerance to psychological pain ([Olié et al., 2017](#)). Thus, our combined findings suggest that the insula may be directly involved in risk-averse tendencies via heightened negative valuation of expected loss, or indirectly via the regulation of negative valuation involving other neural circuits, or both; and that the abnormal insular functioning may be implicated in suicidal behavior, particularly when interacting with psychological pain ([Schmaal et al., 2019](#)).

In our second fMRI finding, related to the negative or loss feedback (balloon pop), the SA group had greater dlPFC activation than the NS and HCs groups. The dlPFC is involved in cognitive flexibility for complex decision making, and recruited to respond to conflicts by supporting top-down control of emotions and behaviors, promoting adaptive, goal-directed outcomes ([Goel and Dolan, 2003](#); [Tanji et al., 2007](#)). Germane to our study, previous research has shown dlPFC activation during engagement of cognitive control to override emotional responses ([Buckholz and Marois, 2012](#); [Sanfey et al., 2003](#)), continuous performance tasks ([Minzenberg et al., 2015](#)) or “cold” reasoning ([Goel and Dolan, 2003](#)). Furthermore, the dlPFC may be a key brain region involved in processing a vicious negative-feedback cycle of increased negative emotional reactions and an increasing probability for incurring losses. Indeed, patients with a suicide history have been reported to be unusually vulnerable to negative feedback ([Hochman and Yechiam, 2011](#); [Olié et al., 2015](#)), and youth at high-risk of suicide showed dlPFC activation when attempting to regulate their emotional responses to negative pictures ([Miller et al., 2018](#); [Pan et al., 2013](#)). A higher sensitivity to incurred losses over that of potential losses may also lead to over-valuation of the advantages of suicide, and thus increase risk of suicidal acts ([Hadlaczky et al., 2018](#)). Combining our behavioral and neuroimaging data, we speculate that the negative feedback triggered increases in dlPFC activation found in our SA group was likely reflecting a heightened need to control negative emotions, as well as neural activities involved in top-down control aimed at minimizing losses (i.e., corresponding to applying fewer balloon pumps). This in turn may also explain the more conservative, risk averse choices made by the SA group. We further speculate that, once negative emotion processing demand is too large and overwhelms one's threshold of rational control, the intrinsic cost-value trade-off valuation may be altered, leading to initiation and execution of suicide attempts in the presence of a negative cognitive bias (e.g. “I need to stop this uncertain intolerable psychological pain immediately” or “suicide is the only way to stop the psychological pain”). It is also in this particular context that heightened impulsivity (found in both SA and NS groups), may play a role in the transition from suicide ideation to attempt.

Finally, it is worth noting functional abnormalities of the insula and dlPFC found in SA group emerged during decision-making and feedback stage are components of the salience network and central executive network, respectively ([Menon, 2011](#)). It has been proposed that patients with MDD may have dysfunctional interactions involving fronto-insular networks, including the salience, central executive, and default mode networks ([Dong et al., 2019](#); [Wang et al., 2016](#)). Our study thus extends prior findings by providing new evidence of abnormal neural activity in the insula and dlPFC of SAs with MDD during dynamic decision-making. More studies are needed to clarify the dysfunctional mechanisms mediating suicide vulnerability at connectivity and network levels.

4.3. Limitations

With respect to limitations, first, the study relied on retrospective information about suicide attempts, and patients with MDD were recruited during an acute episode. Whether there is a difference in decision-making behavior between the period of acute episode and other times, including remission, is unknown. Thus, prospective design and longitudinal studies including both the onset and remission phases of

MDD are further needed to examine the mechanisms of transition from ideation to action. Secondly, given the relatively limited number of subjects, these findings need to be replicated in larger clinical samples. The relatively small numbers of loss events also hindered us from achieving high statistical power. Thirdly, our sample of SAs may not fully represent the true SA population. Since more lethal means of suicide often lead to more fatal consequences, our sample may have overrepresentation of those who employed less lethal suicide means, such as wrist cutting and overdose. This limitation is also related to complex socio-cultural factors: choice of suicide means is affected by China's strict centralized stance on gun control; East Asian traditional and culturally shaped suicide methods; and a high proportion of female suicides (Phillips et al., 2002; World Health Organization, 2014)

Finally, we are always aware that suicidal behavior is a complex entity that is often independent of psychiatric diagnoses (Arsenault-Lapierre et al., 2004; Sisti et al., 2020) accordingly, generalization of our results to other populations, as well as development of new methods to predict and prevent suicide, require further research. In our other study with large behavioral sample, we developed an innovative approach utilizing machine learning (ML) that incorporates features of psychological mechanisms and decision-making characteristics related to suicidality for classifying MDD patients with suicide attempts. The ML model using PW indicator of BART and the TDPPS pain avoidance subscore was able to distinguish MDD with suicide attempts and suicide ideations with 88.2% accuracy; furthermore, ML found hopelessness score was a strong predictor to classify HCs and MDD with only suicidal ideation with 96.3% accuracy (in press). With the strong evidence of the underlying neural mechanisms revealed by this study, that ML model under the framework of motivation-to-action transition in suicide provides a promising approach to predicting and hopefully preventing suicide in patients with MDD, and possibly other populations in the future.

5. Conclusion

By integrating fMRI neuroimaging, BART behavioral data, and computational modeling, the present study highlights the importance of uncertainty aversion in MDD patients with a history of suicide attempts, and supports the possibility that the choice to commit suicide emerges from a strong motivation to avoid psychological pain and an undervaluation of one's life. For more immediate application, the current results could be incorporated in clinical assessments to provide an objective clinical indicator for predicting suicide risks in patients with MDD. The implementation involves a relatively easy process of completing 17 items on the TDPPS scale and a 20 min behavioral task. The fMRI studies have shed more light on the neural mechanism underlying these findings as well.

During decision-making, insular activation may reflect its role in using somatic feedback to guide dynamic decision-making in uncertain contexts. However, the strong motivation to avoid psychological pain may modulate emotion-cognitive integration related to valuation, reducing insular activation during decision-making in SAs with MDD. Conversely, when processing negative feedback, heightened dlPFC activation in SAs might reflect attempts to control hypersensitivity to loss, which may be related to highly conservative decision-making. Once intolerable psychological pain has disrupted valuation functions, higher dlPFC activation may favor initiation of the extreme choice to pursue a suicidal action.

The present study showcases a promising neuroeconomic approach for exploring the motivation-to-action transition in people with suicidal risk. Future longitudinal studies are needed to replicate the current main findings in a larger sample. Open discussion and exploration of value estimation, risk appraisal in patients with MDD could also potentially help to reverse the cognitive framework of patients regarding suicide as gains.

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Author statement

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All authors contributed to drafting and approved the final version of the manuscript.

Declaration of competing interest

Over the past three years, Dr. Pizzagalli has received consulting fee from BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Concert Pharmaceuticals, Engrail Pharmaceuticals, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes; stock options from BlackThorn Therapeutics, and research support from NIMH, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All the other authors declare no competing interests.

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Appendix A. Supplementary data

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