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The neural correlates of low social integration as a risk factor for suicide

Ricardo Cáceda[a,*], **G. Andrew James**[b], **Zachary N. Stowe**[c], **Pedro L. Delgado**[b], **Nolan Kordsmeier**[b], **Clint D. Kilts**[b]

[a]Department of Psychiatry, Stony Brook University, Stony Brook, New York, USA

[b]Psychiatric Research Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

[c]Department of Psychiatry, University of Wisconsin at Madison, Madison, Wisconsin, USA

Abstract

Low social integration is commonly described in acutely suicidal individuals. Neural mechanisms underlying low social integration are poorly understood in depressed and suicidal patients. We sought to characterize the neural response to low social integration in acutely suicidal patients. Adult depressed patients within three days of a suicide attempt (n= 10), depressed patients with suicidal ideation (n= 9), non-suicidal depressed patients (n= 15), and healthy controls (N= 18) were administered the Cyberball Game while undergoing functional magnetic resonance imaging. We used complementary functional connectivity and region of interest data analysis approaches. There were no group differences in functional connectivity within neural network involving the pain matrix, nor in insula neural activity or the insula during either social inclusion. Superior anterior insula activity exhibited an inverted U-shaped curve across the suicide risk spectrum during social inclusion. Superior insula activity during social inclusion correlated with depression severity and psychological pain. Dorsal anterior cingulate cortex activity during social exclusion correlated with physical pain severity. Neural responses in the anterior insula significantly correlated with depression severity and with psychological pain during social inclusion; whereas dACC activity significantly correlated with physical pain during social exclusion. Recent suicidal behavior seems associated with a distinct neural response to social exclusion independently of presence of depression or suicidal thoughts.

Keywords

suicide; depression; social exclusion; pain; fMRI; Cyberball

*__Corresponding author:__ Ricardo Cáceda, MD, PhD, Department of Psychiatry, Stony Brook University; HSC T-10-040D, Stony Brook, NY 11794, Phone: (631) 638-1538; Fax: (631) 444-1560; ricardo.caceda@stonybrookmedicine.edu.

Conflict of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

1. Introduction

Suicide, a growing public health problem in the US [1] and worldwide [33], is a complex and heterogeneous behavior associated with a variety of biological, psychological and social risk factors [47]. A pervasive element in suicide is overwhelming psychological or mental pain [53, 63], usually triggered by psychosocial crises, such as, romantic, familial, social, or work-related conflict [8, 20, 31, 56, 76]. Epidemiological studies have shown incidence of suicide to be negatively correlated with social integration [66, 67]. The relevance of the social milieu, and the reaction of the suicidal individual to it, is further emphasized by the current major theoretical frameworks about suicide. Thwarted belongness, defeat, entrapment, impaired connectedness are considered key elements in the progression to suicidal thoughts and actions [41, 48, 68].

Heightened psychological pain, also referred to as psychache [63], mental pain [51], psychic pain [74], or emotional pain, is considered as a *sin equa non* for suicidal behavior [63]. Elevated psychological pain is shared by both recent suicide attempters and depressed patients with current suicidal ideation [9, 10, 14, 21, 49]. It has been proposed that a diminished ability to tolerate psychological pain may precede suicidal ideation and behavior [45]. Furthermore, only the level of perceived psychological pain and recent social victimization differentiated recent suicide attempters and those with suicidal ideation [9].

A considerable body of evidence demonstrates an overlap between the subjective response to physical and psychological pain (in response to social loss or rejection) and their shared neural representation in the “pain matrix “corresponding to the dorsal anterior cingulate cortex (dACC) and anterior insula [22, 43], which shows marked overlap with the salience network [62]. However, other fMRI studies distinguish the neural processing representations of physical and psychological pain (26, 27). A large-scale functional neuroimaging study (n=114) showed that a neural pattern classifier for somatic pain did not similarly classify social pain (romantic rejection) in healthy subjects [69]. A caveat is that these studies focused on healthy participants, and it is unknown if physical pain and social exclusion share dissociable or common neural processing correlates in patients with depression or suicidal intent [26].

Accumulating evidence suggests that suicide is not only associated with a propensity to be involved in adversarial social situations but limited ability to manage them. Social exclusion allows for a wide array of experimental approaches, including the Cyberball game, a virtual ball tossing game that simulates social exclusion [72]. To date, only one study has focused on the neural substrates of social exclusion in patients with a lifetime history of suicide attempts [50]. In order to explore the underlying brain mechanisms of social exclusion during acute suicidality we compared functional magnetic resonance imaging (fMRI) responses of recent suicide attempters, suicidal ideators, non-suicidal depressed patients and healthy controls while playing the Cyberball game. A data analysis plan of game behavior used both region of interest (ROI) and functional connectivity approaches to examine group differences in neural responses during social exclusion. We focused on the two brain regions traditionally linked to the ‘pain matrix’: insula and dACC. We tested a hypothesis that acutely suicidal patients will show alterations in the neural processing correlates of psychological pain related to social rejection, and that this brain-behavior relationship exhibits individual differences.

2. Methods

2.1. Subjects

Four groups of adults of both sexes, ages 18–60 years, were recruited between March 2014 and March 2016. The specific characteristics of the four assembled groups included:

Recent Suicide Attempters (SA; N=15): depressed adults with a recent (within the previous three days) suicide attempt rated as being moderate–high in intent and lethality as defined by a score of ≥ 2 in the actual lethality/medical damage subscale of the Columbia Suicide Severity Rating Scale (C-SSRS) [57] (19 individuals were screened and 15 met inclusion/exclusion criteria and agreed to participate);

Suicidal Ideators (SI; N=13): depressed adults with current suicidal ideation and no suicidal behavior in the last six months (22 individuals were screened and 13 met inclusion/exclusion criteria and agreed to participate);

Non-Suicidal Depressed patients (NSD; N=18): depressed adults with no self-reported history of suicidal ideation or suicidal behavior in the last six months (all 18 screened individuals met inclusion/exclusion criteria); and

Healthy Controls (HC; N=21): age- and sex-matched adults without a history of mental illness or drug abuse.

Subjects were recruited consecutively from the psychiatric inpatient units of the University of Arkansas for Medical Sciences (UAMS) (SA and SI groups), the psychiatric outpatient clinics of the UAMS Psychiatric Research Institute (SI and NSD), and the local community (NSD and HC). All subjects in the SA, SI and NSD groups fulfilled Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for Major Depressive Episode and either Major Depressive Disorder, Bipolar Disorder or Depression not otherwise specified.

Study exclusion criteria were: a) inability to speak, read and write English; b) inability to provide informed consent; c) history of dementia, neurovascular or neurodegenerative conditions; d) physical disabilities that prohibit task performance, such as blindness or deafness; e) current or chronic pain of any kind; f) use of analgesic agents, either opioid or non-opioids within the last month; g) current or past history of non-suicidal self-harm, h) undergoing alcohol, benzodiazepine, opioid or barbiturate withdrawal; i) non-removable ferromagnetic objects; j) history of claustrophobia; and k) positive pregnancy test. The University of Arkansas for Medical Sciences Institutional Review Board approved all procedures. The study conformed to the principles of the Declaration of Helsinki. Participants were compensated for their participation in the study.

2.2. Procedures

After providing written informed consent, all participants underwent a study interview to obtain demographic data, psychiatric and medical history, behavioral self-ratings, and measurement of pressure pain threshold, followed by fMRI scanning. Psychiatric diagnosis was established with the Structural Clinical Interview for DSM-IV Diagnoses (SCID) [28]. The C-SSRS and Beck Depression Inventory (BDI-2) [6] were used to quantify suicidal ideation and behavior, as well as depression severity. Known risk factors associated with suicide were characterized with the Beck Anxiety Inventory (BAI) [5], Beck Hopelessness Scale (BHS) [4], Psychache Scale [32] and Childhood Trauma Questionnaire (CTQ) [7]. Question 16 of the BDI-2 was used as proxy for sleep health. Self-reported states of physical and psychological pain were measured with the Physical and Psychological Pain Scale [49]. The Trail Making Test was administered to provide a measure of attention, given that attention impairments can affect the perception of pain [16].

Somatic (pressure) pain threshold was measured using standard procedures [2]. Patients were placed supine, and a point five inches below the patella in the medial facet of the tibia was identified in both legs. Pressure was applied using a hand-held gauge with a 1 cm^2 rubber tip (Wagner Instruments, Greenwich, CT, USA) alternately to the left and the right tibia for a total of three times per side. Participants were instructed to verbally report when their sensations change from pressure to pain or discomfort. A mean pressure pain threshold (Lb) was calculated from the six measurements. Measurement of pressure pain threshold was performed immediately before the introduction to lab members as potential confederates in the Cyberball game and the initiation of fMRI scanning.

2.2.1. Analysis of clinical data—Analysis of variance (ANOVA) was used to compare continuous variables. Significant results were followed by Tukey’s test. Chi square tests were used to compare categorical data. All tests were two-tailed. Adjusted p values are reported.

2.2.2. MRI acquisition—Imaging data were acquired using a Philips 3T Achieva X-series MRI scanner (Philips Healthcare, Eindhoven, The Netherlands). Anatomic images were acquired with a MPRAGE sequence (matrix = 256 × 256, 220 sagittal slices, TR/TE/FA = shortest/shortest/8°, final resolution =0.94 × 0.94 × 1 mm^3 resolution). Functional images were acquired using a 32-channel head coil with the following EPI sequence parameters: TR/TE/FA = 2000 msec/30 msec/90°, FOV = 240 × 240 mm, matrix = 80 × 80, 37 oblique slices, ascending sequential slice acquisition, slice thickness = 2.5 mm with 0.5 mm gap, final resolution 3.0 × 3.0 × 3.0 mm^3. Parameters for the 32-channel coil (at an angle 30 degrees from the AC-PC line) were selected to reduce orbitofrontal signal loss due to sinus artifact.

2.2.3. Social Exclusion Task—The Cyberball game is a virtual paradigm that simulates the social interactive experience of being excluded by others [25]. Participants were told that they would play a ball-tossing game via the internet with two other subjects in other scanners, in order to examine their coordinated neural response. In actuality, the ball-tossing behavior of these other ‘players’ were controlled by the computer; this aspect of deceit was disclosed at the completion of the MRI acquisitions. Before the scanning session participants were briefly introduced to two laboratory members (confederates) and told they would be playing with them. During scanning, a screen showed photographs of the individuals just met represented the other players, and a cartoon image of their own ‘hand’ that they used to express a ball-toss using a button-box. See Figure 1. Throughout the game, the ball was thrown back and forth among the three players, with the participant choosing the recipient of their own throws, and the throws of the other two 'players' determined by the pre-set program. Participants played two rounds of Cyberball: one round in which they were 'included' throughout the game, and one round in which they were 'excluded' by the other participants. Each round of Cyberball consisted of 60 ball toss trials. During the inclusion round, the confederate players were equally likely to throw the ball to the participant or the other player. During the exclusion round, the two confederate players stopped throwing the ball to the participant after 30 trials and threw the ball only to each other for the remainder of the round. Following the scan session, participants were asked: a) whether they believed the interaction was real, b) to identify their emotional reaction during social exclusion, and c) quantify the intensity of any negative reaction (0–100).

2.2.4. fMRI preprocessing—All MRI data preprocessing was conducted in AFNI [17] unless otherwise noted. Anatomic data underwent skull stripping, spatial normalization to the icbm452 brain atlas, and segmentation into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) with FSL [37]. Functional imaging data underwent despiking; slice correction; deobliquing (to 3×3×3 mm^3 voxels); motion correction (using the 10^{th} timepoint); transformation to the spatially normalized anatomic image; regression of 6 motion parameters (lateral movement in x, y, and z; rotational movement in roll, pitch, or yaw) and regression of the mean timecourses of WM and CSF voxels; spatial smoothing with a 6-mm FWHM Gaussian kernel; and scaling to percent signal change. Using Matlab (The Mathworks, Inc.), timepoints with brief spikes in head motion were identified via the frame-wise displacement method [58]; any timepoint for which the sum of these differentials exceeded 0.5 in magnitude was excluded from the timeseries, as these sudden head movements introduce greatest fMRI artifact. Mean activity timecourses were calculated for each ROI by averaging the timeseries of voxels within the ROI. Correlation matrices were generated from these ROIs for each participant and scan, then underwent Fisher's z-transformation to approximate linearity for subsequent regression.

2.2.5. ROI-level voxel-wise univariate analysis—The fMRI data were analyzed using MATLAB and AFNI in a two-stage, random effects procedure. In the first stage, task-related changes in blood oxygen dependent (BOLD) activity were modeled for each subject using generalized linear modeling (GLM) via AFNI's 3dDeconvolve command with the standard canonical hemodynamic response function. The GLM included participant head motion as six nuisance parameters. The second stage consisted of one-sample *t*-tests (if contrasting a task condition versus rest) or two-sample *t*-tests (if contrasting two conditions) to test if task-related changes in BOLD contrast were consistent for the entire sample. Planned contrasts for Cyberball game results included 1) Inclusion condition; 2) Exclusion condition; and 3) Exclusion - Inclusion. We used a 200 functional ROI atlas derived from parcellation of task-based and resting-state fMRI data [36] to explore the relatedness of suicidality and social exclusion-related neural processing *a priori* ROIs encompassing dACC, anterior, middle, and posterior insula bilaterally (see supplementary Table 1 for list of ROIs and coordinates). We focused on the dACC and insula as the brain regions with the most supportive data supporting a potential regulatory roles of both physical pain and social exclusion [22, 26, 43, 62].

2.2.6. Regression analysis—For ROIs representing the anterior (L: 113, 33; R: 143, 68) and posterior (L: 165; R: 194) insula, and the dACC (95), timeseries were calculated for each subject and fMRI run by back-projecting specific ROIs spatial β-map to each image timepoint using generalized linear modeling (GLM) via AFNI's 3dDeconvolve command with the standard canonical hemodynamic response function. The GLM included participant head motion parameters, thus generating weighted timeseries of BOLD activity for each subject and ROI. The GLM identified task-related changes in these weighted timeseries for each subject, and two-tailed one-sample *t*-tests determined if group-level engagement of ROIs during the contrasted conditions significantly differed from 0. The GLM had 3 contrasts (Inclusion, Exclusion, and Exclusion- Exclusion).

2.2.7. Multivariate fMRI data analysis—After preprocessing, group-level independent component analysis (ICA) of functional imaging data sets was conducted using MATLAB and the Group ICA of fMRI Toolbox (GIFT v1.3; http://mialab.mrn.org/software/), an approach for blind-source separation of a complex mixture of noise and signals into spatially and temporally distinct sources (independent components [ICs]) [15]. ICA was run using the Infomax algorithm to solve for 30 components (i.e. 30 networks of activation) using the Cyberball fMRI data. The following processes were used: back-reconstruction using GICA3, subject-specific principal component analysis using expectation maximization and stacked datasets, full storage of covariance matrix to double precision, usage of selective eigenvariate solvers, two-step data reduction with 60 principal components in the first step, and scaling to z-scores. ICA was repeated 20 times using the ICASSO algorithm to identify the most reliable and stable components across all iterations. The ICASSO stability indices (all i_Q>0.95) indicated a reliable solution using 30 components.

Based on visual inspection and in comparison with the literature [59], we classified the independent components as follows. Eleven components represented noise (such as ventricle fluctuations or head motion) and were excluded to reduce Type I error. Eight components represented networks not typically associated with decision making and reward processing: four components representing sensorimotor systems, two represented the visual system, and two represented the cerebellum. The eleven remaining ICs represented networks typically associated with cognition and/or pain processing. Three components represented the limbic system, three represented the pain matrix (composed by the insula and anterior cingulate), two components represented the frontoparietal network, and three components represented the default-mode network. See Supplementary Table 1 and Supplementary Figure 1.

To test our study hypotheses, we selected the three components representing the pain matrix and omitted the remaining components from subsequent analyses to reduce Type I error. For these components, timeseries were calculated for each subject and fMRI run by back-projecting the ICA voxelwise spatial β-map to each image timepoint using general linear modeling (GLM) via AFNI's 3dDeconvolve command with the standard canonical hemodynamic response function. GLM included participant head motion as 6 nuisance parameters, thus generating weighted timeseries of network activity for each subject and component. GLM identified task-related changes in these weighted timeseries for each subject, and two-tailed one-sample *t*-tests determined if group-level engagement of ICs for the planned contrasts significantly differed from 0. The GLM had 3 contrasts (Inclusion, Exclusion, and Exclusion-Inclusion).

Next, given the colinearity between some of our behavioral variables, we performed a multiple robust regression (using MATLAB's *robustfit* command with the Huber weighting function and tuning parameter 1.345) to relate behavioral measures to task-related recruitment of ICs. We modeled age, severity of depression (BDI-2), suicidal ideation severity (C-SSRS), pressure pain threshold, physical and psychological pain (Physical and Psychological Pain Scale [49]), CTQ total score, which were regressed to the dependent variable of task-related brain network activity (i.e. the GLM betas derived from deconvolution of ICA timeseries described above). Robust regression was chosen over standard linear regression for its greater resiliency to the effects of outliers, which are common in neuroimaging data [70]. Each condition contrast underwent false discovery rate (FDR) correction for the number of components (n=3) or ROIs (n=7) being studied at $q = 0.05$ using the Matlab FDR program [29]. We report corrected p values.

3. Results

We recruited 88 participants aged 18–60 years, 38 men and 50 women. Twenty-one participants were excluded from the Cyberball brain imaging analysis due to loss of data (n=2), incomplete assessments (n=4), head motion artifact (n = 3) or for either not believing they were playing with real humans or not reporting negative emotional responses during the Cyberball game (n = 12; 5 Attempters, 4 Ideators, 4 Non-Suicidal Depressed, and 3 Healthy Controls). Demographics of the 52 subjects included in the imaging data analysis are provided in Table 1.

There were no significant differences in age, gender, race, marital status, level of functioning, handedness, or years of education between the groups. All depressed subjects (groups 1–3) reported more severe depression ($F(3,50)$=56.2, p<0.001), anxiety ($F(3,50)$=20.6, p<0.001), hopelessness ($F(3,50)$=5.3, p<0.001), and sleep abnormalities ($F(3,50)$=17.4, p<0.001) relative to the healthy control group.

Current ($F(3,51)$=22.9, p<0.001), usual ($F(3,51)$=29.5, p<0.001), an maximal self-rated psychological pain during the last 15 days ($F(3,51)$=42.7, p<0.001), and psychache, another measure of psychological pain ($F(3,51)$=33.6, p<0.001) were higher in the Attempter and Ideator groups compared with Non-Suicidal Depressed subjects, who in turn reported higher psychological pain than Healthy Controls. Pressure pain threshold was higher in the Attempter group compared with the three other groups ($F(3,51)$=2.9, p=0.041). Suicide Attempter and Non-Suicidal Depressed groups reported higher physical pain in the last 15 days than Healthy Controls ($F(3,51)$=5.2, p=0.003). There were no group differences in the subjective negative reaction to social exclusion in the Cyberball Game ($F(3,51)$=1.2, p=0.36).

The three insula subregions ICA timecourses did not significantly differ with task during either Inclusion-Rest, Exclusion-Rest or Exclusion-Inclusion conditions. The correlations of insula-related IC neural activity with depression severity, suicidal ideation severity, psychological or physical pain were non-significant. The dACC ICA timecourses did not significantly differ with task during any condition. See Figure 2.

The right superior anterior insula ROI response (ROI #68) significantly differed between the four groups during Inclusion-Rest $F(3,51)=4.84$, $p=0.005$) (Figure 3a). Group differences for the middle and posterior insula ROI responses were non-significant or did not survive multiple comparison correction (lest superior anterior insula and inferior anterior insula). The bilateral superior anterior insula response during the Inclusion-Rest condition positively correlated with depression severity (right #68; $r = 0.438$, $p = 0.001$; left #33; $r = 0.386$, $p = 0.006$) (Figure 3b and 3c), and usual psychological pain in the last 15 days (right #68; $r = 0.385$, $p = 0.004$; left #33; $r = 0.356$, $p = 0.009$) (Figure 3d and 3e).

Dorsal anterior cingulate cortex (dACC) response (ROI #95) did not differ significantly between the four groups during any of the study conditions. However, dACC (ROI #95) response during social exclusion correlated with current physical pain ($r = 0.367$, $p = 0.005$). See Figure 3f. No significant correlations were found with psychache, suicidal ideation severity, pressure pain threshold, CTQ total score, or subjective negative reaction score.

4. Discussion

The present study sought to define the association between suicidal thoughts and actions on the activation and functional connectivity of major nodes in the human pain matrix response to social exclusion. The cross-sectional design further sought to dissociate the ubiquitous co-occurrence of depression from effects related to suicidal actions and thoughts. We report that despite no group differences in functional connectivity of the 'pain matrix' or the level of recruitment of the three insula or dACC ROIs related to social exclusion, the neural responses of the anterior insula during inclusion trials in suicide attempters exhibited significant group differences with depressed patients with and without suicidal ideation. Additionally, neural responses in the anterior insula correlated positively with depression severity and psychological pain, whereas, dACC activity correlated positively with current physical pain.

We add to the neurobiology of social intercourse developed mostly in healthy individuals [13, 24, 43, 69, 73], by examining severely depressed suicidal patients. We used social exclusion as a proxy for psychological pain. Even though psychological pain is intimately enmeshed with suicidal ideation and behavior [63], and most suicidal crises are triggered by some form of social conflict – usually rejection- social exclusion and psychological pain are not synonymous constructs. This is one of the initial studies to use the Cyberball game to recreate social interaction in suicidal or even depressed patients in combination with brain imaging [50]. Two previous studies had used variations of mental pain or social exclusion to examine patients with a history of suicide attempts. Reisch and collaborators examined eight moderately depressed women who had attempted suicide by overdose within the previous four weeks showing deactivation of frontal cortical areas (BA 46, 10 and 6) while listening to scripts about the circumstances that triggered their suicide attempts compared with neutral scripts [60]. Olie and collaborators showed decreased neural activity in the left insula and supramarginal gyrus during social exclusion in the Cyberball game in women with history of suicide attempts [50]. In a related approach, studying social reactivity, Jollant et al. presented euthymic individuals with a history of suicide attempts with angry faces and elicited increased responses in the right lateral orbitofrontal cortex (BA 47) and decreased responses in the right superior frontal gyrus (BA 6) compared with euthymic patients with a history of depression but no suicide attempts [39]. Recently, the same group described a negative correlation of N-Acetylaspartate concentration in the right dorsolateral prefrontal cortex with psychological pain, and a psychological pain-mediated positive correlation with suicidal ideation severity [40]. Depressed mood induction with an endotoxin challenge increased dACC and anterior insula responses during social exclusion only in female healthy subjects [23]. It is possible that the variability in brain response to social exclusion induced by the Cyberball game may be related to its condition of a mild-moderate social stressor, as evidenced by minimal hypothalamus-pituitary adrenal (HPA) axis activation [77]. The concurring decrease in insula reactivity in suicide attempters during social exclusion in Cyberball [50] may reflect a distinct transient deficit in the neural representation of social perception independent of depression or suicidal ideation. Perhaps this blunted insular responsivity may be associated with the abnormal emotional reactivity described in suicide attempters [3, 64] or to a diminished value of proprioception in decision making. Noteworthy, the significant correlation of anterior insular response with depression severity and psychological pain during social inclusion suggests that even during the pleasurable social interaction of social inclusion there is a degree of baseline anterior insular activity that correlates with underlying negative states, i.e, depression and psychological pain. These findings are suggestive of a general role of the insula in processing social stimuli [19].

The paralimbic anterior insula, with reciprocal connectivity with the limbic system [35, 46], is implicated in the affective processing of physical pain [18] and social exclusion [23]. Even though our subjects were selected for absence of current physical pain and for not taking any type of pain medications, we found that physical pain was associated with individual differences in the dACC response during social exclusion. We replicated previous findings of an increased threshold for experimentally-induced physical pain in recent suicide attempters, independent of depression [10, 52, 54, 55]. The correlation of dACC activity during social exclusion with physical pain may represent a possible mechanism for the decreased physical pain sensitivity found in individuals shortly after engaging in suicidal behavior. We did not explore potential underlying molecular mechanisms. Nonetheless, postmortem increased mu opioid receptor mRNA in the mesolimbic system in suicide completers [27, 34] and a promising clinical trial with buprenorphine [75] support the exploration of the opioid system in relation to suicidal ideation and behavior.

The phenomenon of less severe psychopathology (e.g. depression anxiety, suicidal ideation severity) has been observed in other studies with similar populations [11, 12]. Possible interpretations for this finding are that in suicide attempters the zenith of the suicidal process had already occurred within the last three days, whereas suicidal ideators were still in suicidal crisis mode and endorsed suicidal thoughts upon recruitment and assessed in this study. On these lines, a cathartic effect of suicide attempts had been described previously as approximately 50% report resolution of suicidal ideation shortly after a suicide attempt [61].

The strength of study inferences is clearly limited by aspects of its design. We employed a cross-sectional design for which the four groups had relatively small sample sizes. A clear view of the role of insular and dACC activity during inclusion and exclusion conditions may be obscured by the wide interindividual variability in our sample, which may be related to its limited size. We used an ROI approach of the the anterior insula and dACC, brain regions involved in the pain matrix to circumvent the limited sampe size. Social exclusion induced by the Cyberball game has been considered a mild-moderate social stressor, as evidenced by limited HPA axis activation [77]. It is possible that the ongoing intense social contact as part of inpatient milieu treatment may influence subjects' response during the Cyberball game. Additionally, the experimental social rejection by unknown individuals during Cyberball game may be too removed from real life social rejection or conflict by close friends or family. The available confederates were a white male and a black female. We did not ask for specific differential response to these two confederates, nor quantify sensitivity to social rejection, which may affect the subjective and neural response to social rejection. An inherent limitation to all studies hoping to understand the biology of suicide is that individuals who survive a suicide attempt may differ from those that complete suicide. Three days post-attempt may be too long a delay to capture the state of mind and the neurobiology of an individual during the attempt itself. Our study did not include subjects whose suicide attempts or subsequent treatment prevented them from being able to consent or be MRI scanned. Even though we controlled for use of antidepressants and other psycotropic medications, this strategy is less optimal than studying medication-free individuals (Table 1). The influence of psychotropic medications on social rejection is still formally to be tested. The study did not measure biological markers relevant to pain regulation or stress response, such as enkephalins or cortisol. Finally, Axis II pathology was not systematically measured, however we excluded subjects with nonsuicidal self harm.

The current study has several strengths. To our knowledge this the first brain imaging examination of social inclusion and exclusion in individuals within three days of a suicide attempt. Further, contrasting suicide attempters with suicidal ideation and non-suicidal depressed controls is designed to factor out the ubiquitous influence of depression. We controlled for factors that may influence pain processing such as depression, anxiety, severity of stress, sleep and attention abnormalities, history of self-harm, diagnosis, childhood trauma, substance use, and psychotropic medications. Lastly, in order to avoid confounding factors affecting pain regulation, individuals currently experiencing any type of pain [30], opioid use [65] or non-suicidal self-harm [42] were excluded.

The clinical relevance of social exclusion in suicide is highlighted by the fact that most suicidal crises are triggered by psychosocial conflict. Suicidal individuals show deficits in decision making in social contexts [38] and deficits in verbal communication [71]. Impairment of coping skills in adverse social situations is considered a key element in the progression to suicidal behavior by some of the major suicide theoretical frameworks, i.e. the interpersonal theory of suicide [68], integrated motivational volitional model [48], and the three step theory [41]. Furthermore, improving interpersonal effectiveness is one of the pillars of Dialectical Behavioral Therapy, proven effective in reducing suicide-related events [44].

The decrease in insula reactivity in suicide attempters during social exclusion may reflect a distinct transient deficit in the neural representation of social perception independent of depression or suicidal ideation. The dACC activity correlation with physical pain may represent a possible mechanism for the decreased physical pain sensitivity found in individuals shortly after engaging in suicidal behavior. Overall, our findings illustrate the complexity of physical and psychological pain processing during intricate social contexts in acutely suicidal patients. Addressing the struggles of patients at high risk for suicide in adverse social situations may provide valuable interventions for novel suicide prevention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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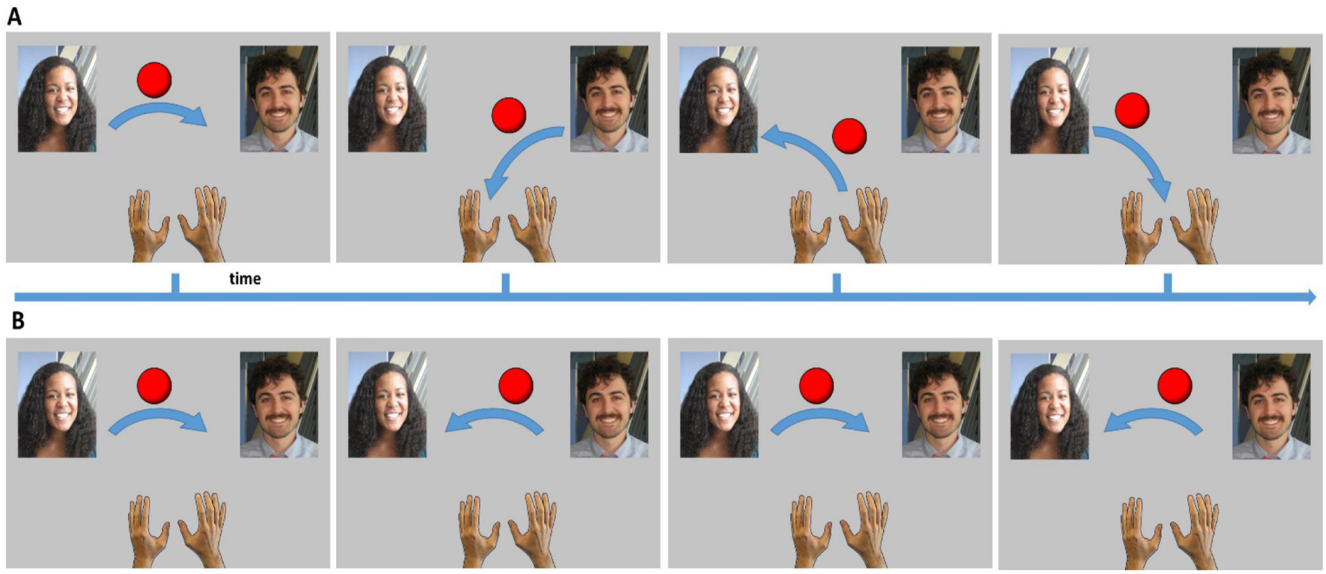

Figure 1.
Outline of social inclusion and social exclusion paradigms presented during the Cyberball game.

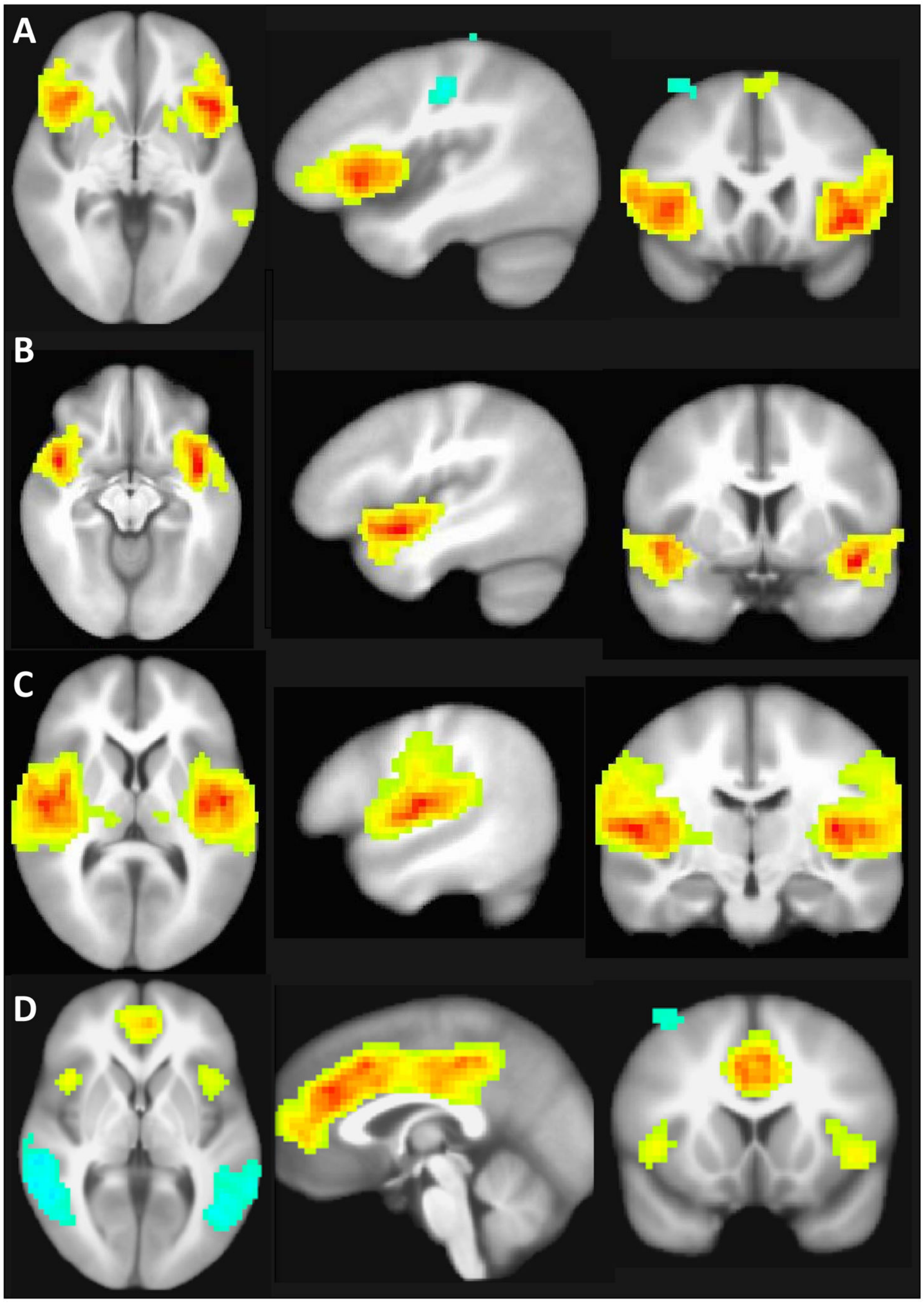

Figure 2.
Brain networks associated with activity in the insula and cingulate cortex. A. Neural network including the posterior insula. B. Neural network associated with anterior dorsal insula. C Neural network associated with anterior ventral insula. D. Dorsal anterior cingulate cortex

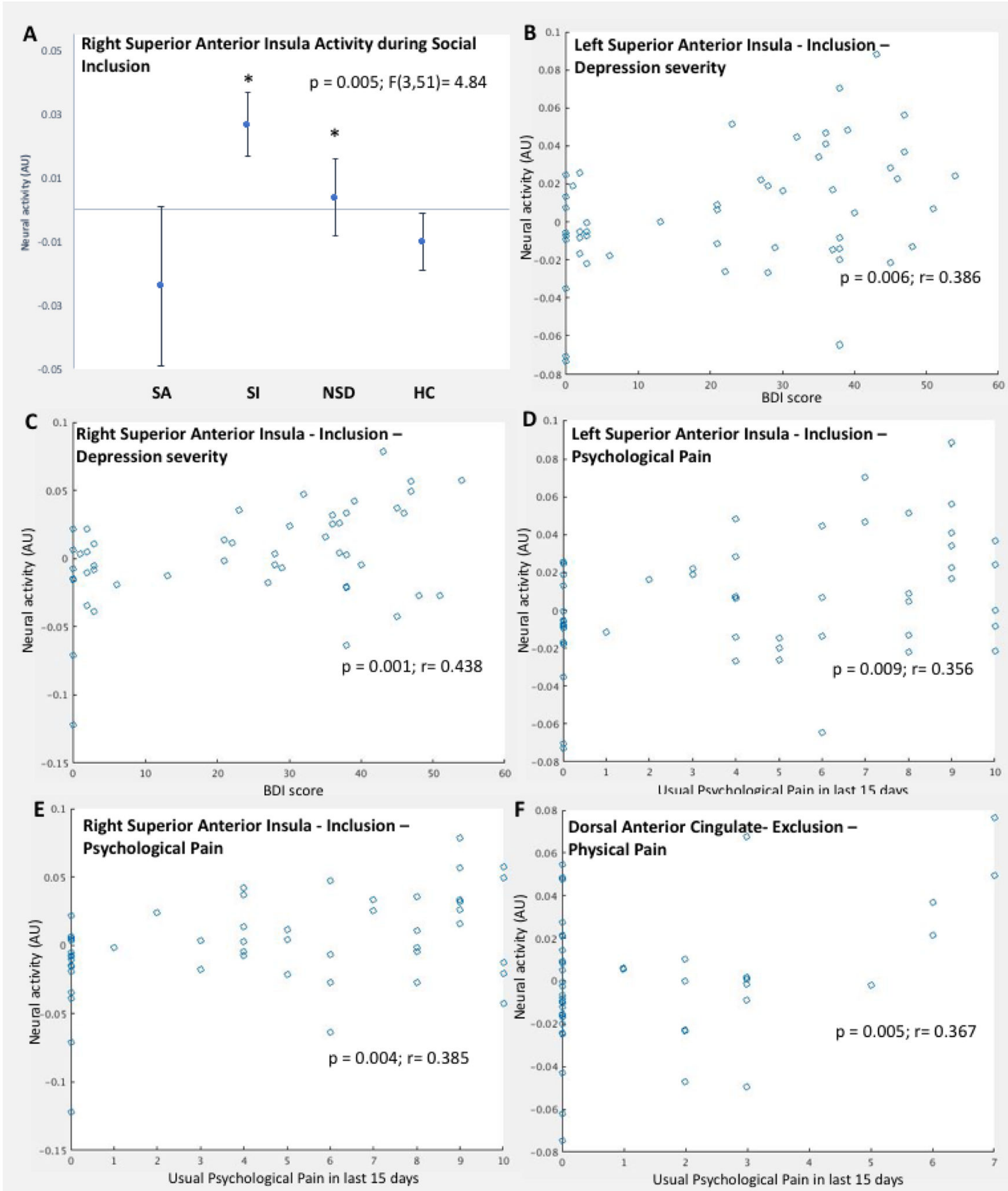

Figure 3.

Neural response to social exclusion or inclusion within the pain matrix and its correlation with clinical characteristics. Robust regression analysis outcomes indicated significant association between clinical and pain variables for neural response in: A. Neural responses in the right anterior superior insula ROI (#68) between the four groups during the Social Inclusion condition of the Cyberball game; B) The left superior anterior insula (#33) during Social Inclusion with depression severity (Beck Depression Inventory score); C. The right superior anterior insula (#68) during Social Inclusion with depression severity; D. The left superior anterior insula (#33) during Social Inclusion with usual psychological pain in the last 15 days; E. The right superior anterior insula (#68) during Social Inclusion with usual psychological pain in the last 15 days; and F. The dorsal anterior cingulate cortex (#95) during Social Exclusion with current physical pain. * $p<0.01$ compared with Suicide attempter group.

Table 1.

Clinical characteristics of depressed patients after a recent suicide attempt (Attempters), depressed patients with suicidal ideation (Ideators), non-suicidal depressed patients and healthy subjects.

	Attempters	Ideators	Non-Suicidal Depressed	Healthy controls	Adjusted p
N	10	9	15	18	
Age	34.2±10.9	30.1±9.4	42.7±14.7	33.0±11.3	0.08
Gender (m)	4 (40%)	3 (33%)	8 (53%)	7 (39%)	0.18
Race					0.64
White	8 (80%)	8 (89%)	10 (67%)	14 (78%)	
Black	2 (20%)	0 (0%)	4 (27%)	3 (17%)	
Other	0 (0%)	1 (11%)	1 (7%)	1 (6%)	
Marital status					0.47
Single	5 (50%)	5 (56%)	9 (60%)	10 (56%)	
Long term relationship	3 (30%)	3 (33%)	2 (13%)	5 (28%)	
Divorced/widow	2 (20%)	1 (11%)	4 (27%)	3 (17%)	
Right handed	10 (100%)	7 (78%)	12 (80%)	15 (83%)	0.87
Education (years)	12.8±1.3	13.7±2.4	13.6±1.9	15.6±4.6	0.08
Functioning level					
Student or working/unemployed, disabled or retired	5 (50%)	7 (78%)	8 (53%)	15 (83%)	0.067
	5 (50%)	2 (22%)	7 (47%)	3 (17%)	
Clinical characteristics					
Diagnosis					0.201 [1]
Major depression	6 (60%)	9 (100%)	11 (73%)	0 (0%)	
Bipolar disorder	3 (30%)	0 (0%)	4 (27%)	0 (0%)	
Depression NOS	1 (10%)	0 (0%)	0 (0%)	0 (0%)	
Depression (BDI)	34.9±16.7 [d]	39.8±7.2 [c,d]	31.2±7.9 [b,d]	1.5±1.7 [a,b,c]	<0.001
Anxiety (BAI)	23.0±17.1 [d]	28.8±7.5 [d]	24.0±10.7 [d]	2.8±3.8 [a,b,c]	<0.001
Hopelessness (BHS)	10.3±1.6 [d]	10.7±1.7 [d]	10.1±2.2 [d]	8.6±0.9 [a,b,c]	0.005
Individuals on medications					
Antidepressants	4 (40%)	5 (56%)	7 (47%)	0 (0%)	0.001
Mood stabilizers	3 (30%)	1 (11%)	1 (7%)	0 (0%)	
Antipsychotic drugs	1 (10%)	3 (33%)	4 (27%)	0 (0%)	
Benzodiazepines	0 (0%)	0 (0%)	3 (20%)	0 (0%)	
Sleep	1.9±1.0 [d]	2.1±.7 [d]	1.9±.7 [d]	.3±.5 [a,b,c]	<0.001
Childhood trauma (CTQ)					
Emotional Abuse	12.0±6.6	14.3±7.0 [d]	10.8±5.6	7.2±3.5 [b]	0.011
Physical Abuse	9.7±5.9	11.9±6.2 [d]	9.9±4.0	6.3±1.7 [b]	0.013
Sexual Abuse	12.5±7.6	9.0±8.4	7.9±5.9	7.1±5.0	0.199
Emotional Neglect	14.3±7.1 [d]	13.2±5.0 [d]	13.8±5.0 [d]	7.0±2.9 [a,b,c]	<0.001

	Attempters	Ideators	Non-Suicidal Depressed	Healthy controls	Adjusted p
Physical Neglect	9.2±3.8	7.0±1.9	7.9±3.6	6.1±2.1	0.06
Total	57.3±10.6 [d]	54.3±10.4 [d]	47.3±9.5	34.7±8.7 [a,b]	0.005
Trail Making A (s)	25.0±7.7	24.0±6.6	24.5±7.2	20.2±5.7	0.202
Suicide related measures					
Presence of suicidal ideation	4 (40%)	8 (89%)	0 (0%)	0 (0%)	<0.001 [1]
Severity of suicidal ideation	1.0±1.6 [c,d]	1.5±1.0 [c,d]	0.0±0 [a,b]	0.0±0.0 [a,b]	<0.001
Lifetime suicide attempts	10 (100%)	4 (44%)	6 (40%)	0 (0%)	0.006 [1]
Number of suicide attempts	2.8±2.2 [b,c,d]	0.4±0.5 [a]	0.6±0.2 [a]	0.0±0.0 [a]	<0.001
Negative reaction to Social exclusion	70.0	63.6	75.0	68.4	0.326
Pain processing					
Pressure pain threshold	13.7±4.5 [b,c,d]	9.8±4.6 [a]	10.2±5.1 [a]	8.8±3.2 [a]	0.041
Psychache	42.4±18.2 [b, d]	53.9±8.4 [a,c,d]	34.9±9.6 [b,d]	15.5±3.7 [a,b,c]	<0.001
Current physical pain	1.8±2.7	0.8±1.2	1.8±2.5	0.5±1.0	0.175
Usual physical pain in last 15 days	2.9±2.9 [d]	1.8±1.7	2.9±2.6 [d]	0.4±0.9 [a,c]	0.004
Maximal physical pain in last 15 days	4.1±3.9 [d]	2.9±3.1	3.9±2.4 [d]	0.8±1.0 [a,c]	0.003
Current psychological pain	7.2±3.0 [c,d]	6.7±2.6 [c,d]	3.9±2.8 [a,b,d]	0.2±0.9 [a,b,c]	<0.001
Usual psychological pain in last 15 days	7.3±3.1 [c,d]	7.7±2.6 [c,d]	4.9±2.1 [a,b,d]	0.7±2.1 [a,b,c]	<0.001
Maximal psychological pain in last 15 days	8.2±3.2 [c,d]	8.7±2.1 [c,d]	6.3±2.6 [a,b,d]	1.1±2.1 [a,b,c]	<0.001
Suicidal Ideas	5.0±3.8 [c,d]	3.8±3.1 [c,d]	0.8±1.9 [a,b]	0.0±.0 [a,b]	<0.001

Mean ± standard deviation

ANOVA was performed for all demographic variables. GLM with correction for age, gender, race, marital status, education years and functioning level was performed to compare all clinical variables between the four groups, except for * Yates chi square

[a] compared to Attempters group;

[b] compared to Ideators group;

[c] compared to depressed non-suicidal group;

[d] compared to healthy control group;

[1] Chi square between Attempters, Ideators and depressed non-suicidal groups