Perception of social inclusion/exclusion and response inhibition in adolescents with past suicide attempt: a multimodal task-based fMRI study

Fabrice Jollant

fabrice.jollant@universite-paris-saclay.fr

Paris-Saclay University https://orcid.org/0000-0001-5809-4503

Anthony Gifuni

Stanford University https://orcid.org/0000-0003-2418-5591

Fabricio Pereira

Mallar Chakravarty

Douglas Mental Health Institute, Montréal, Canada

Martin Lepage

McGill University https://orcid.org/0000-0003-4345-6502

Henry Chase

University of Pittsburgh

Marie-Claude Geoffroy

Université de Montréal

Eric Lacourse

Mary Phillips

University of Pittsburgh School of Medicine https://orcid.org/0000-0003-4958-1291

Gustavo Turecki

McGill University https://orcid.org/0000-0003-4075-2736

Johanne Renaud

Article

Keywords: Adolescent, Attempted Suicide, Functional Neuroimaging, Social Exclusion, Executive Function

Posted Date: January 5th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2271723/v1

Additional Declarations: The authors have declared there is **NO** conflict of interest to disclose

Version of Record: A version of this preprint was published at Molecular Psychiatry on February 29th, 2024. See the published version at https://doi.org/10.1038/s41380-024-02485-w.

Abstract

The occurrence of suicidal behaviors increases during adolescence. Hypersensitivity to negative social signals and deficits in cognitive control are putative mechanisms of suicidal behaviors, which necessitate confirmation in youths. Multidomain functional neuroimaging could enhance the identification of patients at suicidal risk beyond standard clinical measures. Three groups of adolescents (N = 96; 78% females, age = 11.6–18.1) were included: patients with depressive disorders and previous suicide attempts (SA, *n* = 29); patient controls with depressive disorders but without suicide attempt (PC, *n* = 35); and healthy controls (HC, *n* = 32). We scanned participants with 3T-MRI during social inclusion/exclusion (Cyberball Game) and response inhibition (Go-NoGo) tasks. Neural activation was indexed by the blood-oxygenation-level dependent (BOLD) of the hemodynamic response during three conditions in the Cyberball Game (“Control condition”, “Social Inclusion”, and “Social Exclusion”), and two conditions in Go-NoGo task (“Go” and “NoGo” blocks). ANCOVA-style analysis identified group effects across three whole-brain contrasts: 1) NoGo vs. Go, 2) Social inclusion vs. control condition, 3) Social inclusion vs. control condition). Normalized contrasts in significant clusters were used to train a support vector machine-based classifier with a stratified 5-fold cross-validation, and diagnostic performance was assessed. In line with previous adult studies, we found that SA had lower activation in the left insula during social inclusion vs. control condition compared to PC and HC. We also found that SA compared to PC had higher activity in the right middle prefrontal gyrus during social exclusion vs. control condition, and in bilateral precentral gyri during NoGo vs. Go conditions. Task-related measures (Self-reported emotional reactivity in the Cyberball Game, response times and number of errors in the Go-NoGo Task) did not discriminate between groups. Moreover, while clinical data (Self-reported depression and impulsivity scores) yielded moderate accuracy (Accuracy: 70%/ Area Under Curve: 0.81), activity during Go-NoGo (81%/0.90), Cyberball Game (89%/0.90), or a combination (88%/0.95) significantly enhanced identification of past suicidal behaviors. In conclusion, adolescent suicidal behaviors are likely associated with neural alterations across multiple domains. Alterations in the processing of social perception and response inhibition may underlie the development of suicidal crises, from onset with social triggers to susceptibility to act out. Neuroimaging should be further tested as a tool to predict suicidal behavior.

1. Introduction

Adolescent suicidal behaviors are increasingly recognized as a leading public health concern [1, 2]. Suicide ranks as the second or third leading cause of youth mortality worldwide [3], and rates have tended to increase in recent years in the USA and Canada [4, 5]. Alarmingly, non-fatal suicidal ideation and behaviors during adolescence have a prevalence of 12% and 4%, respectively [6, 7]. Adolescence is associated with an abrupt increase in suicidal thoughts and behaviors (STB) [7, 8], which later increases the risk for psychological difficulties [9] and STB in adulthood [10]. During the recent COVID-19 pandemic, an important increase in STB in adolescents but not in adults has been observed in several countries [11,

12]. Despite the burden of adolescent STB, our understanding of adolescent STB neural basis remains rudimentary, limiting preventive and therapeutic approaches.

Clinical evaluation to predict suicidal behavior notoriously lack accuracy, and the use of historical and self-reported data provides marginal improvement to prognostic models [13, 14]. Psychiatric research has emphasized the importance of "biomarkers" as a stepping stone toward developing predictive tools and facilitating personalized care [15]. With its ability to identify brain structural and functional alterations correlating with psychopathology, neuroimaging has emerged as a potential tool to provide biomarkers associated with suicide risk [16]. Most neuroimaging studies have probed brain alterations associated with suicide risk in adult populations [17–20], with studies in adolescents recently increasing in number [21]. To date, a few neuroimaging studies reported on single functional neural modalities, identifying disparate processes linked with STB, including facial emotional processing [22], self-referencing [23], and social cognition [24]. However, single neuroimaging modalities might be insufficient to capture fully the underlying neural predisposition to adolescent STB. In the current study, we jointly examined two distinct functional domains that might both contribute to adolescent suicidal risk from a painful social situation to the emotional and behavioral response: sensitivity to social inclusion/exclusion and response inhibition.

Several theories of suicide recognize that the feeling of social disconnection is an important precipitant of STB [25–27]. From puberty to adulthood, social relationships become increasingly salient for adolescents [28]. Numerous epidemiological and clinical evidence suggests that social exclusion, peer victimization, and cyberbullying contribute to adolescent STB [29–32]. One of the most validated paradigms to investigate the neural correlates associated with social exclusion is the fMRI Cyberball Game [33, 34], a virtual ball-tossing game simulating inclusion and exclusion [35]. While most research has examined the neural correlates of social exclusion among healthy subjects [34, 36], fewer studies have addressed patients with STB. A study in adult females showed altered activity in the left insula and supramarginal gyrus in patients with past suicide attempt vs. control patients during exclusion vs. inclusion [37]. One study in adolescents with depression and non-suicidal self-injury, a behavior overlapping with suicidal behaviors [38], showed elevated activation of the medial and ventrolateral prefrontal cortex during social exclusion relative to inclusion (Groschwitz et al., 2016). Finally, in a sample of adolescents with suicide ideation, another study [39] revealed that the subgroup of adolescents with recent suicide attempts had elevated activity in the anterior cingulate cortex and lateral prefrontal cortex (PFC) during any social interaction, including periods of inclusion and exclusion. Given the heterogeneity of these samples and their small sizes, these findings need further exploration and replication. It also remains unclear whether these anomalies related to social processes correlate with other cognitive processes related to suicidality, such as cognitive control.

Cognitive control, the ability to flexibly orient attention to goal-relevant information and discard irrelevant information, has been implicated in the suicidal transition from suicidal ideas to acts [40–42]. Cognitive control is notably instrumental to efficient regulation of emotions [43]. In adolescents, however, the association between cognitive control and suicidal behaviors is still unclear [44], which might be

explained by at least two reasons. First, suicidal behaviors are notoriously heterogeneous, with some suicidal attempts done with minimal premeditation, while others are planned over several days or weeks [45]. Second, adolescence is characterized by rapid developmental shifts in cognitive control [46]. Adolescents' cognitive skills are typically characterized by higher variability between assessments and lacking the flexibility seen in adulthood [47]. Substantial empirical evidence shows that immaturity in cognitive control systems predisposes youth to impulsive sensation-seeking and riskier decision-making [48, 49]. A common paradigm to investigate neural correlates of cognitive control is the Go-NoGo Task [50], which is not only sensitive to age-related maturation [51] but also disorder-related alterations [52]. One previous study in a small sample [53] found that adolescents with past suicide attempts exhibited decreased neural activation in the right anterior cingulate cortex compared to depressed controls, but not compared to healthy controls.

In the current study, the Cyberball Game and Go-NoGo tasks during fMRI in three groups: depressed adolescents with past suicidal behaviors, depressed adolescents without past suicidal behaviors, and healthy controls. We expected to find neural disturbances in each functional domain in adolescents with past suicidal behaviors compared to control groups, including in regions involved in emotional and mentalizing processes, such as the anterior cingulate cortex, the striatum, the insula, or the precuneus; and in cognitive control regions, such as the lateral prefrontal cortex [17]. Additionally, we explored the potential diagnostic utility of neuroimaging disturbances using either linear regression or supervised machine learning classifiers. We posited that each task-based neuroimaging modality would provide superior diagnostic accuracy compared to clinical data such as depressive symptoms or self-reported impulsivity. Furthermore, we expected that combining functional domains would be better than single domains and that using supervised machine learning methods would improve the identification of adolescents with past suicidal behaviors.

2. Methods

2.1 Participants

From September 2012 to January 2019, three groups of adolescents (N = 104) aged 11 to 18 years were recruited: 1) Adolescents with a depressive disorder and a history of at least one suicide attempt (SA; *n* = 30); 2) Adolescents with a depressive disorder without a lifetime history of suicide attempt (Patient controls, PC; *n* = 38); and 3) Adolescents without a personal history of psychiatric disorder or a suicide attempt (healthy controls, HC; *n* = 36).

A suicide attempt was defined as any self-injurious behavior carried out with the intent to die [54]. This did not include aborted suicide attempts (i.e., halted by oneself), interrupted suicide attempts (i.e., halted by someone), or non-suicidal self-injuries. Depressive disorders, defined by DSM-IV criteria [55], included major depressive disorders, dysthymia, and depressive disorder not otherwise specified.

Participants with a depressive disorder (SA and PC) were primarily recruited from a third-line psychiatric clinic specialized in adolescent depressive disorders (at the Douglas Mental Health University Institute, Montreal, Canada), with additional cases recruited from affiliated community clinics. Access to these specialized psychiatry services is limited to patients aged below 18 years. HC were recruited from the community through advertisements posted in schools, local clinics, youth centers, and groups of parents on social media. HC were initially screened through a phone interview by a trained research assistant to exclude adolescents with a history of psychiatric disorders or a suicide attempt.

Exclusion criteria included neurological disorders (e.g., epilepsy, brain tumor), traumatic brain injury (> 1 min loss of consciousness, neuroimaging anomaly, or persistent post-concussive symptoms), autistic spectrum disorder, bipolar disorders, psychotic disorders, intelligence quotient (IQ) less than 70, pregnancy, and any contraindication for magnetic resonance neuroimaging (e.g., dental apparatus). A family history of suicidal behavior was an additional exclusion criterion for the HC group (but not the SA or PC groups) because of evidence that some neural phenotypes are transmitted within families with suicide histories [56, 57]

Neuroimaging data were not available for 5 participants (2 PC and 3 HC) either due to claustrophobia (n = 1), refusal (n = 2), or corrupted or irretrievable data (n = 2). Three additional participants (1 SA, 1 PC, 1 HC) were excluded from analyses due to poor data quality (see below for quality check criteria). Hence, after exclusion and missing data, the final analyzed sample (N = 96) included 29 SA, 35 PC, and 32 HC.

The research protocol was approved by the Douglas Institute Research Ethics Board (Protocol 12/20). Consent was provided by at least one parent or legal guardian, and all adolescents assented to the experiment. All participants were compensated when completing the assessment procedure (50 CAD).

2.2 Assessment

Assessments were completed in two or three visits, which included clinical and neuropsychological assessments and a neuroimaging session performed within the same week. Suicidal behaviors were assessed with the Suicide History Questionnaire [see Appendix in 58], a clinical interview with a child and adolescent psychiatrist (JR), and cross-validation with notes from patients' medical files (reviewed by AJG). Psychiatric disorders were characterized by the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime [59, K-SADS-PL; 60]. Current depressive symptoms were measured with the Beck Depression Inventory-II [BDI-II, 61]. Full-scale IQ was measured using the Wechsler Intelligence Scale for Children − 4th edition [WISC-IV; 62] in participants younger than 17 years and with the Wechsler Adult Intelligence Scale − 4th edition [WAIS-IV; 63] for participants aged 17–18 years. Self-reported impulsivity was assessed with the Barratt Impulsivity Scale [BIS-11; 64].

2.3 Imaging procedure

2.3.1 Description of tasks

Cyberball Game. The Cyberball Game is a computer ball-tossing game seeking to simulate social exclusion [33, 35, 65]. Through instructions given in the scanner, participants were invited to play online with two other players, which were presented as real, although they were pre-programmed. Participants were represented by a pair of hands in the lower center portion of the screen, while other players were represented by animated cartoons next to a named profile picture in each upper corner of the screen. After receiving the virtual ball, subjects could throw it to either player by selecting one of two buttons on a remote control in their right hand. The Cyberball Game consisted of three rounds lasting 2:30 minutes following fixed order: 1) Passive viewing, 2) Social inclusion, 3) Social exclusion. In the first round ("Passive viewing"), participants were told that a connection problem prevented them from joining the game and that they were to watch the two other players exchange the ball. This first round serves as a baseline for the following rounds and aims to increase the realism of the task. In the second round ("Social inclusion"), participants receive the ball randomly one-third of the time and can throw back the ball to either player. The third round ("Social exclusion") starts as the second one, but after 60 seconds and without any warning, the other players stop throwing the ball toward the participant. The total duration of the task was 10 minutes. After the scanning session, the distress induced by social exclusion was documented with the Need-Threat Scale [NTS; 66, 67], which includes ratings of self-esteem (e.g., "I felt liked"), belongingness (e.g., "I felt rejected"), meaningful existence (e.g., "I felt invisible"), and control (e.g., "I felt powerful"), scaled from 1 (not at all) to 5 (very much). Items were reverse-coded when appropriate and averaged to create a composite score. After completing the NTS, participants were debriefed about the task.

Go-NoGo Task. Cognitive inhibition was tested with a classical version of the Go-NoGo task [68], implemented in E-Prime 2.0.10.182 (USA). The task comprised a block-design paradigm in which participants were shown a total of 144 letters across 6 blocks for a total duration of 6.1 minutes. Trials were distributed in 2 block types: 3 "Go" blocks (Block A), and 3 "NoGo" blocks (Block B), presented in an ABBAAB order. In "Go" blocks, participants were instructed to press a button in response to visually presented letters using their right index finger as quickly as possible. In "NoGo" blocks, participants were instructed to avoid pressing the button to a non-target letter (letter X), while still pressing the button in response to target letters (i.e., letters other than X). Each block (either "Go" or "NoGo") started with a 20-second blank-screen resting period and 5-second instructions followed by 24 trials. Each trial consisted of a black fixation cross on a white screen followed by a letter. The duration of the fixation cross varied between 700, 900, 1100, or 1300 milliseconds, randomized to prevent habituation, with 6 trials of each duration resulting in an average of 1000 milliseconds. Letters (target or non-target) were presented for 500 milliseconds on a white screen. In each block ("Go" or "NoGo"), 12 target letters (50%) and 12 non-target letters (50%) were presented in a pre-determined pseudorandomized order. For all trials, reaction time (time between stimulus onset and button press response), omission errors (i.e., not responding to a target error), and commission errors (i.e., responding to a non-target letter during a "NoGo" Block) were recorded. The sum of omission errors is usually interpreted as indicative of attentional or speed deficits, whereas commission scores would reflect inhibition deficits [69]

2.3.2 Imaging Acquisition and preprocessing

Magnetic resonance imaging (MRI) scans were acquired at the Douglas Cerebral Imaging Centre using a Siemens Magnetom Trio (Tim System 3T, MR B17) scanner equipped with a 12-channel head coil. The complete scanning procedure (see **Supplements -** *Scanning Protocol* and *Neuroimaging acquisition* for full description) included a high-resolution T1 anatomical scan (repetition time [TR] = 2300 ms; echo time [TE] = 2.98 ms; inversion time [TI] = 900 ms; flip angle [FA] = 9°; field of view [FOV] = 256 mm; voxel size [VS] = 1x1x1 mm; matrix =: 256x256, acquisition time [T] = 9.23 min), task-based functional MRI with a socio-emotional paradigm (Cyberball Game; TR = 3000ms; TE = 25ms; FA = 90°, FOV = 200 mm; matrix = 64x64; VS = 3.1x3.1x4.0 mm; T = 5.5 min) and a cognitive control paradigm (Go-NoGo task; TR = 2090ms; TE = 30 ms ; FA = 90°; FOV = 224 mm; matrix: 64x64; voxel = 3.5x3.5x3.5 mm; T = 6.27 min). The functional images were quality controlled and preprocessed using fMRIPrep 1.4.1 [70–72].

2.4 Statistical analyses

2.4.1 Demographic and clinical differences

Statistical analyses were performed in R v3.6.0 [73], implemented in Rstudio v1.1.383 [74]. Clinical and behavioral continuous data were compared across groups with 3-way ANOVAs, and Tukey's HSD Post Hoc tests for bivariate comparisons. Categorical group data were compared with chi-square tests. Correlations between clinical measures and brain activity extracted from significant clusters were computed with Spearman's rank-order correlation. The alpha level was set a priori at p = 0.05 with Bonferroni correction based on the number of significant clusters in across both fMRI tasks.

2.4.2 Neuroimaging analysis

See the **Supplements -** *Anatomical data preprocessing* and *Functional data preprocessing* for the complete neuroimaging analysis procedure. In brief, we derived within-subject contrasts maps of interest using a block-designed models. For the Cyberball Game, we calculated an inclusion and an exclusion contrast, using the "Passive viewing" condition as the control condition. For the Go-NoGo Task, the contrast of interest was NoGo vs. Go blocks, reflecting activity when the task demands cognitive inhibition as opposed to a simple motor response. Between-participants whole-brain analyses were conducted with 3dMVM in AFNI version 19.3.11 [75]. Given the effect of age, sex, and IQ on neural activity and cortical anatomy [76, 77], the group analyses controlled for these covariates. Significance thresholds were set at voxel level p-uncorrected < 0.005. To minimize false-positives, a more stringent level at p < 0.001 was also tested. The resulting statistical maps were corrected for multiple comparisons at p-corrected < 0.05 using AFNI's 3dClustsim algorithm. Noise volume was simulated assuming a spatical autocorrelation function (ACF) given by a mixed-model of the form a*exp(-r*r/(2*b*b))+(1-a)*exp(-r/c), where a, b, c parameters were estimated by 3dFWHMx using residual timeseries leftovers post-GLM fitting. The cluster size surviving whole brain correction, using a grey-matter mask, was determined to be k > 517 for Cyberball Game and k > 504 for Go-NoGo. Post-hoc pairwise analyses were only conducted in clusters that were found to be significant at the three-group comparison level in order to limit false positives. Normalized cluster contrast were extracted for correlational analyses with clinical, behavioral, and neuroimaging data.

2.4.3 Diagnostic accuracy provided by multidomain functional MRI

Classification models identifying participants with past suicide attempts were computed with a support vector machine (SVM) based-classifier, a supervised learning method already tested in suicide prediction [78]. We adopted an SVM-based model using a linear kernel, which calculates high-dimension linear decision boundaries (“hyperplanes”) using the “max-margin principle”. For comparison, we computed a conventional classification model using a standard logistic regression. The analysis aimed to classify suicidal (SA) vs. non-suicidal participants (PC and HC). Two baseline models were computed: 1) Only sociodemographic data (age, sex, IQ), 2) Sociodemographic and clinical data (age, sex, IQ, BDI, and BIS total scores). Models with extracted fMRI contrast coefficients from single or combined tasks were built on top of each baseline model for a total of 8 models. Models only used contrast coefficients from significant clusters at the three-group level at $p < 0.005$. The performance of each model was estimated via a stratified 5-fold cross-validation. Classification accuracy and receiver operating characteristic curves (ROC) area under the curve (AUC) were averaged across each fold ($k = 5$) and compared with baseline models with Welch’s t-tests. Training and testing classification models were implemented in Scikit-learn (v0.23.1; [79]), a machine learning toolkit for python.

3. Results

3.1 Group sociodemographic and clinical characteristics

Sociodemographic and clinical characteristics of the three groups are presented in Table 1. Groups were broadly similar, notably SA and PC. See **sTable 1** for medication use and dose ranges.

Table 1
Comparison of sociodemographic, clinical and task-related behavioral variables between the three groups

	Suicide Attempt	Patient Controls	Healthy Controls	Group comparison		
	(N = 29)	(N = 35)	(N = 32)			
				χ^2/ F-stat	p-value	Post-hoc comparison
Sex						
Female, n (%)	25 (86)	28 (80)	22 (73)	2.8 (df = 2)	0.24	-
Age (years)						
Mean (sd)	16.3 (1.0)	16.0 (1.5)	15.3 (1.4)	4.5 (df = 2,93)	0.01*	SA > HC
Race/Ethnicity						
Asian, n (%)	< 5	< 5	< 5	0.3 (df = 2)	0.9	
Black, n (%)	< 5	0	< 5	1.7 (df = 2)	0.4	
White, n (%)	22 (76)	25 (71)	19 (69)	2.1 (df = 2)	0.4	
First Nations, n (%)	< 5	5 (14)	< 5	6.4 (df = 2)	0.04*	PC > SA,HC
Latinx/Hispanic, n (%)	< 5	0	0	4.7 (df = 2)	0.09	
Multiethnic, n (%)	< 5	< 5	8 (25)	6.9 (df = 2)	0.03	HC > SA,PC
Parental Education						
Elementary, n (%)	8 (28)	< 5	0 (0)	11.6 (df = 2)	0.003*	SA > PC,HC
High School, n (%)	5 (18)	5 (14)	7 (23)	0.8 (df = 2)	0.7	-
College, n (%)	< 5	< 5	6 (19)	1.6 (df = 2)	0.4	-
University, n (%)	12 (43)	24 (69)	18 (58)	4.8 (df = 2)	0.09	-
Intelligence Quotient (WISC/WAIS)						

	Suicide Attempt	Patient Controls	Healthy Controls	Group comparison		
	(N = 29)	(N = 35)	(N = 32)			
Total, Mean (sd)	102.3 (15.9)	108.4 (13.7)	111.0 (12.7)	2.45 (df = 2,93)	0.1	-
Beck Depression Scale - II						
Total, Mean (sd)	30.2 (12.7)	25.6 (12.3)	5.9 (5.8)	46.4 (df = 2,93)	< 0.001*	SA,PC > HC
Barratt Impulsivity Scale						
Total, Mean (sd)	73.4 (9.1)	65.26 (11.1)	58.9 (11.0)	10.4 (df = 2,93)	< 0.001*	SA,PC > HC
Attention, Mean (sd)	20.5 (3.4)	17.4 (3.5)	14.8 (4.3)	15.5 (df = 2,93)	< 0.001*	SA > PC > HC
Motor, Mean (sd)	21.4 (4.6)	19.5 (4.3)	18.4 (3.7)	3.0 (df = 2,93)	0.06	-
Non-Planning, Mean (sd)	30.5 (3.6)	28.4 (5.6)	25.7 (5.7)	6.0 (df = 2,93)	0.003	SA,PC > HC
NSSI Lifetime history						
NSSI lifetime history, n (%)	25 (86)	22 (63)	5 (16)	31.2 (df = 2)	< 0.001*	SA,PC > HC
Psychiatric diagnosis						
MDD, n (%)	14 (48)	25 (71)	-	2.7 (df = 1)	0.1	-
Dysthymia, n (%)	5 (17)	8 (23)	-	0.1 (df = 1)	0.8	-
DDNOS, n (%)	11 (38)	< 5	-	4.8 (df = 1)	0.03*	SA > PC
Anxiety disorder/PTSD, n (%)	12 (41)	18 (51)	-	0.6 (df = 1)	0.4	-
Eating Disorder, n (%)	< 5	< 5	-	0.1 (df = 1)	0.8	-
ADHD, n (%)	9 (32)	< 5	-	2.8 (df = 1)	0.09	-
Psychotropic medication						
Antidepressant, n (%)	15 (52)	20 (57)	-	6.0 (df = 1)	0.5	-

	Suicide Attempt	Patient Controls	Healthy Controls	Group comparison		
	(N = 29)	(N = 35)	(N = 32)			
Mood Stabilizer, n (%)	< 5	< 5	-	0.02 (df = 1)	0.9	-
Low-Dose Neuroleptic, n (%)	12 (41)	8 (23)	-	1.7 (df = 1)	0.2	-
Benzodiazepine, n (%)	< 5	< 5	-	0 (df = 1)	1	-
Stimulant, n (%)	8 (28)	< 5	-	6.1 (df = 1)	0.01*	SA > PC
Task-related variables						
Go-NoGo : **Response Time (ms)**						
Go Blocks, Mean (sd)	269 (36)	257 (34)	278 (31)	3.4 (df = 2,92)	0.04*	PC < HC
NoGo Blocks, Mean (sd)	301 (50)	284 (33)	310 (34)	4.2 (df = 2,92)	0.02*	PC < HC
Go-NoGo : **Errors (Count)**						
Omission Errors, Go Blocks	9.8 (10.1)	8.1 (6.2)	10.1 (9.0)	0.5 (df = 2,92)	0.6	-
Omission Errors, NoGo Blocks	3.5 (4.9)	2.9 (2.6)	3.0 (3.0)	0.3 (df = 2,92)	0.7	-
Commission Errors, NoGo Blocks	6.7 (4.4)	8.4 (3.4)	6.2 (3.3)	3.7 (df = 2,92)	0.03*	PC > HC
Cyberball - Need-Threat Scale						
Belonging, Mean (sd)	12.7 (4.3)	14.1 (3.2)	16.3 (3.9)	6.6 (df = 2,87)	0.002	SA,PC < HC
Self-Esteem, Mean (sd)	13.1 (4.4)	13.6 (3.9)	18.2 (4.0)	14.5 (df = 2,87)	< 0.001*	SA,PC < HC
Significant Existence, Mean (sd)	12.8 (5.2)	14.4 (3.5)	17.4 (3.2)	10.0 (df = 2,87)	< 0.001*	SA,PC < HC
Sense of Control, Mean (sd)	10.1 (3.7)	11.0 (2.9)	13.4 (4.0)	7.5 (df = 2,87)	< 0.001*	SA,PC < HC
Total, Mean (sd)	48.7 (14.8)	53.3 (10.4)	65.5 (12.5)	7.7 (df = 2,87)	< 0.001*	SA,PC < HC

Among SA, the average time between the last suicide attempt and the scanning session was 13.5 months (standard deviation (sd) = 12.0, range=[0.9–42.3]). The average number of suicide attempts was 2.0 (1.6, [1–7]), and the average age at the first suicide attempt was 14.3 years (1.3, [10.6–16.6]).

Participants with missing neuroimaging data (N = 8) did not differ from the rest of the sample (N = 96) in terms of age, sex, or race/ethnicity but not parental education (**sTable 2**).

3.2 Cyberball Game

Both patient groups had lower post-task NTS scores than HC, suggesting higher emotional impact in patients in general unrelated to a history of suicide attempt (**see** Table 1). Correlations between NTS scores and sociodemographic and clinical variables are presented in **sTables 3 and 4.**

Neuroimaging results for the Cyberball Game are presented in Table 2 **and** Fig. 1 (at voxel-correction $p < 0.005$) and **sTable 5** (at $p < 0.001$). For the inclusion vs. control condition contrast, a significant group effect was detected in the left insula. Post-hoc analyses showed lower insular activity in SA compared to both PC and HC. For the exclusion vs. control condition contrast, a significant group effect was found in three clusters located in the left and right inferior frontal gyrus, and the right middle/superior frontal gyrus. In SA vs. PC, lower activation was found in the right inferior frontal gyrus and higher activation in the right middle/superior frontal gyrus. In SA vs. HC, lower activation was found in the left and right inferior frontal gyri. Finally, in PC vs. HC a lower activation was found in the left inferior frontal gyrus and the right middle/superior frontal gyrus. At a more stringent voxel threshold ($p < 0.001$), findings remained significant in the left insula (Inclusion contrast) and the right superior frontal gyrus (Exclusion contrast).

Table 2
Group difference in fMRI activity elicited by the Cyberball Game and Go-NoGo Task (3 contrasts, voxel threshold p < 0.005; Cluster correction p < 0.05)

			Size	Peak voxel	Statistics	
Region	**Brodmann Area**	**Side**	**Voxels (n)**	**Coordinates (MNI)**	**(F/t-stat)**	**Direction of effects**
Contrast: Inclusion - Control						
Insula †	BA13	L	629	[-36,-6,8]	F = 12.3	SA < PC, SA < PC, PC = HC
Contrast: Exclusion - Control						
Inferior Frontal Gyrus	BA45	L	660	[-50,24,14]	F = 11.9	SA = PC, SA < HC, PC < HC
Middle/Superior Frontal Gyrus †	BA9, BA10	R	593	[34, 40, 32]	F = 11.5	SA > PC, SA = HC, PC < HC
Inferior Frontal Gyrus	BA10	R	520	[33, 44, 4]	F = 9.9	SA < PC, SA < HC, PC = HC
Contrast: NoGo vs. Go						
Precentral Gyrus †	BA6, BA9	R	3,409	[37, 1, 27]	F = 15.6	SA > PC, SA > HC, PC = HC
Precentral Gyrus †	BA6	L	1,549	[-47,-6,32]	F = 9.2	SA > PC, SA = HC, PC < HC
Inferior Frontal Gyrus	BA46	L	690	[-39,31,8]	F = 6.9	SA = PC, SA > HC, PC > HC
Fusiform Gyrus	BA20,BA36	R	512	[46,−35,−27]	F = 7.7	SA = PC, SA > HC, PC = HC
† Cluster significant at voxel threshold p < 0.001; Cluster correction p < 0.05, cf. **sTable 5** for details.						
R = right, L = left; SA: Patient with past suicide attempt; PC: Patient controls; HC: Healthy controls						

Correlations between significant brain cluster activity and sociodemographic and clinical variables are presented in **sTables 3 and 4.** Left Insula activity in the inclusion-minus contrast correlated significantly total score on the NTS (ρ = 0.29, p corrected = 0.04), specifically with Belonging (ρ = 0.33, p corrected = 0.008) and Significant Existence (ρ = 0.34, p corrected = 0.007). Activity exclusion-related clusters did not correlate with NTS Score (**sTable 6**).

3.3 Go-NoGo Task

Behavioral performance is presented in Table 1. PC showed lower reaction times and more commission errors than HC. There was no difference between SA versus PC or HC. Correlations between behavioral performance and sociodemographic and clinical variables are presented in **sTables 3 and 4.**

Multivariate analysis, controlling for age, sex, and IQ, indicated group differences for the NoGo vs. Go contrast in four significant large clusters (see Table 2 **and** Fig. 1 at voxel-correction $p < 0.005$ and **sTable 4** at $p < 0.001$): the left and right precentral gyri, the left inferior frontal gyrus, and the right fusiform gyrus. Pairwise post-hoc comparisons showed higher activity in bilateral precentral gyri in SA vs. PC. Increased activity was also found in SA vs. HC in the left inferior frontal gyrus, the right precentral gyrus, the right fusiform gyrus. Finally, PC vs. HC had lower activity in the left precentral gyrus and higher activity in the left inferior frontal gyrus. Sensitivity analysis controlling for medication status, psychiatric diagnoses, or head motion (average framewise displacement) did not change the pattern of neural activity related to group effects. At a more stringent voxel threshold ($p < 0.001$), findings remained significant in both precentral clusters.

Correlations between significant brain cluster activity and sociodemographic and clinical variables are presented in **sTables 3 and 4.** Activity in the left precentral gyrus correlated significantly with response times in NoGo Blocks. No other correlation between group-discriminating clusters in the Go-NoGo Task correlated with behavioral outcomes on the task (**sTable 7**).

The correlation matrix between activation contrasts in the Cyberball Game and the GoNo-Go Task is presented in **Supplementary Fig. 1**. Activation in the left insula (Inclusion contrast) correlated negatively ($r=-0.32$, p uncorrected = 0.00002) with activity in the right precentral gyrus (GoNo-Go contrast).

3.4 Diagnostic accuracy provided by multimodal task-based fMRI

Classification performance is reported in Table 3 and ROC curves of all compared conditions are shown in Fig. 2. Classification models attempting to discriminate adolescents with past suicidal behaviors from the whole sample were built hierarchically using sociodemographic, clinical, single, or combined neuroimaging data. In line with our hypothesis, combining neuroimaging data extracted from significant clusters (Go-NoGo: Right and left precentral gyri, left inferior frontal gyrus, fusiform gyrus; Cyberball Game: Left insula, left inferior frontal gyrus, right middle/superior frontal Gyrus, right inferior frontal gyrus) from both tasks improved classification performance, both in terms of classification accuracy and AUC: Classification accuracy increased by approximately 20% and AUC increased by 0.25 compared to baseline models, indicating a significant enhancement in diagnostic power. The SVM classifier using combined neuroimaging data without clinical data provided the highest classification accuracy (92.6%) and highest AUC (0.96). Classification accuracy and AUC were not significantly different between models using combined vs. single neuroimaging modalities. Of note, clinical variables (BDI and BIS) did not significantly enhance classification on their own, and their inclusion did not enhance models with neuroimaging features. Finally, the SVM-based classifier did not significantly surpass conventional regression models.

Table 3
Classification performance of sociodemographic data, clinical data, and functional neuroimaging markers (single task or combined tasks) with either a logistic regression or a Support Vector Machine-based learning model.

	Statistical Model (5-fold Cross-Validation)			
Variables	**Logistic Regression**		**Support Vector Machine**	
	Accuracy (%/sd)	**AUC (sd)**	**Accuracy (%/sd)**	**AUC (sd)**
1. Baseline[1]	69.1 (6.2)	0.70 (0.09)	70.2 (2.3)	0.50 (0.23)
2. Clinical[2]	70.3 (9.57)	0.80 (0.10)	70.3 (8.3)	0.81 (0.10)*
3. GNG[3]	82.0 (5.2)*	0.87 (0.04)*	79.8 (5.0)*	0.87 (0.04)*
4. CB[4]	83.0 (6.0)*	0.90 (0.06)*	83.0 (6.0)*	0.89 (0.05)*
5 GNG + CB[5]	92.6 (2.5)**	0.95 (0.03)**	92.6 (2.5)**	0.96 (0.03)*
6. Clinical + GNG	83.0 (5.0)*	0.91 (0.04)**	80.9 (6.2)*	0.90 (0.05)*
7. Clinical + CB	87.19 (4.35)**†	0.93 (0.05)**	89.4 (4.6)**†	0.90 (0.06)*
8. Clinical + GNG + CB	86.3 (7.1)*†	0.95 (0.05)**†	88.4 (9.0)*†	0.95 (0.06)*†
Footnotes:				
1. Baseline variables: Age, sex, and IQ				
2. BDI and BIS Scores, with baseline variables				
3. Go-No-Go fMRI BOLD extracted signals in significant ROIs, with baseline variables				
4. Cyberball fMRI BOLD extracted signals in significant ROIs, with baseline variables				
5. Combined Go-No-Go and Cyberball fMRI BOLD extracted signals in significant ROIs, with baseline variables				
* $p < 0.05$ Compared to Baseline model (1)				
** $p < 0.005$ Compared to Baseline model (1)				
† $p < 0.05$ Compared to Clinical model (2)				
Abbreviations: CB: Cyberball Game, AUC: Area Under Curve, GNG: Go-NoGo Task; sd: Standard Deviation,				

4. Discussion

The objective of the current study was to identify task-related fMRI markers associated with past suicide attempts, assessing two putatively relevant aspects of adolescent suicidality: perception of social

inclusion/exclusion and cognitive control. In summary, our study revealed two major findings. First, we observed a set of neural disturbances during both social inclusion/exclusion and cognitive inhibition tests in adolescent suicide with past suicide attempt in comparison to both control groups. These alterations were mainly located in the left insula and prefrontal cortex for social perception and interaction; and motor and prefrontal cortices for inhibition of action (at a more stringent level of correction). Interestingly, behavioral performances (self-report of emotional feelings during the Cyberball Game and reactions times and omission/commission errors at the Go-NoGo task) were similar between both patient groups suggesting that functional MRI may yield finer properties than neuropsychological tests and questionnaires to discriminate patients with and without a personal history of suicide attempt. Second, activity in these significant brain clusters enhanced the identification of a past history of suicidal attempt, outperforming clinical and sociodemographic variables.

During the Cyberball Game, adolescent SA displayed distinct neural functional alterations in relation to both inclusion and exclusion conditions, as compared to PC and HC. In contrast to previous studies (Harm et al. 2019), we found that the set of anatomical regions distinguishing suicidal adolescents depended on the valence of social circumstances (i.e., inclusion or exclusion). In the inclusion situation, SA showed reduced neural activity in the left insula, a region involved in the salience network [80]. Decreased activity in left insula (although more posterior) during inclusion vs. control condition at the Cyberball Game was also found in adult females with past attempts (Olié et al, 2017). In our study, lower insular activity was associated with lower feeling of belongingness and having a less meaningful existence during perceived social exclusion. These two factors are in line with psychological risk factors associated with suicide [81], somewhat paralleling the concepts of “thwarted belongingness” and “perceived burdensomeness” found in the Interpersonal Theory of Suicide [27]. Thus, it is possible that the lower activation of the left insula during inclusion in SA may interfere with the normally reinforcing feelings associated with inclusive social interactions [82]. These findings may also reflect a lower ability of SA to feel connected to others. It may be hypothesized that in SA this may both limit their pleasantness of being with others and also their will to seek help when in difficulty. Reduced disclosure of suicidal ideas has indeed been associated with increased risk of social isolation and suicide attempt in adolescents [83, 84]. Of note, lower insular activity during inclusion was also correlated with higher depressive state, suggesting a significant effect of the negative mood state that may be stronger in individuals at risk of suicide.

In contrast to inclusion, social exclusion in SA was associated with increased activity in right middle/superior frontal gyrus (surviving at a more stringent correction level) and lower activity in the right inferior frontal gyrus compared to PC (and in the left inferior frontal gyrus compared to HC although activity also seems to be lower in SA than PC). These differences in prefrontal cortex activation point toward possible difficulties in regulating emotions and behaviors [85, 86]. Of note, activity in the left (but not right) inferior frontal gyrus during exclusion correlated negatively with depressive symptoms, suggesting that depression might again interfere with regulatory prefrontal control during social interaction. Previous studies using the Cyberball Game also observed alterations in prefrontal cortex activation during exclusion in adolescents with a history of suicide attempt or non-suicidal self-injury [39,

87]. Social processing abnormalities in the prefrontal cortex have also previously been described in SA, for instance while viewing angry faces in adults [88, 89] and adolescents [22]. Interestingly, while neuroimaging during exclusion was able to discriminate patients with and without a history of suicidal acts, this was not the case for the social threat questionnaire, questioning the limits of self-reports.

During the Go-NoGo Task, adolescent SA mainly exhibited greater bilateral activity in the precentral gyri – primary motor brain regions - compared to PC (surviving more stringent correction). We did not observe behavioral differences between SA and PC, only between patients and HC. Activity in these motor regions during the Go-NoGo task did not correlate with impulsivity measured with self-questionnaires. However, they were negatively correlated with response time in our study, suggesting that increased activity may lead to slower response times. The Go-NoGo task specifically demands inhibition of a prepotent motor response [68]. Increased activation in SA may therefore reflect excessive activity to achieve the same outcome, and, therefore indirectly inefficient functioning. Furthermore, these findings corroborate an earlier adolescent study (Pan et al. 2011) which also found that neural activity patterns during response inhibition discriminated between SA and PC, but that behavioral measures did not. Hence, functional markers might be more sensitive than neuropsychological measures.

We found that the activities of left insula during inclusion and right precentral gyrus during inhibition were correlated, suggesting a functional connection between the networks underlying social perception/interactions and cognitive inhibition. Overall, it could be hypothesized that in situation of stress and emotional disturbances (e.g., a depressive episode), this inefficient functioning of brain networks encompassing both the left insula and motor and precentral regions may translate into a lower feeling of social connectedness, lower ability for self-disclosure and help-seeking and inefficient emotional and behavioral regulation facilitating both the emergence of suicidal ideas and acting out. Recent studies have shown that suicidal behaviors are associated with the dysfunctional connectivity of various brain regions [90].

Finally, exploratory results from our study indicate that considering functional alterations related to cognitive and socio-emotional processing significantly enhanced the identification accuracy of adolescents with past suicidal behaviors from PC and SA. According to two classification performance metrics (ROC AUC, classification accuracy), neuroimaging modalities significantly improved baseline models that used sociodemographic data with or without clinical variables. It should be noted, however, that while the most accurate model was provided by the combination of both fMRI modalities without clinical variables (> 90% accuracy, > 95% AUC), the difference between combined models and single modalities was marginal. An important caveat is that the diagnostic validity of these functional markers were tested on the same cohort from which they were derived, which can lead to an overestimation of their effect [91]. Their combination within this sample might not be as effective as their combined use in an independent sample, where each neuroimaging modality might separately be less diagnostically efficacious [92]. We also found that an SVM-based learning method did not outperform conventional logistic regressions. While non-linear kernels with SVM, or other supervised learning methods such as decision trees might have provided better fit [78], logistic regressions already provided high diagnostic

utility. Deep learning methods are promising methods to integrate neuroimaging and clinical data to assess suicide risk, but they require large-size data for training [93].

We must highlight a few limitations of the current study. Firstly, even with a substantial number of participants with past suicidal behaviors, we may have lacked the statistical power to detect effects at more conservative levels of correction [94]. Our main results are based on a voxel-wise threshold of $p < 0.005$, which carries a higher likelihood of false-positives than a typically recommended voxel-wise threshold of $p < 0.001$ [95]. However, supplementary analyses at a threshold of $p < 0.001$ yielded significant and concordant results across all contrasts. Besides, these analyses did not account for the variability of cluster-size threshold across all brain regions. While our strategy to simulate noise volume with a mixed-model ACF is deemed acceptable, newer methods using randomization and permutation are considered more accurate at controlling false positive rates [96]. Second, participants had a wide age range (11–18), which probably introduced developmental variability in our analysis despite controlling for age. We previously reported structural brain differences across ages in this sample [58]. Third, despite recruiting in a relatively homogeneous second-line psychiatric clinic, several clinical heterogeneities still characterized our sample, including features of suicidal behaviors, psychiatric comorbidities, and environmental factors. These heterogeneities may prevent generalization to different populations. Finally, while controlling for medication status did not change our findings, we did not account for more complex pharmacological effects, such as dose effects, duration of treatment, and interactions.

In conclusion, our study revealed discrete sets of functional alterations associated with suicidal behaviors during social interactions and cognitive inhibition, two important features that underlie the development of a suicidal crisis. These alterations may furthermore enhance diagnostic identification of adolescents with previous suicide attempts. These findings highlight the complex mechanisms underlying suicidal behaviors. The capacity of neural measures to predict suicidal behavior beyond clinical and sociodemographic variables will have to be tested in large-scale longitudinal studies.

Abbreviations

SA: Patient with Past suicide Attempt; PC : Patient Controls; HC : Healthy Controls; df : degree of freedom; sd : standard deviation; ADHD: Attention Deficit Hyperactivity Disorder; DDNOS: Depressive Disorder Not Otherwise Specified; MDD: Major Depressive Disorder; NSSI: Non-suicidal Self-injury; WISC: Wechsler Intelligence Scale for Children; WAIS: Wechsler Adult Intelligence Scale.

Declarations

Acknowledgments

This research was financed by Manulife Research Fund in Teen Depression, which supports the Manulife Centre for Breakthroughs in Teen Depression and Suicide Prevention in Montréal, Canada. AJG was supported the Fonds de Recherche du Québec – Santé (FRQS/MSSS Resident Physician Health Research

Career Training Program). MMC was supported by a Junior 2 Research Scholar Salary from the FQRS. ML was supported by a Research Chair from FRQS and from a James McGill Professorship. MCG holds a Canada Research Chair Tier-2 and both JR and MCG are supported by the Fonds de recherche du Québec – Société et Culture research team on youth suicide prevention. The content is solely the responsibility of the authors.

We thank Daysi Zentner, Geneviève Laurent, and Léa Perret for their assistance with data collection and organization. Finally, we thank the participants and their families participating in this study as well as the clinicians involved with adolescents and their families (Theodora Mikedis, Jean-Chrysostome Zanga, Didier Blondin-Lavoie).

Conflict of interest statement

The authors declare no conflict of interest. The funding agencies played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Gordon JA, Avenevoli S, Pearson JL. Suicide Prevention Research Priorities in Health Care. JAMA Psychiatry. 2020;77:885–886.
2. Patton GC, Sawyer SM, Santelli JS, Ross DA, Afifi R, Allen NB, et al. Our future: a Lancet commission on adolescent health and wellbeing. The Lancet. 2016;387:2423–2478.
3. Mokdad AH, Forouzanfar MH, Daoud F, Mokdad AA, El Bcheraoui C, Moradi-Lakeh M, et al. Global burden of diseases, injuries, and risk factors for young people's health during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2016;387:2383–2401.
4. Ruch DA, Sheftall AH, Schlagbaum P, Rausch J, Campo JV, Bridge JA. Trends in Suicide Among Youth Aged 10 to 19 Years in the United States, 1975 to 2016. JAMA Netw Open. 2019;2:e193886–e193886.
5. Zulyniak S, Wiens K, Bulloch AGM, Williams JVA, Lukmanji A, Dores AK, et al. Increasing Rates of Youth and Adolescent Suicide in Canadian Women. Can J Psychiatry. 2021:07067437211017875.
6. Brezo J, Paris J, Tremblay R, Vitaro F, Hébert M, Turecki G. Identifying correlates of suicide attempts in suicidal ideators: a population-based study. Psychological Medicine. 2007;37:1551–1562.
7. Nock MK, Green JG, Hwang I, McLaughlin KA, Sampson NA, Zaslavsky AM, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA Psychiatry. 2013;70:300–310.
8. Orri M, Scardera S, Perret LC, Bolanis D, Temcheff C, Séguin JR, et al. Mental Health Problems and Risk of Suicidal Ideation and Attempts in Adolescents. Pediatrics. 2020. 8 June 2020. https://doi.org/10.1542/peds.2019-3823.

9. Goldman-Mellor SJ, Caspi A, Harrington H, Hogan S, Nada-Raja S, Poulton R, et al. Suicide attempt in young people: a signal for long-term health care and social needs. JAMA Psychiatry. 2014;71:119–127.
10. Geoffroy M-C, Orri M, Girard A, Perret LC, Turecki G. Trajectories of suicide attempts from early adolescence to emerging adulthood: prospective 11-year follow-up of a Canadian cohort. Psychol Med. 2020:1–11.
11. Jollant F, Blanc-Brisset I, Cellier M, Ambar Akkaoui M, Tran VC, Hamel J-F, et al. Temporal trends in calls for suicide attempts to poison control centers in France during the COVID-19 pandemic: a nationwide study. Eur J Epidemiol. 2022. 30 August 2022. https://doi.org/10.1007/s10654-022-00907-z.
12. Charpignon M-L, Ontiveros J, Sundaresan S, Puri A, Chandra J, Mandl KD, et al. Evaluation of Suicides Among US Adolescents During the COVID-19 Pandemic. JAMA Pediatrics. 2022;176:724–726.
13. Nock MK, Millner AJ, Ross EL, Kennedy CJ, Al-Suwaidi M, Barak-Corren Y, et al. Prediction of Suicide Attempts Using Clinician Assessment, Patient Self-report, and Electronic Health Records. JAMA Netw Open. 2022;5:e2144373.
14. Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X, et al. Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. Psychological Bulletin. 2017;143:187–232.
15. Oquendo MA, Sullivan GM, Sudol K, Baca-Garcia E, Stanley BH, Sublette ME, et al. Toward a Biosignature for Suicide. AJP. 2014;171:1259–1277.
16. Mann JJ, Rizk MM. A Brain-Centric Model of Suicidal Behavior. AJP. 2020;177:902–916.
17. Auerbach RP, Pagliaccio D, Allison GO, Alqueza KL, Alonso MF. Neural Correlates Associated With Suicide and Nonsuicidal Self-injury in Youth. Biological Psychiatry. 2021;89:119–133.
18. Jollant F, Lawrence NL, Olié E, Guillaume S, Courtet P. The suicidal mind and brain: a review of neuropsychological and neuroimaging studies. World J Biol Psychiatry. 2011;12:319–339.
19. Schmaal L, van Harmelen A-L, Chatzi V, Lippard ETC, Toenders YJ, Averill LA, et al. Imaging suicidal thoughts and behaviors: a comprehensive review of 2 decades of neuroimaging studies. Mol Psychiatry. 2020;25:408–427.
20. Campos AI, Thompson PM, Veltman DJ, Pozzi E, van Veltzen LS, Jahanshad N, et al. Brain Correlates of Suicide Attempt in 18,925 Participants Across 18 International Cohorts. Biol Psychiatry. 2021:S0006-3223(21)01174-4.
21. van Velzen LS, Dauvermann MR, Colic L, Villa LM, Savage HS, Toenders YJ, et al. Structural brain alterations associated with suicidal thoughts and behaviors in young people: results from 21 international studies from the ENIGMA Suicidal Thoughts and Behaviours consortium. Mol Psychiatry. 2022:1–11.
22. Pan LA, Hassel S, Segreti AM, Nau SA, Brent DA, Phillips ML. Differential patterns of activity and functional connectivity in emotion processing neural circuitry to angry and happy faces in

adolescents with and without suicide attempt. Psychological Medicine. 2013;43:2129–2142.

23. Quevedo K, Ng R, Scott H, Martin J, Smyda G, Keener M, et al. The Neurobiology of Self-Face Recognition in Depressed Adolescents with Low or High Suicidality. J Abnorm Psychol. 2016;125:1185–1200.
24. Oppenheimer CW, Silk JS, Lee KH, Dahl RE, Forbes E, Ryan N, et al. Suicidal Ideation Among Anxious Youth: A Preliminary Investigation of the Role of Neural Processing of Social Rejection in Interaction with Real World Negative Social Experiences. Child Psychiatry Hum Dev. 2020;51:163–173.
25. Baumeister RF. Suicide as escape from self. Psychological Review. 1990;97:90–113.
26. Shneidman ES. Suicide as psychache. J Nerv Ment Dis. 1993;181:145–147.
27. Van Orden KA, Witte TK, Cukrowicz KC, Braithwaite S, Selby EA, Joiner TE. The Interpersonal Theory of Suicide. Psychol Rev. 2010;117:575–600.
28. Nelson EE, Leibenluft E, McClure EB, Pine DS. The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. Psychol Med. 2005;35:163–174.
29. Geoffroy M-C, Boivin M, Arseneault L, Renaud J, Perret LC, Turecki G, et al. Childhood trajectories of peer victimization and prediction of mental health outcomes in midadolescence: a longitudinal population-based study. CMAJ. 2018;190:E37–E43.
30. Klomek AB, Sourander A, Gould M. The Association of Suicide and Bullying in Childhood to Young Adulthood: A Review of Cross-Sectional and Longitudinal Research Findings. Can J Psychiatry. 2010;55:282–288.
31. Perret LC, Orri M, Boivin M, Ouellet-Morin I, Denault A-S, Côté SM, et al. Cybervictimization in adolescence and its association with subsequent suicidal ideation/attempt beyond face-to-face victimization: a longitudinal population-based study. J Child Psychol Psychiatry. 2020. 3 February 2020. https://doi.org/10.1111/jcpp.13158.
32. Stewart JG, Valeri L, Esposito EC, Auerbach RP. Peer Victimization and Suicidal Thoughts and Behaviors in Depressed Adolescents. J Abnorm Child Psychol. 2018;46:581–596.
33. Eisenberger NI, Lieberman MD, Williams KD. Does Rejection Hurt? An fMRI Study of Social Exclusion. Science. 2003;302:290–292.
34. Cacioppo S, Frum C, Asp E, Weiss RM, Lewis JW, Cacioppo JT. A quantitative meta-analysis of functional imaging studies of social rejection. Sci Rep. 2013;3:2027.
35. Williams KD, Jarvis B. Cyberball: A program for use in research on interpersonal ostracism and acceptance. Behavior Research Methods. 2006;38:174–180.
36. Rotge J-Y, Lemogne C, Hinfray S, Huguet P, Grynszpan O, Tartour E, et al. A meta-analysis of the anterior cingulate contribution to social pain. Soc Cogn Affect Neurosci. 2015;10:19–27.
37. Olié E, Jollant F, Deverdun J, Champfleur NM de, Cyprien F, Bars EL, et al. The experience of social exclusion in women with a history of suicidal acts: a neuroimaging study. Sci Rep. 2017;7:1–8.

38. Klonsky ED, May AM, Glenn CR. The relationship between nonsuicidal self-injury and attempted suicide: converging evidence from four samples. J Abnorm Psychol. 2013;122:231–237.
39. Harms MB, Casement MD, Teoh JY, Ruiz S, Scott H, Wedan R, et al. Adolescent suicide attempts and ideation are linked to brain function during peer interactions. Psychiatry Research: Neuroimaging. 2019;289:1–9.
40. Huber RS, Hodgson R, Yurgelun-Todd DA. A qualitative systematic review of suicide behavior using the cognitive systems domain of the research domain criteria (RDoC) framework. Psychiatry Research. 2019;282:112589.
41. Richard-Devantoy S, Berlim MT, Jollant F. A meta-analysis of neuropsychological markers of vulnerability to suicidal behavior in mood disorders. Psychological Medicine. 2014;44:1663–1673.
42. Saffer BY, Klonsky ED. Do neurocognitive abilities distinguish suicide attempters from suicide ideators? A systematic review of an emerging research area. Clinical Psychology: Science and Practice. 2018;25:e12227.
43. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends in Cognitive Sciences. 2005;9:242–249.
44. Gifuni AJ, Perret LC, Lacourse E, Geoffroy M-C, Mbekou V, Jollant F, et al. Decision-making and cognitive control in adolescent suicidal behaviors: a qualitative systematic review of the literature. Eur Child Adolesc Psychiatry. 2020. 9 May 2020. https://doi.org/10.1007/s00787-020-01550-3.
45. Witte TK, Merrill KA, Stellrecht NE, Bernert RA, Hollar DL, Schatschneider C, et al. “Impulsive” youth suicide attempters are not necessarily all that impulsive. Journal of Affective Disorders. 2008;107:107–116.
46. Larsen B, Luna B. Adolescence as a neurobiological critical period for the development of higher-order cognition. Neuroscience & Biobehavioral Reviews. 2018;94:179–195.
47. Luna B, Marek S, Larsen B, Tervo-Clemmens B, Chahal R. An Integrative Model of the Maturation of Cognitive Control. Annu Rev Neurosci. 2015;38:151–170.
48. Casey BJ. Beyond Simple Models of Self-Control to Circuit-Based Accounts of Adolescent Behavior. Annu Rev Psychol. 2015;66:295–319.
49. Spear LP. The adolescent brain and age-related behavioral manifestations. Neuroscience & Biobehavioral Reviews. 2000;24:417–463.
50. Chikazoe J. Localizing performance of go/no-go tasks to prefrontal cortical subregions. Current Opinion in Psychiatry. 2010;23:267–272.
51. Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, et al. A Developmental Functional MRI Study of Prefrontal Activation during Performance of a Go-No-Go Task. Journal of Cognitive Neuroscience. 1997;9:835–847.
52. Erickson K, Drevets WC, Clark L, Cannon DM, Bain EE, Zarate CA, et al. Mood-Congruent Bias in Affective Go/No-Go Performance of Unmedicated Patients With Major Depressive Disorder. AJP. 2005;162:2171–2173.

53. Pan LA, Batezati-Alves SC, Almeida JRC, Segreti A, Akkal D, Hassel S, et al. Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. J Am Acad Child Adolesc Psychiatry. 2011;50:602–611.e3.
54. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. Am J Psychiatry. 2007;164:1035–1043.
55. Diagnostic and statistical manual of mental disorders: DSM-IV. Fourth edition. Washington, DC : American Psychiatric Association, [1994] ©1994; 1994.
56. Ding Y, Pereira F, Hoehne A, Beaulieu M-M, Lepage M, Turecki G, et al. Altered brain processing of decision-making in healthy first-degree biological relatives of suicide completers. Mol Psychiatry. 2017;22:1149–1154.
57. Jollant F, Wagner G, Richard-Devantoy S, Köhler S, Bär K-J, Turecki G, et al. Neuroimaging-informed phenotypes of suicidal behavior: a family history of suicide and the use of a violent suicidal means. Translational Psychiatry. 2018;8:1–10.
58. Gifuni AJ, Chakravarty MM, Lepage M, Ho TC, Geoffroy M-C, Lacourse E, et al. Brain cortical and subcortical morphology in adolescents with depression and a history of suicide attempt. J Psychiatry Neurosci. 2021;46:E347–E357.
59. Kaufman J, Birmaher B, Brent DA, Ryan ND, Rao U. K-SADS-PL. J Am Acad Child Adolesc Psychiatry. 2000;39:1208.
60. Kaufman J, Birmaher B, Brent D, Rao U, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. Journal of the American Academy of Child & Adolescent Psychiatry. 1997;36:980–988.
61. Beck AT, Steer RA, Brown G. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
62. Wechsler D. Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). San Antonio, TX: The Psychological Corporation; 2003.
63. Wechsler D. Wechsler Adult Intelligence Scale. 4th edition. San Antonio, TX: Pearson Assessment; 2008.
64. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. Journal of Clinical Psychology. 1995;51:768–774.
65. Williams KD, Cheung CKT, Choi W. Cyberostracism: Effects of being ignored over the Internet. Journal of Personality and Social Psychology. 2000;79:748–762.
66. Gerber JP, Chang S-H, Reimel H. Construct validity of Williams' ostracism needs threat scale. Personality and Individual Differences. 2017;115:50–53.
67. Zadro L, Williams KD, Richardson R. How low can you go? Ostracism by a computer is sufficient to lower self-reported levels of belonging, control, self-esteem, and meaningful existence. Journal of Experimental Social Psychology. 2004;40:560–567.

68. Simmonds DJ, Pekar JJ, Mostofsky SH. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia. 2008;46:224–232.
69. Criaud M, Boulinguez P. Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. Neurosci Biobehav Rev. 2013;37:11–23.
70. Esteban O, Markiewicz CJ, Goncalves M, DuPre E, Kent JD, Salo T, et al. FMRIPrep. Zenodo; 2018.
71. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nature Methods. 2019;16:111–116.
72. Esteban O, Ciric R, Finc K, Blair RW, Markiewicz CJ, Moodie CA, et al. Analysis of task-based functional MRI data preprocessed with fMRIPrep. Nat Protoc. 2020;15:2186–2202.
73. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
74. RStudio Team. RStudio: Integrated Development Environment for R. Boston, MA: RStudio, Inc.; 2016.
75. Chen G, Adleman NE, Saad ZS, Leibenluft E, Cox RW. Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. Neuroimage. 2014;99:571–588.
76. Gong G, Rosa-Neto P, Carbonell F, Chen ZJ, He Y, Evans AC. Age- and Gender-Related Differences in the Cortical Anatomical Network. J Neurosci. 2009;29:15684–15693.
77. Graham S, Jiang J, Manning V, Nejad AB, Zhisheng K, Salleh SR, et al. IQ-related fMRI differences during cognitive set shifting. Cereb Cortex. 2010;20:641–649.
78. Boudreaux ED, Rundensteiner E, Liu F, Wang B, Larkin C, Agu E, et al. Applying Machine Learning Approaches to Suicide Prediction Using Healthcare Data: Overview and Future Directions. Frontiers in Psychiatry. 2021;12.
79. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: Machine Learning in Python. Journal of Machine Learning Research. 2011;12:2825–2830.
80. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010;214:655–667.
81. O'Connor RC, Nock MK. The psychology of suicidal behaviour. Lancet Psychiatry. 2014;1:73–85.
82. Eisenberger NI. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. Nature Reviews Neuroscience. 2012;13:421–434.
83. Apter A, Horesh N, Gothelf D, Graffi H, Lepkifker E. Relationship between self-disclosure and serious suicidal behavior. Compr Psychiatry. 2001;42:70–75.
84. Husky MM, Zablith I, Alvarez Fernandez V, Kovess-Masfety V. Factors associated with suicidal ideation disclosure: Results from a large population-based study. J Affect Disord. 2016;205:36–43.
85. Dixon ML, Thiruchselvam R, Todd R, Christoff K. Emotion and the prefrontal cortex: An integrative review. Psychol Bull. 2017;143:1033–1081.

86. Mitchell DGV. The nexus between decision making and emotion regulation: A review of convergent neurocognitive substrates. Behavioural Brain Research. 2011;217:215–231.
87. Groschwitz RC, Plener PL, Groen G, Bonenberger M, Abler B. Differential neural processing of social exclusion in adolescents with non-suicidal self-injury: An fMRI study. Psychiatry Res Neuroimaging. 2016;255:43–49.
88. Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, et al. Orbitofrontal Cortex Response to Angry Faces in Men With Histories of Suicide Attempts. AJP. 2008;165:740–748.
89. Olié E, Ding Y, Le Bars E, de Champfleur NM, Mura T, Bonafé A, et al. Processing of decision-making and social threat in patients with history of suicidal attempt: A neuroimaging replication study. Psychiatry Res. 2015;234:369–377.
90. Wagner G, Li M, Sacchet MD, Richard-Devantoy S, Turecki G, Bär K-J, et al. Functional network alterations differently associated with suicidal ideas and acts in depressed patients: an indirect support to the transition model. Transl Psychiatry. 2021;11:100.
91. Poldrack RA, Huckins G, Varoquaux G. Establishment of Best Practices for Evidence for Prediction: A Review. JAMA Psychiatry. 2020;77:534–540.
92. Dinga R, Schmaal L, Penninx BWJH, van Tol MJ, Veltman DJ, van Velzen L, et al. Evaluating the evidence for biotypes of depression: Methodological replication and extension of Drysdale et al. (2017). NeuroImage: Clinical. 2019;22:101796.
93. Roy A, Nikolitch K, McGinn R, Jinah S, Klement W, Kaminsky ZA. A machine learning approach predicts future risk to suicidal ideation from social media data. Npj Digit Med. 2020;3:1–12.
94. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2 edition. Hillsdale, N.J: Routledge; 1988.
95. Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA. FMRI Clustering in AFNI: False-Positive Rates Redux. Brain Connect. 2017;7:152–171.
96. Cox RW. Equitable Thresholding and Clustering: A Novel Method for Functional Magnetic Resonance Imaging Clustering in AFNI. Brain Connect. 2019;9:529–538.

Figures

Figure 1: Group Differences on the Go-NoGo Task and Cyberball Game fMRI (voxel threshold p<0.005, Cluster corrected p<0.05)

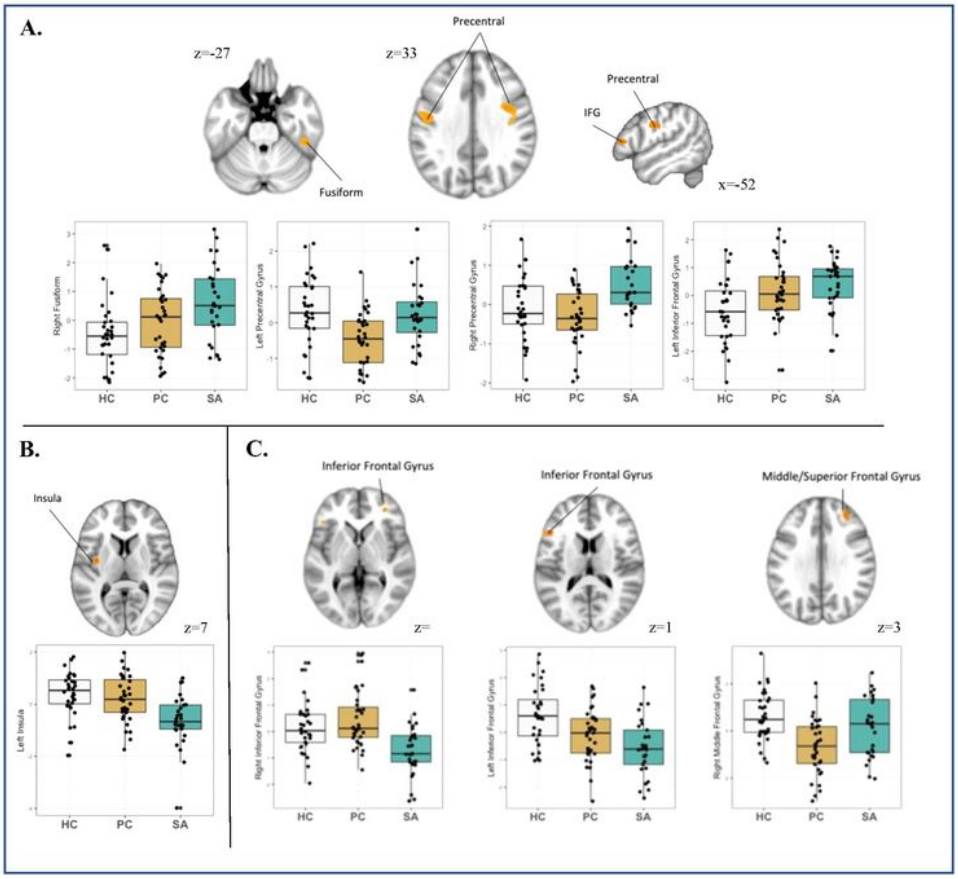

Figure 1

Group Differences on the Go-NoGo Task and Cyberball Game fMRI (voxel threshold p<0.005, Cluster corrected p<0.05)

Caption:

A. Go-NoGo Task (NoGo vs Go Contrast)

B. Cyberball Game (Inclusion vs Control Contrast)

C. Cyberball Game (Exclusion vs Control Contrast)

Figure 2 : Diagnostic accuracy provided by Socio-Demographic Data, Clinical Variables, and Neural Contrast Extracted from Significant Clusters in the Go-NoGo Task and the Cyberball Game fMRI - Receiver Operant Curves (ROC) Based on k=5 Cross-Validation

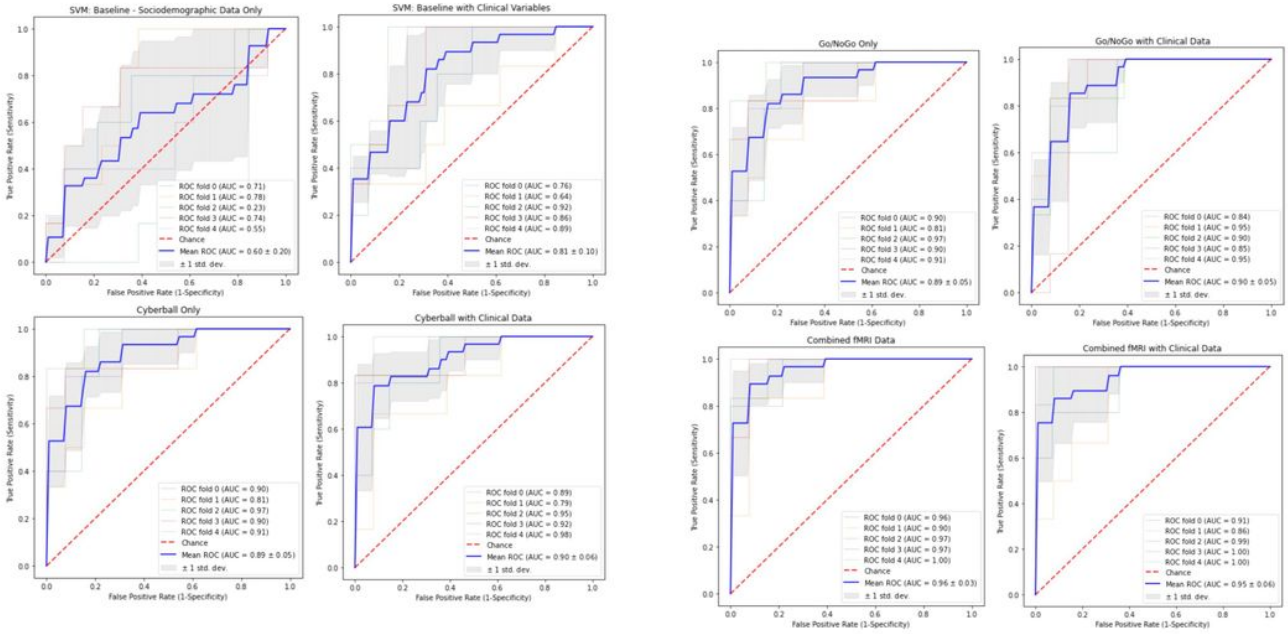

Figure 2

Diagnostic accuracy provided by Socio-Demographic Data, Clinical Variables, and Neural Contrast Extracted from Significant Clusters in the Go-NoGo Task and the Cyberball Game fMRI - Receiver Operant Curves (ROC) Based on k=5 Stratified Cross-Validation

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplements.docx