Article

Brain Responses to Unfairness in Older People With a History of Suicide Attempt, and Their Association With Mental Pain

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Abstract

Background: Suicidal behavior is associated with higher sensitivity to social signals and disadvantageous decision-making. Here, we aimed to assess behavioral and brain responses to unfairness in older people, a population insufficiently characterized.

Methods: Three groups of participants aged >60 were recruited: depressed patients with (N = 19) or without (N = 19) a history of suicide attempt, and healthy controls (N = 19). Participants played the Ultimatum Game while being scanned with 3-T magnetic resonance imaging. Four offers differing in unfairness level and two decision types (accept/reject the offer) were analyzed. Mental and physical pain were measured with the Physical and Psychological Pain-Visual Analog Scale (PPP-VAS).

Results: While unfairness level modulated subsequent decisions in all groups, there was no group difference in behavioral measures (acceptance rates, reaction times) at any level of unfairness. However, during offers, differences in brain activation between suicide attempters and patient controls, but not between suicide attempters and healthy controls, were observed in left cerebellum, right inferior parietal lobule/supramarginal gyrus and right superior frontal gyrus. Activation values in these regions were correlated with depression severity scores. During decisions, brain activation differed between suicide attempters and both patient and healthy controls in the right cerebellum and left superior frontal gyrus, and was not correlated with depression. Controlling for group, significant correlations were found between activation in these regions and mental pain measures.

Conclusions: In the context of unfair social interaction, older suicide attempters differed from non-attempters in their pattern of brain responses involving regions implicated in emotion regulation, social cognition and choice valuation, which may modulate a feeling of mental pain and impact decisions. These findings confirm specific neurocognitive impairments in patients with histories of suicidal acts and extend these findings to older people.

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Keywords

neuroimaging; suicidal behavior; geriatric psychiatry; Ultimatum Game; mental pain

Introduction

Understanding the complex mechanisms underlying suicidal behavior necessitates multilevel investigation. Cognitive neuroscience has identified important processes and redesigned the classical stress-diathesis model of suicidal behavior [1]. In this study, we continued this investigation of suicidal behavior while focusing on older individuals.

In many countries, suicide rates are highest among older people, especially men [2]. Mechanisms leading to suicide in older people may be different from those in adolescents and middle-aged adults [2,3], necessitating specific research. Unfortunately, cognitive neuroscience studies in this age group have been limited to date compared with those in younger adults [4]. Published studies have reported deficits in decision-making [5–7], reversal learning [8], reward discounting [9], or cognitive inhibition [10] in suicide attempters (SA) compared with patient controls (PC) and healthy controls (HC). These findings suggest that neurocognitive impairments in older SA may largely mirror those observed in younger SA.

Here, we were interested in investigating the brain response to a potent social stressor: the feeling of unfairness. A desire for equity is part of the human condition [11,12]. A feeling of unfairness is likely to produce strong emotional and behavioral reactions [12,13], including frustration, anger, protest, refusal and retaliation. It may also produce mental pain, a key factor contributing to suicidal ideas and acts [14]. A classic test for measuring responses to unfairness under laboratory conditions is the Ultimatum Game [15]. This task combines elements of sensitivity to negative social stressors and decision-making.

A few studies have previously used the Ultimatum Game to investigate suicidal behavior. Szanto *et al*. [16] used the classical version in older individuals and showed a higher rate of rejection at low levels of unfairness in high-lethality SA vs. low-lethality SA, PC and HC. Inequity seemed to be the main motive for rejection at the expense of stake magnitude and costs. In contrast, Carbajal *et al*. [17] found higher rates of rejection in younger suicidal patients (attempters and ideators) compared with HC and PC without suicidal ideas. However, this applied only to low stakes while responses to unfairness were similar across groups. Finally, a recent study by Liu *et al*. [18] measuring event-related potentials during the Ultimatum Game in middle-aged adults showed a pattern of differential responses to unfair offers in SA compared with age-matched PC and HC.

In this study, we aimed to clarify the brain responses to unfairness in older SA using functional magnetic resonance imaging (fMRI). We hypothesized that SA, as compared to both PC and HC, would show: (1) lower acceptance of unfair offers at intermediate levels of unfairness (e.g., 60:40 or 70:30) as previously shown; (2) a set of differential activations affecting the prefrontal and parietal cortices, insula and subcortical regions, brain regions previously associated with suicidal behaviors [19], during unfair offers and subsequent decisions. Finally, we hypothesized that activation in these brain regions would be correlated with feelings of mental pain.

Materials and Methods

Population

Right-handed male and female individuals aged 60 years and above were recruited between November 2017 and December 2019.

Three groups were a priori recruited with the following inclusion criteria: (i) Depressed patients with a lifetime history of suicide attempt (Suicide Attempters, SA); (ii) Depressed patients with no lifetime history of suicide attempt (Patient Controls, PC); (iii) Healthy controls (HC) with no lifetime history of suicide attempt or severe mental disorder.

Patients suffered from a current moderate-to-severe major depressive episode as part of a major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria. They were recruited in an outpatient clinic or during full-time hospitalization at the academic hospital (CHU) of Nîmes, France, during their depressive episode.

HC were recruited through word of mouth and local advertisements.

A suicide attempt was defined as a self-injurious act carried out with at least some intent to die, consistent with standard definitions of suicidal behavior in the Columbia-Suicide Severity Rating Scale [20]. Aborted and interrupted suicidal acts, as well as non-suicidal self-injury, were not considered suicide attempts.

Non-inclusion criteria were bipolar disorders,

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schizophrenia or any psychotic disorder, a Mini-Mental Status Examination (MMSE; [21]) score below 24, a known central nervous system disease (including, but not limited to, any degenerative disorder, head trauma, cerebrovascular disease), a major physical disorder preventing clinical or neuroimaging investigations, electroconvulsive therapy (ECT) over the last 12 months, and an inability to attend the magnetic resonance imaging (MRI) session (e.g., inability to lie on the back for one hour, sight problems, tremors, contraindication to MRI).

Clinical Assessment

All participants were clinically assessed by experienced clinicians using the French versions of the Mini-International Neuropsychiatric Interview (MINI 7.0) [22], MMSE [21], National Adult Reading Test (NART) [23], Beck Depression Inventory-II (BDI-II) [24], Montgomery–Åsberg Depression Rating Scale (MADRS) [25], Beck Scale for Suicide Ideation (SSI) [26], Columbia-Suicide Severity Rating Scale (C-SSRS) [20], Clinical Global Impression-Severity (CGI-S) [27], and the Physical and Psychological Pain-Visual Analog Scale (PPP-VAS) [28]. The MINI 7.0 was used to assess psychiatric diagnoses according to DSM criteria. The MMSE ranges from 0 to 30, with lower scores indicating greater global cognitive impairment. The NART was used as an estimate of premorbid intellectual functioning, with higher scores reflecting better-preserved premorbid verbal ability (range 0–40). The BDI-II ranges from 0 to 63 and the MADRS from 0 to 60, with higher scores indicating greater depressive symptom severity. The SSI ranges from 0 to 38, with higher scores indicating more severe suicidal ideation. The C-SSRS was used to characterize suicidal ideation and behavior, including the occurrence, number, recency, and lethality of suicide attempts. The CGI-S ranges from 1 to 7, with higher scores indicating greater overall illness severity. The PPP-VAS assesses current, mean, and maximal psychological and physical pain using visual analog scales ranging from 0 to 10, with higher scores indicating greater pain intensity.

MRI Acquisition

All participants underwent MRI on a 3.0-T MRI scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany), which included both high-resolution structural images and task-related functional images. The former sequence was acquired using T1-weighted images with a repetition time (TR)/echo time (TE)/inversion time (TI) of 1570/2.55/922 ms, a field of view (FOV) of 250 × 250, and voxels reconstructed to 0.5 × 0.5 × 1.0 mm^3. The latter was produced using EPI sequences with axial T2*-weighted images, a TR/TE of 2000/20 ms, a resolution of 2.0 × 2.0 × 5.0 mm^3, an FOV of 192 × 192, a set of 32 axial slices per volume, and 300 volumes per session.

Ultimatum Game

Participants were scanned while performing the French-adapted version of the Ultimatum Game task [29]. In this task, a proposer must decide how to split a sum of money between oneself and a second participant, known as the responder. If the responder rejects the offer, neither participant receives any money. This creates tension for the responder between self-interest (reward) and the social norms of fairness. The responder can accept the offer if it is judged fair or if the reward overcomes unfairness, or "punish" the proposer by refusing the offer at the expense of their own pay-off. Participants were informed that they had been randomly assigned to one of the roles in a game in which a sum of 10 euros would be split. They were also informed that they would be playing the game with an anonymous individual online. However, the participant's role (as responder) and the offers in the game were all predetermined.

Presentation of offers was randomized across four different levels of unfairness (proposer/participant): 50:50 (equal offers), 60:40, 70:30, or 90:10 (very unfair offers). A total of 32 offers were made, with 8 offers per level.

The participants were instructed to use a push-button box to indicate their responses to the offers displayed on an MRI-compatible screen. Each trial lasted 18 seconds and was composed of (i) a fixation cross (8 sec) (ii) the offer written on the screen in French ("You receive XX euros, the proposer receives XX euros") and the participant's manual response (6 sec); and (iii) feedback on the screen (4 sec) ("You have accepted the offer from the proposer. You receive XX euros and the proposer receives XX euros" or "You rejected the offer from the proposer. Nobody receives any money"). The total duration of the task was 9.6 minutes. The MRI trigger, individual responses (accept or reject) and reaction times were automatically recorded using E-Prime software (version 3.0; Psychology Software Tools, Inc., Sharpsburg, PA, USA).

Image Pre-Processing

See **Supplementary Material**.

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Image Analyses

Two events were determined for analyses: (i) Offer between the start of the offer view on the screen and decision and (ii) Decision at the time when participants clicked on the button.

Four contrasts of interest related to offers were specified: (1) 50:50 offers vs. cross (fair), (2) 60:40 offers vs. cross (mildly unfair), (3) 70:30 offers vs. cross (unfair), and (4) 90:10 offers vs. cross (very unfair). A combined analysis across all offer types was used to capture the global neural response to the social bargaining context of the Ultimatum Game. This choice was also motivated by the modest sample size and the limited number of trials per offer level, which reduced statistical power for condition-specific group comparisons. In addition, three of the four offer types were unfair, meaning that participants were mainly, but not exclusively, exposed to an overall context of unfair social interaction.

Additionally, three contrasts of interest were specified regarding decision type: (1) Accept vs. cross, (2) Reject vs. cross, and (3) Accept vs. Reject. We also examined a combined decision-related response versus fixation cross. The rationale was to identify brain activation associated with the decision-making process itself, independently of the specific motor/choice outcome. This was particularly important because the number of trials differed across accept and reject responses depending on participants' choices, especially at the most unfair offer levels. Pooling decisions therefore increased statistical power and provided a more stable estimate of neural activity related to decision-making during the task.

Neural correlates of offers and decisions were examined using a General Linear Model (GLM), which was independently used to model the preprocessed images for contrasts. Offers and decisions were included as regressors while motion parameters were treated as nuisance factors.

The individual beta-value maps derived from these contrasts were subsequently used in group comparison analyses, with MMSE scores and age included as covariates. Depression severity scores were not included as covariates in the full three-group models because BDI-II and MADRS were highly confounded with group status, with HC showing minimal depressive symptoms by design.

Group comparisons were performed using the 3dMVM program from the AFNI software suite (Analysis of Functional NeuroImages; Scientific and Statistical Computing Core, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA). This analysis aimed to evaluate the effects of three factors: group, contrast, and subject. A multivariate modeling approach was employed to handle data incorporating both fixed and random effects. The 3dMVM program provides a flexible framework for analyzing complex experimental designs, enabling the examination of main effects and interactions among factors. This approach offers a robust statistical framework for understanding neural responses to offers and decisions across different participant groups.

The resulting outcomes were thresholded at a voxel level of $p < 0.001$, and correction for Type I error was applied to the surviving voxels to determine significant clusters ($p_{corrected} < 0.05$). This procedure was carried out using the AFNI toolbox and consisted of using the spatial smoothness parameters previously estimated in the preprocessing step using the spatial autocorrelation function (ACF), followed by permutation tests with 10,000 iterations.

Clusters that survived the second-level analysis were subsequently subjected to a post-hoc analysis comprising exhaustive pairwise group comparisons using the 3dttest++ command in AFNI. This step allowed for the comparison of mean activation levels between groups while accounting for within-group variability. The directionality of the differences (i.e., higher or lower neural responses between groups) was determined by examining the mean activation values and the t-statistics from the pairwise comparisons.

In addition, surviving clusters were mapped onto the "Montreal Neurological Institute (MNI) Glasser Human Connectome Project (HCP)" atlas to identify the brain regions exhibiting different functional activity among groups.

Finally, the average beta-values within these clusters were computed from the respective contrast of interest for each participant and correlated with sociodemographic, clinical, and behavioral variables.

Statistical Analysis of Other Data

Additional analyses were conducted with IBM SPSS Statistics software version 29.0.0 (IBM; Armonk, NY, USA) (www.ibm.com/products/spss-statistics) for group comparisons of sociodemographic, clinical, behavioral, and neuroimaging (beta-values) variables.

Descriptive statistics were computed for all variables, with ordinal variables reported as medians and minimum–maximum ranges, and categorical variables as frequencies and percentages.

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Due to small sample sizes, group comparisons were all conducted with non-parametric tests using the Kruskal–Wallis test for continuous variables and Fisher's exact tests for categorical variables. An a priori significance level of $p < 0.05$ was set. Post-hoc analyses for pairwise group comparisons were performed on the survival variables using the Mann–Whitney U test, with significance set at $p < 0.05$. However, we used a GLM for two variables, namely acceptance rates and reaction times, to examine the effects of levels of unfairness, group, and their interaction. This approach allowed us to model the repeated-measures structure of the data and to apply the Greenhouse–Geisser correction when the assumption of sphericity was violated. In contrast, a Kruskal–Wallis test would only allow group comparisons at each level of unfairness separately and would not appropriately model the levels of unfairness × group interaction.

Partial correlations with group as a covariate and a Bonferroni correction were additionally run to test the association between the 6 measures of pain and selected activation beta-values.

Results

Population

Sixty-two participants were recruited. Two PC and 2 SA were excluded as they did not complete MRI. One HC was excluded due to a high MADRS score. Analyses were therefore conducted in 19 participants per group (Total N = 57).

The sociodemographic and clinical description of the three groups can be found in Table 1 and **Supplementary Table 1** for detailed post-hoc analyses.

HC were younger than PC, whereas SA did not differ significantly from either group. MMSE scores were higher in HC than in PC and SA, with no difference between the two depressed groups. As expected, BDI-II, MADRS, CGI, and current, mean, and maximal mental pain scores were significantly higher in both depressed groups than in HC, while PC and SA did not differ significantly on these measures. No significant group differences were observed for sex, living alone, education, BMI, NART, suicidal ideation, or physical pain. Professional occupation differed at the omnibus level, although no adjusted pairwise comparison was significant. Remitted neoplasia also differed across groups, driven by a higher frequency in SA than in PC.

Among SA, 10 (52.6%) were considered recent attempters based on the DSM-5 two-year cutoff, and 7 (36.8%) past attempters. Fourteen (73.7%) attempted suicide once in their lifetime, 2 (10.5%) twice, 1 (5.3%) three times, and 1 (5.3%) four times (1 unknown). According to the C-SSRS grading of suicide lethality, 10 (52.7%) had low–to-moderate lethality and 8 (42.1%) had severe-to-very severe lethality.

Behavioral Measures During the Ultimatum Game

Acceptance rates differed significantly according to the level of unfairness as expected (Greenhouse–Geisser corrected $F(2.34,126.40) = 78.72$, $p < 0.001$), with higher levels of unfairness leading to more rejections. However, there was no interaction with group (Greenhouse–Geisser corrected $F(4.68,126.40) = 0.66$, $p = 0.643$) and there was no between-group difference in acceptance rates at any of the four levels of unfairness (all $p > 0.05$) (Fig. 1A).

Similarly, reaction times differed significantly according to the level of unfairness (Greenhouse–Geisser corrected $F(2.51,135.61) = 12.20$, $p < 0.001$) but there was no interaction with group (Greenhouse–Geisser corrected $F(5.02,135.61) = 1.58$, $p = 0.168$) and there was no between-group difference in reaction times at any of the four levels of unfairness (all $p > 0.05$) (Fig. 1B).

Additional sensitivity analyses including age and MMSE as covariates yielded the same pattern of results.

At Bonferroni's level of correction, there was no significant correlation between these behavioral measures and MADRS scores, BDI-II scores, recency of the suicidal act, number of suicidal acts, or lethality of the last suicidal act among SA.

Brain Responses to Offers (4 Levels of Unfairness)

Analyses are reported in Table 2.

In the whole population, differences between the four levels of unfairness were found in the left cerebellum and left postcentral gyrus, although post-hoc analyses on extracted beta-values could not identify significant pairwise differences (**Supplementary Fig. 1)**.

For all levels of unfairness combined, between-group differences were observed in the left cerebellum, right inferior parietal lobule/supramarginal gyrus and right superior frontal gyrus. Post-hoc analyses revealed significant differences (all $p < 0.001$) between SA and PC and between PC and HC, with no difference between SA and HC (Fig. 2A,C).

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Table 1. Comparison of sociodemographic, clinical and pharmacological variables between the three groups.

Variable	Healthy controls (HC)	Patient controls (PC)	Suicide attempters (SA)	*p* value
N	19	19	19	—
Female, n/N (%)	10/19 (52.6)	16/19 (84.2)	14/19 (73.7)	0.126
Age, median (Q1–Q3)	65 (63–70.5)	72 (67.5–78)	70 (63.5–77.5)	0.043
Living alone, n/N (%)	7/16 (43.8)	8/18 (44.4)	6/19 (31.6)	0.688
Education, n/N (%)				0.165
Elementary	3/17 (17.6)	2/18 (11.1)	2/19 (10.5)	—
High school	9/17 (52.9)	15/18 (83.3)	16/19 (84.2)	—
University	5/17 (29.4)	1/18 (5.6)	1/19 (5.3)	—
Professional occupation, n/N (%)				0.041
Disability	0/17 (0.0)	0/18 (0.0)	1/19 (5.3)	—
Employed	3/17 (17.6)	0/18 (0.0)	4/19 (21.1)	—
Retired	14/17 (82.4)	15/18 (83.3)	14/19 (73.7)	—
Unemployed	0/17 (0.0)	3/18 (16.7)	0/19 (0.0)	—
BMI, median (Q1–Q3)	24.4 (22.6–26.7)	23.5 (20.9–27.0)	26.8 (22.7–31.1)	0.230
MMSE, median (Q1–Q3)	30 (28–30)	26 (25.5–28)	27 (26.5–28)	<0.001
NART, median (Q1–Q3)	33 (30–33)	29 (25.5–34)	28 (25–33)	0.151
BDI-II, median (Q1–Q3)	0 (0–2)	12 (8–15)	11.5 (7.5–16.5)	<0.001
MADRS, median (Q1–Q3)	0 (0–0)	14 (14–28)	16 (14–23.5)	<0.001
SSI, median (Q1–Q3)	2 (2–2)	2 (2–2.2)	2 (2–3)	0.562
CGI, median (Q1–Q3)	1 (1–1)	4.5 (3–5)	4 (3–4.8)	<0.001
Current mental pain, median (Q1–Q3)	0 (0–0)	6 (4–8)	5 (3.2–6)	<0.001
Mean mental pain, median (Q1–Q3)	0 (0–0)	7 (5–8)	7 (6–8)	<0.001
Maximal mental pain, median (Q1–Q3)	0 (0–0)	8 (5–10)	7 (6–8)	<0.001
Current physical pain, median (Q1–Q3)	1.5 (0–2.2)	5 (1–6)	2.5 (0–5)	0.085
Mean physical pain, median (Q1–Q3)	2 (0–3)	5 (1–6)	5 (0–6)	0.125
Maximal physical pain, median (Q1–Q3)	2 (0–3.2)	5 (1–6)	5 (0–6)	0.182
Psychiatric disorders (PC vs. SA only)	—			—
Obsessive-compulsive disorder, n/N (%)	—	1/18 (5.6)	0/18 (0.0)	1.000
Anxiety disorders, n/N (%)	—	7/18 (38.9)	3/18 (16.7)	0.264
Alcohol disorder, n/N (%)	—	1/18 (5.6)	0/18 (0.0)	1.000
Substance disorder, n/N (%)	—	0/18 (0.0)	0/18 (0.0)	—
Depressive episode with psychotic features, lifetime, n/N (%)	—	1/18 (5.6)	1/18 (5.6)	1.000
Anorexia nervosa, n/N (%)	—	0/18 (0.0)	0/17 (0.0)	—
Bulimia nervosa, current, n/N (%)	—	0/18 (0.0)	1/18 (5.6)	1.000
Binge eating disorder, current, n/N (%)	—	1/18 (5.6)	1/18 (5.6)	1.000
Psychiatric treatments (PC vs. SA only)	—			—
Antidepressants, n/N (%)	—	14/15 (93.3)	17/18 (94.4)	1.000
Antipsychotics, n/N (%)	—	6/15 (40.0)	11/18 (61.1)	0.303
Benzodiazepines, n/N (%)	—	8/15 (53.3)	14/18 (77.8)	0.163
Antihistaminics, n/N (%)	—	0/15 (0.0)	1/18 (5.6)	1.000
Lithium, n/N (%)	—	0/15 (0.0)	0/18 (0.0)	—
Antiepileptics, n/N (%)	—	0/16 (0.0)	1/17 (5.9)	1.000
Hypnotics, n/N (%)	—	0/16 (0.0)	1/17 (5.9)	1.000
Analgesics, n/N (%)	—	1/16 (6.2)	1/17 (5.9)	1.000
High blood pressure, n/N (%)	4/19 (21.1)	9/18 (50.0)	7/19 (36.8)	0.206
Diabetes, n/N (%)	0/19 (0.0)	2/18 (11.1)	2/19 (10.5)	0.449

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Table 1. Continued.

Variable	Healthy controls (HC)	Patient controls (PC)	Suicide attempters (SA)	*p* value
Cardiovascular failure, n/N (%)	0/19 (0.0)	0/18 (0.0)	0/19 (0.0)	—
Respiratory failure, n/N (%)	0/19 (0.0)	0/18 (0.0)	1/19 (5.3)	1.000
Renal deficiency, n/N (%)	0/19 (0.0)	0/18 (0.0)	0/19 (0.0)	—
Asthma, n/N (%)	0/19 (0.0)	0/18 (0.0)	2/19 (10.5)	0.322
Chronic obstructive pulmonary disease, n/N (%)	0/19 (0.0)	0/18 (0.0)	1/19 (5.3)	1.000
Current neoplasia, n/N (%)	0/19 (0.0)	0/18 (0.0)	0/19 (0.0)	—
Remitted neoplasia, n/N (%)	2/19 (10.5)	0/18 (0.0)	8/19 (42.1)	0.002
Past stroke, n/N (%)	0/19 (0.0)	1/18 (5.6)	1/19 (5.3)	0.765
Myocardial infarction, n/N (%)	1/19 (5.3)	0/18 (0.0)	0/19 (0.0)	1.000
Hypercholesterolemia, n/N (%)	3/19 (15.8)	5/18 (27.8)	4/19 (21.1)	0.663
Rheumatological disease, n/N (%)	6/19 (31.6)	8/18 (44.4)	8/19 (42.1)	0.786
Somatic treatments (PC vs. SA only)	—			—
Cardiology, n/N (%)	—	5/15 (33.3)	7/17 (41.2)	0.726
Dermatology, n/N (%)	—	0/16 (0.0)	0/17 (0.0)	—
Antidiabetics, n/N (%)	—	1/16 (6.2)	1/17 (5.9)	1.000
Endocrinology, n/N (%)	—	3/16 (18.8)	7/17 (41.2)	0.259
Hepatogastroenterology, n/N (%)	—	3/16 (18.8)	8/17 (47.1)	0.141
Gynecology, n/N (%)	—	0/16 (0.0)	1/17 (5.9)	1.000
Infectiology, n/N (%)	—	0/16 (0.0)	0/17 (0.0)	—
Hematology, n/N (%)	—	0/16 (0.0)	0/17 (0.0)	—
Immunology, n/N (%)	—	0/16 (0.0)	0/17 (0.0)	—
Neurology, n/N (%)	—	0/16 (0.0)	1/17 (5.9)	1.000
Ophthalmology, n/N (%)	—	1/16 (6.2)	0/17 (0.0)	0.485
Otorhinolaryngology, n/N (%)	—	0/16 (0.0)	0/17 (0.0)	—
Pneumology, n/N (%)	—	0/16 (0.0)	3/17 (17.6)	0.227
Rheumatology, n/N (%)	—	0/16 (0.0)	2/17 (11.8)	0.485
Stomatology, n/N (%)	—	0/16 (0.0)	0/17 (0.0)	—
Urology, n/N (%)	—	1/16 (6.2)	0/17 (0.0)	0.485

Notes. Continuous variables are reported as median (Q1–Q3) and were compared using Kruskal–Wallis tests. Categorical variables are reported as n/N (%) and were compared using Fisher's exact tests when expected cell counts were small or zero; tests marked as not applicable were not performed because there was no variability across groups. For significant omnibus tests, post-hoc pairwise comparisons were performed with Bonferroni correction. Psychiatric disorders, psychiatric treatments, and somatic treatments were compared between PC and SA only. H = Kruskal–Wallis statistic; *p*_adj = Bonferroni-adjusted *p* value.

Data missing. Gender, age, MMSE: 0; living alone, education, professional activity, BMI: 2 HC, 1 PC; NART: 4 PC, 2 SA; MADRS: 2 PC, 1 SA; SSI: 2 HC, 3 PC, 2 SA; mental and physical pain, BDI-II: 3 HC, 2 PC, 1 SA; CGI and psychiatric disorders: 1 PC, 1 SA (except anorexia nervosa: 2 SA); psychiatric medications: 4 PC, 1 SA for antidepressants, antipsychotics, benzodiazepines, antihistaminic, and lithium; 3 PC, 2 SA for antiepileptics, hypnotics, and analgesic; somatic disorders: 1 PC; somatic treatments: 3 PC, 2 SA, except cardiology: 4 PC; data unavailable for most HC somatic treatment entries where coded as unavailable.

Abbreviations: HC, healthy controls; PC, patient controls; SA, suicide attempters; BMI, body mass index; MMSE, Mini-Mental State Examination; NART, National Adult Reading Test; BDI-II, Beck Depression Inventory-II; MADRS, Montgomery–Åsberg Depression Rating Scale; SSI, Scale for Suicide Ideation; CGI, Clinical Global Impression.

Finally, significant group x level of unfairness interactions were found in left anterior cingulate cortex and right middle frontal cortex, but no significant group differences at any individual level of unfairness could be found in post-hoc analyses on extracted beta-values (**Supplementary Fig. 2**).

Mean activation beta-values in the 3 regions differentially activated between groups were extracted. Controlling for group, these activations were not correlated with age, and there were no sex differences. Moreover, they were not correlated with any Ultimatum Game behavioral measures. Activations were, however, correlated with both BDI-II and

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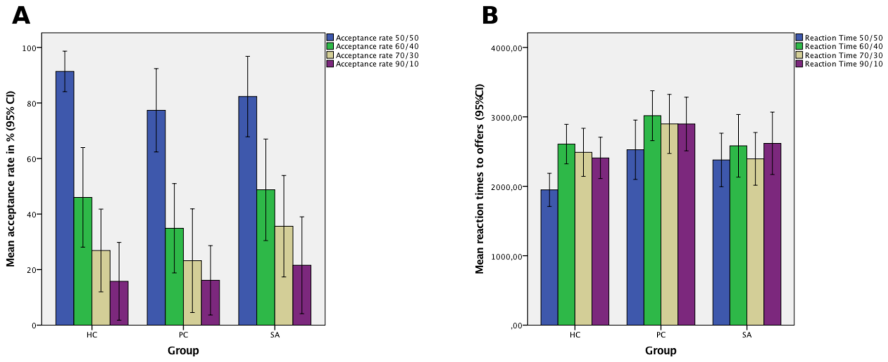


Fig. 1. Behavioral responses during the Ultimatum Game. (A) Mean acceptance rates (%) and (B) mean reaction times (ms) to offers, by group and offer level. Error bars indicate 95% confidence intervals. HC, healthy controls; PC, patient controls; SA, suicide attempters.

Table 2. Brain responses to offers (4 levels of unfairness) in suicide attempters, patient controls and healthy controls.

Contrast	Cluster size (Voxels)	Peak voxel coordinates (x,y,z)	F-value	Side	Brain region	Post-hoc analyses
Between-offer type differences						
	199	–39, –62, –46	7.4	Left	Cerebellum	NS
	60	–36, –29, 62	7.4	Left	Postcentral gyrus (BA3/4)	NS
Between-group differences						
	93	–26, –79, –46	14.7	Left	Cerebellum	PC < HC, SA*
	64	52, –28, 33	11.4	Right	Inferior parietal lobule, supra-marginal gyrus (BA40)	PC > HC, SA*
	50	19, 32, 40	12.2	Right	Superior Frontal gyrus (BA8)	PC < HC, SA*
Group x offer interaction						
	59	–19, 26, 12	7.4	Left	Anterior cingulate cortex (BA32)	NS
	54	35, 45, 34	5.7	Right	Middle frontal gyrus (BA9/46)	NS

HC, healthy controls; PC, patient controls; SA, suicide attempters; BA, Brodmann Area; NS, non-significant; *, all significant at $p < 0.001$.

MADRS depression scores (partial r between –0.36 and –0.59; all $p < 0.01$).

Controlling for group and at Bonferroni's level of correction (corrected $p = 0.003$), activation values in the left cerebellum were correlated with all three measures of mental pain (partial r between –0.45 and –0.47; all $p < 0.001$) but with no measure of physical pain. Activation in the right inferior parietal lobule/supramarginal gyrus was not significantly correlated with any pain measures (a trend toward significance for maximal mental pain: partial r = 0.40; $p = 0.004$). Activation in the right superior frontal gyrus were correlated with maximal (partial r = –0.52; $p < 0.001$) and mean (partial r = –0.41; $p = 0.003$) mental pain, with a trend toward significance for current mental pain (partial r = –0.36; $p = 0.009$) and for maximal physical pain (partial r = –0.37; $p = 0.008$).

Brain Responses to Decisions (Accept or Reject)

Analyses are reported in Table 3.

In the whole population, significant differences in activation between accept and reject choices were found in the right inferior parietal lobe and left frontal pole, with higher activation for reject than accept choices **(Supplementary Fig. 3).**

During both types of decision combined, between-group differences were observed in right cerebellum and left superior frontal gyrus with SA differing from both PC and HC (Fig. 2B,C).

Moreover, no significant group x decision interaction was found.

Finally, when directly contrasting accept vs. reject, no significant group difference was found after correction.

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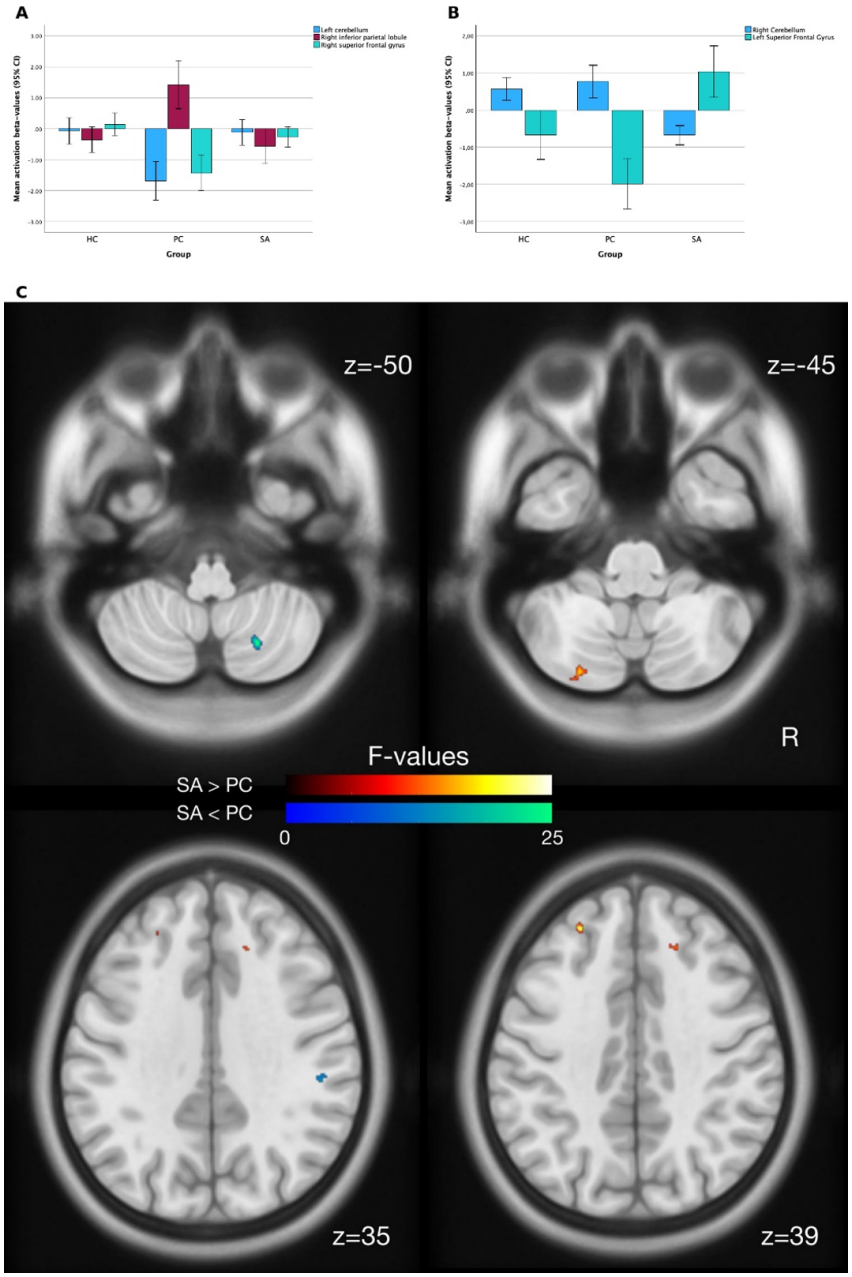


Fig. 2. Between-group differences in brain activation during the Ultimatum Game. (A) Mean activation beta-values during offer presentation across all four offer levels combined. (B) Mean activation beta-values during decision across accept and reject choices combined. (C) Brain regions showing significant between-group differences during offer presentation and decision. HC, healthy controls; PC, patient controls; SA, suicide attempters; CI, confidence interval.

Mean activation beta-values in the 2 regions differentially activated between groups were extracted. Covariating for group, they were not correlated with age, and there were no sex differences. Moreover, activations in these 2 regions were not correlated with any Ultimatum Game behavioral measures or with MADRS and BDI-II scores.

Controlling for group and at Bonferroni's level of correction (corrected $p = 0.004$), activation values in the right cerebellum were not correlated with any pain measures (a trend toward significance for mean mental pain: partial r = 0.34; $p = 0.015$). Activation values in the left superior frontal gyrus were correlated with mean mental pain (partial r = –0.45; $p = 0.001$), with a trend toward significance for maximal (partial r = –0.38; $p = 0.007$) and current (par-

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Table 3. Brain responses during decision (accept or reject) in suicide attempters, patient controls and healthy controls.

Contrast	Cluster size (Voxels)	Peak voxel coordinates (x,y,z)	F-value	Side	Brain region	Post-hoc analyses
Between-decision type differences						
	60	29, –45, 41	25.1	Right	Inferior parietal lobe (BA7)	Accept < Reject
	51	–13, 69, –9	25.0	Left	Frontal pole (BA10)	Accept < Reject
Between-group differences						
	98	21, –66, –50	24.4	Right	Cerebellum	SA < HC, PC
	53	–26, 41, 39	18.3	Left	Superior Frontal Gyrus (BA9)	SA > HC, PC
Group x decision interaction						
	NS					

HC, healthy controls; PC, patient controls; SA, suicide attempters; BA, Brodmann Area; NS, non-significant; *, all significant at $p < 0.001$.

tial r = –0.30; $p = 0.03$) mental pain.

Discussion

In a population of depressed patients aged 60 years and above, we report novel findings. First, as expected, acceptance rates of offers varied according to levels of unfairness, with increasing levels of unfairness leading to decreasing acceptance. However, we did not find any group difference in acceptance rates at any level of unfairness as previously reported. Notably, SA did not appear to reject unfair offers more than the control groups. Second, during offers, brain activations in SA differed from PC but not HC in three brain regions: the left cerebellum, right inferior parietal lobule/supramarginal gyrus and right superior frontal gyrus. Activation in these brain regions were correlated with mental pain measures but also depression severity scores. Third, during decisions, activations differed between SA and both control groups in two brain regions, namely the right cerebellum and left superior frontal gyrus. Activation in the latter region correlated with mental pain but not depression. In sum, SA differed from PC in brain (but not behavioral) responses, both when they received (mainly) unfair offers and when they made the decision to accept or reject the offer.

Our study has several limitations that we should highlight here before discussing findings in more detail. The first is the small sample size. This may have reduced the likelihood of observing some group differences in behavioral and neuroimaging measures. Notably, this may explain the lack of significant group differences when analyses were conducted according to the 4 levels of unfairness or to the 2 types of choice. It may explain the fact that we only found significant findings when comparing groups at a global level of analysis (all decisions or all unfairness levels combined). One should, however, keep in mind that during the Ultimatum Game, participants are mainly exposed to a global context of unfairness and are more likely to reject offers as three-quarters of offers are unfair. Second, unavoidable heterogeneity within groups may have influenced findings. While groups were largely similar on most measures collected, many unmeasured individual factors may have contributed to differences, including genetic factors, personal history of trauma or life stressors. It was also not possible to determine the effects of current comorbid mental and physical disorders or medication. SA also differed with regard to the recency of the suicide attempt, the number of lifetime suicide attempts, and the lethality of suicidal behavior. These dimensions may influence neurocognitive performance and brain functioning and may therefore have reduced our ability to detect more specific subgroup effects. However, the present study was grounded in a stress-vulnerability model of suicidal behavior, which posits that vulnerability to suicidal acts reflects, at least in part, long-lasting trait-like characteristics that may persist beyond the acute suicidal crisis [1,30,31]. From this perspective, including individuals with both recent and more remote suicide attempts remains relevant for identifying vulnerability markers associated with a history of suicidal behavior. Nevertheless, given the modest sample size, we were unable to conduct adequately powered subgroup analyses according to attempt recency, lethality, or repetition. Future studies with larger samples should specifically examine whether these clinical dimensions are associated with distinct behavioral and neural responses to unfairness. Third, this study is cross-sectional and retrospective. It is, therefore, subject to memory bias. It is also not possible to determine the exact contribution of these findings to the occurrence of suicidal behaviors. Fourth, laboratory tests, such as the Ultimatum Game, artificially represent real-life social interactions. This may have limited the emotional impact of unfairness, notably in a numerical environment that may be unfamiliar to many older participants. Fifth, we examined offers and decisions separately, as done in many studies. However, the duration of the BOLD signal does not prevent "cross-

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contamination" of activation. We will, therefore, largely discuss findings from both analyses together.

During the Ultimatum Game, we observed activations across groups in several regions reported in a previous meta-analysis of the task [32]. Cerebellar activation was previously associated with offers, notably fair offers, emphasizing its increasingly recognized role in emotional processes [33] and the prediction of social interaction [34]. Activation of the left postcentral gyrus has also been implicated in fairness contrasts in the Ultimatum Game [32]. The inferior parietal lobe has been associated with behavioral responses [32] as found in our study, notably during rejection. This may be related to a postulated role of this region in the processing of violations of expected offers [35]. In contrast, the role of the frontal pole has not been fully recognized during this task [32]. Yet, the ventromedial part of this region has been implicated in both emotional and cognitive processing [36] notably in choice value decision-making [37]. Therefore, its involvement could be expected during the decision part of the Ultimatum Game.

Overall, SA differed from PC in the activation of a set of brain regions including bilateral cerebellum, right inferior parietal/supramarginal gyrus, and bilateral superior frontal gyrus/dorsomedial prefrontal cortex. During offer presentation, SA differed from PC but not from HC, whereas during the decision phase SA differed from both PC and HC. Therefore, offer-related differences in activation cannot be interpreted as unequivocally suicide-specific alterations. Rather, they may partly reflect depression-related mechanisms. This interpretation is supported by the correlation analyses, as activation values in the offer-related regions showing group differences were significantly correlated with depression severity, as measured by both BDI-II and MADRS scores. In contrast, decision-related differences, in which SA differed from both PC and HC, were not significantly correlated with BDI-II or MADRS scores. These findings may therefore be more closely associated with a history of suicidal behavior. This is in line with previous studies reporting deficits in decision-making using different tasks [5–7].

The role of the cerebellum in the suicidal process has certainly been overlooked. Yet, altered structural measures and functional activity have previously been reported in several studies of SA and relatives of suicide victims [38–40]. The cerebellum has notably been implicated in emotion regulation and social cognition [34]. Its position as a connectivity hub gives the cerebellum a potentially significant role in pathological mental states [41], including the suicidal crisis. The supramarginal gyrus has also been associated with suicidal behaviors [42], notably in the context of social exclusion [43]. This region has multiple roles [44], the most relevant to understanding suicidal behavior being social cognition and self-perception. Finally, altered decision-related processing in the superior frontal gyrus/dorsomedial prefrontal cortex has been reported in healthy first-degree relatives of people who died from suicide [45]. This region is pivotal in decision-making [46], including in conditions of fairness [47]. Therefore, in a situation requiring decision-making in conditions of adverse social interactions, SA were found to differentially activate a network of brain regions implicated in emotion regulation, social cognition, and choice valuation.

Interestingly, these neural differences were observed in the absence of significant group differences in behavioral performance, as acceptance rates and reaction times did not differ between SA, PC, and HC across levels of unfairness. This suggests a dissociation between overt behavioral responses and the neural mechanisms engaged during the processing of unfairness. One possible interpretation is that SA may rely on partly different neural processes to achieve similar behavioral outcomes, reflecting compensatory mechanisms, altered neural efficiency, or differences in the emotional and cognitive appraisal of unfair social interactions. Thus, although behavior during the Ultimatum Game appeared globally preserved, brain activation patterns during fMRI may reveal more subtle alterations in the processing of unfairness in older individuals with a history of suicide attempt.

Finally, we also observed significant correlations between mental pain and the activation of several of these regions, notably the left cerebellum and bilateral superior frontal gyrus. Interestingly, we previously observed significant correlations between at-rest activation in these regions and mental pain in a different population of depressed patients [48]. Although we did not observe differences between patient groups in mental pain levels, variations in activity in these brain regions during adverse social interactions may lead to individual variations in the perception of mental pain.

Conclusions

In the present study, we report differences in brain activation in prefrontal and parietal cortices and in the cerebellum in older depressed SA during the Ultimatum Game. Offer-related differences distinguished SA from PC, but not from HC, and were associated with depression severity, suggesting that these findings may partly reflect depressive symptomatology or broader alterations in the processing of social interaction. In contrast, decision-related differ-

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ences distinguished SA from both control groups and were not correlated with depression severity, suggesting that they may be more closely related to a history of suicidal behavior.

Although these findings cannot be considered biomarkers and require replication in larger samples, they support the view that older depressed patients with a history of suicide attempt may differ from other depressed patients not only clinically but also in the neural processes engaged during social decision-making. More broadly, our results highlight the relevance of investigating sensitivity to negative social signal and decision-making processes in the prevention of suicidal behavior and repeat attempts.

Availability of Data and Materials

The data supporting the findings of this study will be made available from the corresponding author upon reasonable request once the results have been published.

Author Contributions

FJ: Conceptualization, Funding acquisition, Methodology, Formal analysis, Supervision, Writing—original draft; MA: Conceptualization, Investigation, Writing—review & editing; CG: Writing—original draft; JPB: Methodology, Writing—review & editing; FP: Conceptualization, Methodology, Formal analysis, Writing—original draft. We confirm that all authors meet all four ICMJE criteria for authorship, including substantial contribution to the work, critical involvement in manuscript preparation, final approval of the version to be published, and accountability for the integrity of the work.

Ethics Approval and Consent to Participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All patients gave oral and written informed consent before inclusion. The study (named SPAD-IRM) was approved by the local ethics committee ("Sud Méditerranée III") on 13/01/2017, and by the national authority ANSM on 17/03/2017. The protocol was registered on clinicaltrial.gov: NCT03287986.

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Conflict of Interest

All authors have no conflict of interest to disclose.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.2308.

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