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Longitudinal associations between executive function impairments and suicide risk in patients with major depressive disorder: A 1-year follow-up study

Pau Riera-Serra [a,b], Margalida Gili [a,b,c], Guillem Navarra-Ventura [a,b,*], Antonio Riera-López Del Amo [a,b], Juan José Montaño [b,c], Victoria Coronado-Simsic [a,b], Adoración Castro [a,b], Miquel Roca [a,b,d]

[a] Research Institute of Health Sciences (IUNICS), University of the Balearic Islands (UIB), Palma (Mallorca), Spain
[b] Health Research Institute of the Balearic Islands (IdISBa), Hospital Universitario Son Espases, Edificio S, Palma (Mallorca), Spain
[c] Department of Psychology, University of the Balearic Islands (UIB), Palma (Mallorca), Spain
[d] Department of Medicine, University of the Balearic Islands (UIB), Palma (Mallorca), Spain

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ABSTRACT

Impaired executive function (EF) is a key feature of patients with major depressive disorder (MDD) that several studies have linked to suicidal ideation and suicide attempts. This is the first longitudinal study to examine the association between impaired EF and suicide risk in adult patients with MDD. Longitudinal prospective study with 3 assessment points: baseline, 6 and 12 months. The Columbia-Suicide Severity Rating Scale (C-SSRS) was used to assess suicidality. The Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to assess EF. The association between EF impairments and suicidality was analyzed using mixed-effects models. Out of 167 eligible outpatients, 104 were included in the study. Of these, 72 were re-evaluated at 6 months and 60 at 12 months, obtaining 225 complete observations of the EF. Impaired decision-making and risk-taking behavior were associated with suicidal ideation. Difficulty in impulse control was related to suicidal ideation and to greater severity of suicidal ideation. Impaired spatial planning and working memory was linked to suicide attempts. Our results add to previous literature that the association between EF impairments and suicidality is maintained over the long term, supporting it as a longitudinal risk factor and a possible neurocognitive marker of suicide in patients with MDD.

1. Introduction

Suicidal behavior is a major public health problem that represents one of the leading causes of death and disability worldwide (WHO, 2019). Research on populations at high risk for suicide shows that people with mental disorders are more prone to suicidal ideation and suicide attempts than others (Nock et al., 2010), with affective disorders as a whole and major depressive disorder (MDD) in particular being at highest risk (Gili et al., 2019). Severity of depression, comorbid disorders and personal and family history of suicide are also possible risk factors. However, robust predictors of suicide have not yet been found (Franklin et al., 2017).

MDD is primarily defined as a mood disorder, but cognitive impairment is a key feature of the disease (Bora et al., 2013) that is also part of its nosological definition (American Psychiatric Association, 2022). Cognitive impairment is especially pronounced in attention, memory, executive function (EF) and processing speed (Rock et al., 2014) and has been linked to suicidal ideation and suicide attempts. Indeed, there is evidence that, beyond depressed mood, global cognitive impairment and executive dysfunction in particular is a relevant aspect to take into account when assessing suicide risk in this clinical population (Ho et al., 2018), as it poses additional difficulties in interpreting and managing life events.

Executive dysfunction is especially pronounced during acute depressive episodes and often remains during remission (Roca et al., 2015; Semkovska et al., 2019). Moreover, it is an important determinant

* Corresponding author: Guillem Navarra-Ventura, Research Institute of Health Sciences (IUNICS), University of the Balearic Islands (UIB), Palma (Mallorca), Spain.
E-mail address: g.navarra@uib.es (G. Navarra-Ventura).

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of disease progression and prognosis (Withall et al., 2009) and has been linked to functional disability (Rock et al., 2014) and decreased quality of life (Cotrena et al., 2016). There is evidence in other clinical and non-clinical populations that impaired EF represents an obstacle to stop ruminating, shifting to more positive thoughts and making correct decisions (Chamberlain et al., 2013; Miranda et al., 2013, 2012; Miranda and Nolen-Hoeksema, 2007). In this context, and given its contribution to the self-regulation of behavior, (Hofmann et al., 2012), executive dysfunction as a whole and cognitive inflexibility in particular is a presumed vulnerability factor for suicide risk in depressed patients (Bredemeier and Miller, 2015).

The most frequently impaired EFs in patients with MDD are working memory, planning and verbal fluency (Snyder, 2013). To date, several case-control and cross-sectional studies have specifically addressed the relationship between impaired EF and suicidal behavior in patients with MDD. In a qualitative systematic review by Lalovic et al. (2022), 63 studies were identified that examined the relationship between neurocognition, suicidal ideation and suicide attempts in different psychiatric populations, of which 32 did so in patients with MDD. Among depressed patients who attempted suicide, decision-making, cognitive inhibition, selective attention and working memory were found to be the most impaired domains. In contrast, no clear pattern of executive dysfunction was observed in studies of depressed patients with suicidal ideation, nor was a clear transdiagnostic neurocognitive profile found.

To our knowledge, no study has yet examined whether impaired EF is longitudinally associated with suicidal behavior in depressed patients. In this sense, the overall picture of executive dysfunction as risk factor (vs. correlate) for suicidality in patients with MDD remains formally underexplored (Cha et al., 2019). Results from prospective studies that examined cognitive domains other than EF suggest that better cognitive performance in verbal memory and processing speed is associated with better outcomes in terms of suicidal ideation and suicide attempts (Gorlyn et al., 2015; Lan et al., 2020). In the present study we set out to examine, using a prospective longitudinal design spanning 12 months of follow-up, the association between impaired EF, suicidal ideation, and suicide attempts in a group of adult patients with MDD.

2. Method

2.1. Study design

A prospective study with 4 data collection points (baseline, 6, 12 and 24 months) was designed to examine the associations between EF impairments and suicide risk in patients with a first MDD episode (Roca et al., 2019). However, to overcome recruitment difficulties due to the COVID-19 pandemic, both patients with a first episode and those with recurrent episodes were included. In addition, assessments could only be performed at baseline, 6 and 12 months, as follow-up at 24 months was not possible due to the overload of the public primary care system in Spain. Ethical approval was provided by the Research Ethics Committee of the Balearic Islands (#IB3697/18PI).

2.2. Participants and procedure

Eligible participants were adult outpatients aged 18–65 years, diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria (American Psychiatric Association, 2013), and with a score ≥18 on the Inventory of Depressive Symptomatology-Self Rated (IDS-SR30) (Rush et al., 1996). Participants were excluded if they had psychotic symptoms, neurological disease, cognitive impairment resulting from other medical conditions, a diagnosis of borderline personality disorder, were being treated with antipsychotic or euthymizing drugs, had received electroconvulsive therapy in the past, or were unable to understand the study tests.

A total of 167 outpatients were screened for eligibility in the Balearic Islands, Spain (Fig. 1). Of these, 104 (62.3%) subjects were recruited from different primary care centers, mental health units and hospital outpatient clinics (40 patients), through brochures and posters placed in care centers and public areas (34 patients), through the SOPHIA database of the Health Service of the Balearic Islands (27 patients), and through articles in local newspapers (3 patients).

The researchers contacted all potential participants by telephone, informed them of the characteristics of the study, and scheduled an initial face-to-face visit if they were deemed eligible. At baseline,

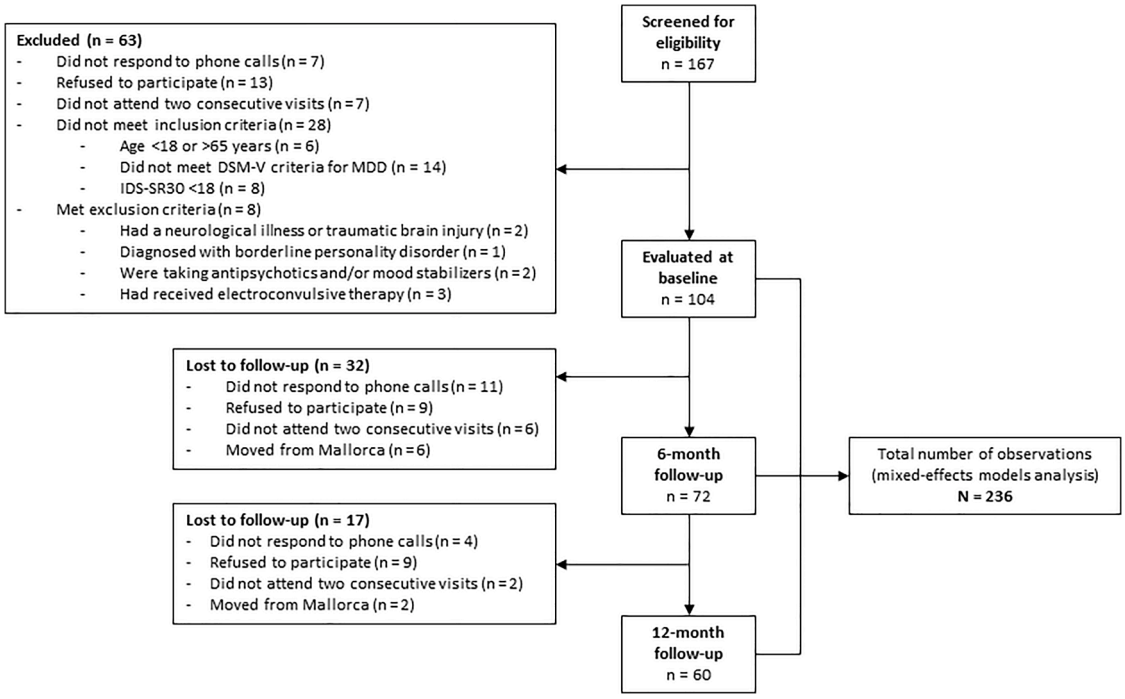

Fig. 1. Flowchart of the study. Enrollment took place between November 2018 and July 2021 in the Balearic Islands, Spain. Of the 236 total observations, 225 (95.34%) have the full cognitive assessment. MDD: major depressive disorder; IDS-SR30: Inventory of Depressive Symptomatology-Self Rated.

eligibility criteria were confirmed and informed consents were signed. The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) in its Spanish version (Ferrando et al., 1998) was administered to confirm the diagnosis of MDD and explore possible comorbid disorders. During follow-up, researchers contacted enrolled participants by telephone and/or e-mail every 6 months, requesting their availability for the next follow-up evaluation. All assessments were conducted in a quiet room at the participant's primary care center or at the Research Institute of Health Sciences of the University of the Balearic Islands by an experienced psychiatrist or psychologist and lasted 90–120 min distributed over one or two visits depending on the patient's fatigue. None of the participants received cognitive remediation during the study.

2.3. Sociodemographic and clinical variables

The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011) in its Spanish version (Al-Halabí et al., 2016) was used to assess suicide risk. This semi-structured interview has shown good psychometric properties and it has been validated in both clinical and research settings (Al-Halabí et al., 2016; Posner et al., 2011). For the purposes of this study, three C-SSRS subscales were used: suicidal ideation (yes/no), severity of suicidal ideation (range 0–5), and suicide attempt (yes/no). "Suicidal ideation (last month)" was defined as the number of patients showing any thoughts of killing oneself or wishing oneself dead assessed with the suicidal ideation subscale of the C-SSRS, where ideation corresponds to patients with a score between 1 and 5 and no ideation corresponds to patients with a score <1. "Severity of suicidal ideation (last month)" was defined as the raw ordinal score obtained on this same C-SSRS subscale ranging from (0) "Absence of Suicidal Ideation" to (5) "Active Suicidal Ideation with Specific Plan and Intent", where a higher score indicates more severe ideation. "Suicide attempt (during the 3 months prior to enrollment and throughout the study)" was defined as the number of patients who performed any potentially self-injurious act committed with at least some wish to die, i.e., a "yes" response to the "actual attempt" item of the suicidal behavior subscale of the C-SSRS.

To measure the severity of depression, the Spanish version of the IDS-SR30 was used (Chronbach's α =0.94) (Gili et al., 2011). This questionnaire assesses 9 core symptoms of depression and its total score ranges 0–84, where a higher score indicates more severe depression. MDD was considered in remission when scores at 6 and 12 months were ≤13.

Other variables such as age, sex, education, professional and marital status, type of depressive episode, duration of current episode, being on antidepressant treatment, number of psychiatric comorbidities and family history of suicide were also collected.

2.4. Executive function variables

EF was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) installed on a touch-screen tablet, as it has demonstrated high sensitivity to executive dysfunction in depression (Rock et al., 2014). Although still subject to further investigation (Karlsen et al., 2022; Skirrow et al., 2022), the test-retest reliability of the CANTAB tests offers positive results (Lowe and Rabbitt, 1998). The following CANTAB tasks were used: 1) Spatial Working Memory (SWM), a measure of visuospatial working memory and strategy; 2) One Touch Stockings (OTS) of Cambridge, which assesses spatial planning and working memory; 3) Stop Signal Task (SST), a measure of response inhibition; and 4) Cambridge Gambling Task (CGT), which assesses decision making and risk-taking behavior. For the purposes of this study, the following main variables were used: 1) SWM Between Errors; 2) SWM Strategy (6–8 boxes); 3) OTS Problems Solved on First Choice; 4) OTS Median Latency to First Choice; 5) SST Stop Signal Reaction Time; 6) CGT Delay Aversion Total; 7) CGT Decision Making Quality Total Merged; and 8) CGT Risk Adjustment Merged. Descriptions of these variables and details of how they were combined to compose each EF domain (i.e., SWM, OTS, SST, and CGT) are given in Table S1 (see Supplementary materials, SM). Impaired EF was defined as a z-score ≤−1 standard deviation (SD) below the mean (Taylor and Heaton, 2001). Z-scores have a mean of 0 and a SD of ±1.

2.5. Primary outcome measures

Suicidal ideation (yes/no) and severity of suicidal ideation (range 05) during the past month, and patients who attempted suicide (yes/no) during the 3 months prior to enrollment and throughout the study, assessed by the C-SSRS at baseline, 6 and 12 months, were our main outcome measures.

2.6. Statistical analysis

Analyses were performed using STATA v.17.0. Statistical significance was set at $p<0.05$. Data normality was tested by P-P plots and the Shapiro-Wilk test. Descriptive data are shown as mean (SD) or frequency and %. Impairment of EF is presented at the task and variable level. The longitudinal associations (i.e., from baseline to 12 months) between EF impairments, suicidal ideation and suicide attempts at the task and variable levels were estimated using logistic mixed-effects models. Because the severity of suicidal ideation was positively skewed and overdispersed, the longitudinal effects of task- and variable-level EF impairments were analyzed using negative binomial mixed-effects models. Sociodemographic and clinical variables used to adjust the models were selected based on their potential to influence both suicide and EF outcomes based on previous literature (Franklin et al., 2017; Gregory et al., 2020; Hawton et al., 2013; Lee et al., 2011; Semkovska et al., 2019; Wagner et al., 2012). The goodness-of-fit of the computed mixed-effect models was gradually tested considering the inclusion of different sets of confounders: (1) time of follow-up, (2) socio-demographic variables, (3) clinical variables, and (4) time-level random slope. Goodness-of-fit measures based on AIC and BIC reported a better fit for those models with all covariates and subject-level intercept (see Table S4). Models with time-level random slope provided analogous coefficient results to those without random slope, but with a worse fit to the data. Therefore, the final models chosen, based on best model fit measures, include a subject-level random intercept with an unstructured covariance matrix, but no random slope.

3. Results

3.1. Sample characteristics

The sociodemographic, clinical, and cognitive characteristics of the sample are shown in Table 1. During the study, 42.31% ($n = 44/104$) of participants were lost to follow-up, 29.81% at 6 months and 16.35% at 12 months. Four patients (3.85%) that did not attend the 6-month follow-up completed the 12-month follow-up (Fig. 1). Dropout was more frequent among unemployed (OR = 0.408; 95% CI: 0.181–0.920; $p = 0.031$) and first-episode patients (OR = 2.797; 95% CI: 1.110–7.062; $p = 0.029$). No significant differences were found in any other variable between first episode and recurrent episode patients.

At baseline, 82 (78.85%) patients had a history of suicidal ideation and 24 (23.08%) of suicide attempt. Similar to the frequency and severity of depression, the prevalence of suicidal ideation and the severity of suicidal ideation tended to decrease throughout the study, with a marked decrease during the first follow-up (6-months) and a slight increase at the second follow-up (12-months). Nine participants attempted suicide over the course of the study: 8 during the first follow-up, 3 during the second follow-up, and 2 at both follow-ups. Most suicide attempts involved some medical attention and risk of injury (for details, see Table S2). There were no suicide deaths.

Impairment in at least one EF was observed in approximately one

Table 1
Sociodemographic, clinical and cognitive characteristics of patients ($N = 236$ observations).

Mean (SD) or frequency and % are reported	**Baseline** ($n = 104$)		**6 months** ($n = 72$)		**12 months** ($n = 60$)		*P* value[e]
Sociodemographic characteristics							
Age, years	41.44	(12.89)	42.57	(12.98)	43.88	(12.46)	0.240
Female sex	66	63.46	43	59.72	38	63.33	0.923
Education (≥12 years)	33	31.73	22	30.56	23	38.33	0.446
Professional status (employed)	46	44.23	35	48.61	32	53.33	0.258
Civil status (married)	45	43.27	16	22.22	15	25.00	N/A
Clinical features							
Current MDD episode	104	100	60	83.33	48	80.00	N/A
First MDD episode	73	70.19	45	62.50	37	61.67	0.229
IDS-SR30 total score	42.79	(11.70)	29.53	(16.44)	30.58	(17.97)	**<0.001**
Duration of the MDD episode							0.966
<12 months	60	57.69	39	54.17	32	53.33	
≥12 – 24 months	15	14.42	12	16.67	11	18.33	
>24 months	29	27.88	21	29.17	17	28.33	
Antidepressant treatment	80	76.92	50	69.44	44	73.33	0.551
Psychiatric comorbidities							0.542
0	55	52.88	37	51.39	32	53.33	
1	31	29.81	25	34.72	23	38.33	
≥2	18	17.31	10	13.89	5	8.33	
Suicide outcomes							
History of suicidal ideation	82	78.85	62	83.78	51	85.00	0.268
Suicidal ideation	61	58.65	22	30.56	26	43.33	**0.018**
Severity of suicidal ideation	1.46	(1.59)	0.67	(1.29)	1.05	(1.48)	**0.031**
Suicide attempt	8	7.69	7	9.72	3	5.00	0.354
Mean number of suicide attempts	1.25	(0.77)	1.14	(0.38)	1	(0.00)	0.495
Family history of suicide attempt/death	23	22.11	18	25.00	15	25.00	0.644
EF impairments							
Impairment in at least one EF	33	31.73	24	33.33	16	26.67	0.550
Spatial Working Memory (SWM)[a]	9	8.65	11	15.28	5	8.33	0.898
SWM Between Errors	13	12.50	12	16.67	7	11.67	0.978
SWM Strategy (6–8 boxes)	12	11.54	10	13.89	6	10.00	0.832
One Touch Stockings (OTS) of Cambridge[b]	8	7.77	4	5.63	2	3.33	0.258
OTS Problems Solved on First Choice	12	11.65	12	16.67	8	13.33	0.661
OTS Median Latency to First Choice	9	8.74	4	5.63	5	8.33	0.824
Stop Signal Task (SST Stop Signal Reaction Time)[c]	15	15.00	8	11.59	6	10.17	0.362
Cambridge Gambling Task (CGT)[d]	11	11.11	7	10.14	6	10.34	0.864
CGT Delay Aversion Total	15	15.15	12	17.39	5	8.62	0.293
CGT Decision Making Quality Total Merged	13	13.13	10	14.49	9	15.52	0.672
CGT Risk Adjustment Merged	13	13.13	10	14.49	10	17.24	0.494

MDD: major depressive disorder; IDS-SR30: Inventory of Depressive Symptomatology-Self Rated; EF; executive function; SD: standard deviation; N/A: not applicable.
[a] SWM completed tests at baseline, $n = 104$; 6 months, $n = 72$; and 12 months, $n = 60$.
[b] OTS completed tests at baseline, $n = 103$; 6 months, $n = 71$; and 12 months, $n = 60$.
[c] SST completed tests at baseline, $n = 100$; 6 months, $n = 69$; and 12 months, $n = 59$.
[d] CGT completed tests at baseline, $n = 99$; 6 months, $n = 69$; and 12 months, $n = 58$.
[e] *P* values were determined by orthogonal polynomial trend analysis for linear effects, except in variables with >2 categories, where chi-square tests were performed. Statistically significant results ($p < 0.05$) are highlighted in bold.

third of the patients, with SST and CGT being the tasks with the highest prevalence of impairment. The prevalence of EF impairment remained relatively stable throughout the study, regardless of changes in depression severity.

3.2. Longitudinal associations between EF impairments and suicidal ideation

At the task level, CGT impairment was associated with a higher prevalence of suicidal ideation throughout the study (OR = 5.319; 95% CI: 1.393 – 20.320) (Table 2; Fig. 2A). At the variable level, only impairment in CGT Delay Aversion Total emerged as a longitudinal significant factor (OR = 3.722; 95% CI: 1.216 – 11.400) (Table 3; Fig. 2B). Other factors that showed a significant association with higher prevalence of suicidal ideation were younger age, higher education (only in the variable-level model), more severe depressive symptoms (IDS-SR-30 total score), and lifetime suicidal ideation. Both task-level (X^2 (14,225) = 38.66; $p < 0.001$) and variable-level (X^2 (18,225) = 41.12; $p = 0.002$) models showed adequate goodness-of-fit. Additional analyses are shown in Table S3 (SM).

3.3. Longitudinal associations between EF impairments and severity of suicidal ideation

Impairment in CGT Delay Aversion Total variable was the only cognitive factor that showed a significant association with greater severity of suicidal ideation throughout the study (IRR = 1.556; 95% CI: 1.025 – 2.362) (Tables 2 and 3; Fig. 2C). Again, younger age, more severe depressive symptoms, and lifetime suicidal ideation showed significant longitudinal associations with greater severity of suicidal ideation. Both task-level (X^2 (14,225) = 75.15; $p < 0.001$) and variable-level (X^2 (18,225) = 83.80; $p < 0.001$) models showed adequate goodness-of-fit. Additional analyses are shown in Table S3 (SM).

3.4. Longitudinal associations between EF impairments and suicide attempt

Impairment in OTS Problems Solved on First Choice variable was the only cognitive factor that showed a significant association with suicide attempt throughout the study (OR = 8.810; 95% CI: 1.616 – 47.134) (Table 3; Fig. 2D). Another factor that showed a significant longitudinal association with this suicide outcome was greater severity of suicidal

Table 2
Longitudinal associations between task-level EF impairments and suicide outcomes ($N = 225$ observations).

	Suicidal ideation			Severity of suicidal ideation			Suicide attempt		
	OR[c]	95% CI	*P* value	IRR	95% CI	*P* value	OR[c]	95% CI	*P* value
Time of follow-up (ref. baseline)									
6 months	0.443	0.184 – 1.067	0.069	0.576	0.378 – 0.880	**0.011**	0.361	0.037 – 3.493	0.379
12 months	1.048	0.423 – 2.582	0.925	0.860	0.583 – 1.267	0.446	0.190	0.016 – 2.246	0.188
Age, years	0.952	0.922 – 9.823	**0.003**	0.979	0.963 – 0.995	**0.011**	1.025	0.956 – 1.099	0.489
Sex (ref. male)	0.775	0.372 – 1.616	0.497	0.841	0.560 – 1.265	0.406	0.328	0.056 – 1.916	0.216
Education (ref. <12 years)	2.210	0.971 – 5.031	0.058	1.378	0.889 – 2.135	0.151	2.196	0.360 – 13.410	0.394
First MDD episode (ref. recurrent)	1.213	0.563 – 2.614	0.621	1.484	0.952 – 2.314	0.082	1.117	0.188 – 6.631	0.903
IDS-SR30 total score[a]	1.095	1.060 – 1.131	**<0.001**	1.050	1.035 – 1.066	**<0.001**	1.033	0.969 – 1.102	0.315
Psychiatric comorbidities (ref. none)									
1	1.147	0.510 – 2.579	0.739	0.865	0.579 – 1.294	0.482	0.863	0.161 – 4.634	0.864
≥2	0.537	0.143 – 2.014	0.357	0.718	0.394 – 1.307	0.278	1.442	0.111 – 18.700	0.779
Lifetime suicidal ideation (ref. no)	5.867	1.851 – 18.600	**0.003**	3.402	1.785 – 6.486	**<0.001**			
Severity of suicidal ideation[a]							3.439	1.418 – 8.338	**0.006**
Family history of suicide attempt/death (ref. no)							4.716	0.272 – 81.815	0.287
Spatial Working Memory (SWM) (ref. preserved)[a]	1.906	0.567 – 6.410	0.297	1.471	0.887 – 2.440	0.135	0.598	0.045 – 8.044	0.698
One Touch Stockings (OTS) of Cambridge (ref. preserved)[a]	0.554	0.131 – 2.345	0.422	1.148	0.578 – 2.279	0.693	1.181	0.592 – 23.566	0.913
Stop Signal Task (SST) (ref. preserved)[a]	0.754	0.131 – 2.148	0.598	1.167	0.719 – 1.893	0.533	0.369	0.037 – 3.631	0.393
Cambridge Gambling Task (CGT) (ref. preserved)[a]	5.319	1.393 – 20.320	**0.015**	1.406	0.855 – 2.312	0.179	0.387	0.026 – 5.703	0.489
Subject-level random intercept[b]	0.281	0.003 – 25.407		0.343	0.125 – 0.939		5.068	0.495 – 51.844	

EF: executive function; MDD: major depressive disorder; IDS-SR30: Inventory of Depressive Symptomatology-Self Rated; OR: odds ratio; CI: confidence interval; IRR: incidence-rate ratio.

[a] Time-varying variable.

[b] Standard deviation and 95% CI is reported.

[c] Absence of suicidal ideation or suicide attempt is the reference group.
Statistically significant results ($p < 0.05$) are highlighted in bold.

ideation. Only the variable-level model (X^2 (19,225) = 37.97; p = 0.006), but not the task-level model (X^2 (15,225) = 15.45; p = 0.419), showed adequate goodness-of-fit. Therefore, caution is advised when interpreting the latter model. Additional analyses are shown in Table S3 (SM).

4. Discussion

To our knowledge, this is the first prospective study that has specifically examined longitudinal associations between EF impairments and suicide risk in adult patients with MDD. Our results show that patients with increased risk-taking and impulse control difficulties in decision-making had a higher prevalence of suicidal ideation and greater severity of suicidal ideation than patients without EF impairments. Also, that patients with impaired spatial planning and working memory were more prone to suicide attempts. Overall, these results endorse previous case-control and cross-sectional studies showing that cognitive impairment and executive dysfunction in particular are related to suicide risk in depression (Lalovic et al., 2022). Furthermore, they add to this literature that this association would be maintained in the long term, supporting it as a longitudinal risk factor for suicide.

In a more detailed analysis, higher prevalence of suicidal ideation showed significant longitudinal associations with both impairment in the domain of decision-making (i.e., task-level CGT) and impairment in the specific outcome variable CGT Delay Aversion Total. Similarly, greater severity of suicidal ideation showed a significant longitudinal association with impairment on this specific outcome variable, but not with task-level CGT. Impairment in CGT Delay Aversion Total indicates the presence of risk-taking behavior and impulsive responses during task performance, suggesting that, within impaired decision-making, these deficits would be the main neuropsychological feature of MDD patients with suicidal ideation. This contrasts with previous studies that found no relationship between suicidal ideation, poor decision making and increased risk taking assessed by the CGT (Dombrovski et al., 2010) or the Iowa Gambling Task [a measure that simulates real-life decision--making] (Gorlyn et al., 2013), but are consistent with other cross-sectional studies that did find relationships between these variables (Cáceda et al., 2014; Chamberlain et al., 2013; Clark et al., 2011; Harfmann et al., 2019; Westheide et al., 2008). More recently, Liaugaudaite et al. (2020) suggested that outpatients with anxiety and mood disorders with suicidal ideation could be distinguished from those without suicidal ideation by the presence of executive dysfunction, particularly in impulse control and risk-taking behavior. Indeed, impulsivity has been linked to impaired cognitive inhibition (Logan et al., 1997), which may translate into difficulty resisting the urge to act on suicidal thoughts (Marzuk et al., 2005; Richard-Devantoy et al., 2012a), supporting the notion that impairments in these domains of EF and especially in decision-making and cognitive inhibition are possible neurocognitive markers of suicide risk in this clinical population (Allen et al., 2019; Richard-Devantoy et al., 2012b).

In contrast to other studies that found a direct relationship between suicide attempts, poor decision making, increased risk taking and impulse control difficulties (Cáceda et al., 2014; Clark et al., 2011; Dombrovski et al., 2010; Harfmann et al., 2019; Ho et al., 2018; Jollant et al., 2005; Moniz et al., 2017; Richard-Devantoy et al., 2012b; Szanto et al., 2015), we found that this suicide outcome only showed a significant longitudinal association with impairment in the specific outcome variable OTS Problems Solved on First Choice, a measure of spatial planning, and also of working memory. Research that has examined the relationship between suicide attempts and planning is limited compared to that which has examined working memory. Almost contrary to our results, Dombrovski et al. (2010) found that patients with depression and a history of suicide attempt have intact spatial planning and working memory assessed with the OTS, with no significant differences from patients with suicidal ideation, non-suicidal patients, and healthy controls. However, this study is limited by its cross-sectional design. Moniz et al. (2017) concluded that patients with depression and history of suicide attempt have better planning skills than those without previous suicide attempts assessed with the Tower of London [a problem-solving-based planning measure], with no significant differences from healthy controls. However, this difference was no longer significant when the Bonferroni correction was applied, so caution is advised when interpreting their results. In our study, the results suggest planning impairment being longitudinally associated with the occurrence of suicide attempts. In this context of highly variable data, one could speculate that MDD patients with impairment in this EF might

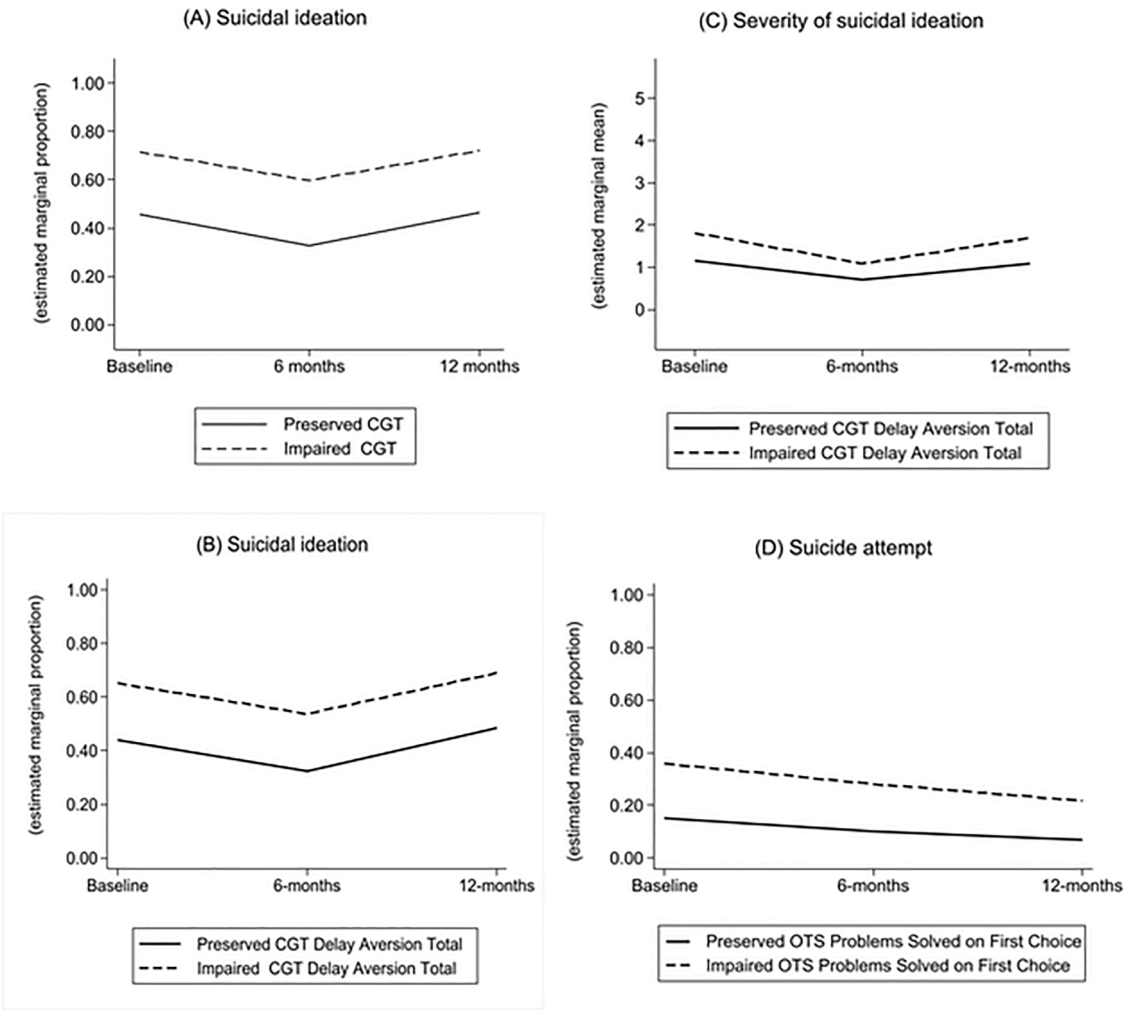

Fig. 2. Graphical representation of significant longitudinal associations between time-varying EF impairments and suicide outcomes. CGT: Cambridge Gambling Task; OTS: One Touch Stockings of Cambridge; EF: executive function. Data are adjusted for significant sociodemographic and clinical variables according to results in Tables 2 and 3. (A) Longitudinal association between task-level CGT and suicidal ideation. Statistically significant at $p = 0.015$. (B) Longitudinal association between variable-level CGT Delay Aversion Total and suicidal ideation. Statistically significant at $p = 0.021$. (C) Longitudinal association between variable-level CGT Delay Aversion Total and severity of suicidal ideation. Statistically significant at $p = 0.038$. (D) Longitudinal association between variable-level OTS Problems Solved on First Choice. Statistically significant at $p = 0.011$.

have additional difficulties in adequately managing and organizing their daily lives, worsening stress levels, and further depreciating their already devalued self-esteem, which could increase the risk of suicide.

Regarding working memory, several systematic reviews and meta-analyses have found that people who attempt suicide show deficits in this EF (Allen et al., 2019; Lalovic et al., 2022). In our study we found both positive and negative results between working memory impairments and suicide attempts. Whereas the OTS Problems Solved on First Choice variable shows a longitudinal association with a higher prevalence of suicide attempts, the SWM task [a measure of working memory and strategy] yields negative results. The efficient functioning of working memory has been related to inhibitory processes that filter access to information and update its content by eliminating representations that are no longer important (Logan and Cowan, 1984). In this sense, patients with an inhibitory deficit are more prone to be distracted by irrelevant information and thoughts than patients without cognitive impairment. Indeed, a reduced ability to inhibit irrelevant information is a well-established predictor of impaired working memory (Kane and Engle, 2002). This may translate into an inability to reduce the intrusion of suicidal thoughts that would invade working memory and diminish its performance, accentuating the impression of being unable to cope with the situation and, therefore, the risk of suicide (Keilp et al., 2013; Richard-Devantoy et al., 2012a). In fact, executive dysfunction has been found to be evident in all MDD patients with suicidal risk, but greater in those with a history of suicide attempt and current suicidal ideation, as they show a processing bias and inhibitory deficit for negative and mood-congruent information (Harfmann et al., 2019). Consistent with these results, we found that risk-taking behavior and difficulty in impulse control were the main neuropsychological features of MDD patients with suicidal ideation, and that impaired planification, working memory functioning and greater severity of suicidal ideation showed significant longitudinal associations with suicide attempts. However, further studies are needed to confirm whether risk-taking behavior and impulse control difficulties in patients with suicidal ideation immediately precede suicide attempts, and to clarify the possible longitudinal relationships between working memory and suicide risk given our conflicting result between OTS and SWM.

As expected, younger age (McGirr et al., 2008) and more severe depressive symptoms showed significant longitudinal associations with a higher prevalence of suicidal ideation and greater severity of suicidal ideation (Franklin et al., 2017; Hawton et al., 2013). In turn, greater severity of suicidal ideation was the only non-cognitive factor with a significant longitudinal association with suicide attempts (Shelef et al., 2019). The fact that patients with higher education showed a higher

Table 3
Longitudinal associations between variable-level EF impairments and suicide outcomes ($N = 225$ observations).

	Suicidal ideation			Severity of suicidal ideation			Suicide attempt		
	OR[c]	95% CI	*P* value	IRR	95% CI	*P* value	OR[c]	95% CI	*P* value
Time of follow-up (ref. baseline)									
6 months	0.482	0.201 – 1.154	0.101	0.601	0.406 – 0.890	**0.011**	0.488	0.668 – 3.572	0.480
12 months	1.30	0.519 – 3.261	0.574	0.933	0.644 – 1.352	0.714	0.252	0.031 – 2.051	0.198
Age, years	0.955	0.925 – 0.986	**0.005**	0.981	0.966 – 0.997	**0.023**	1.035	0.981 – 1.091	0.213
Sex (ref. male)	0.807	0.385 – 1.692	0.570	0.853	0.570 – 1.276	0.438	0.410	0.124 – 1.361	0.145
Education (ref. <12 years)	2.499	1.077 – 5.794	**0.033**	1.482	0.949 – 2.314	0.083	3.371	0.862 – 13.189	0.081
First MDD episode (ref. recurrent)	1.415	0.665 – 3.054	0.377	1.520	0.979 – 2.360	0.062	1.421	0.381 – 5.324	0.599
IDS-SR30 total score[a]	1.093	1.058 – 1.128	**<0.001**	1.051	1.035 – 1.067	**<0.001**	1.022	0.974 – 1.072	0.383
Psychiatric comorbidities (ref. none)									
1	1.311	0.565 – 3.045	0.529	0.906	0.612 – 1.342	0.623	1.045	0.275 – 3.970	0.949
≥2	0.630	0.159 – 2.490	0.509	0.799	0.445 – 1.436	0.453	2.991	0.436 – 20.538	0.265
Lifetime suicidal ideation (ref. no)	4.771	1.541 – 14.771	**0.007**	3.116	1.650 – 5.887	**<0.001**			
Severity of suicidal ideation[a]							2.674	1.519 – 4.710	**0.001**
Family history of suicide attempt/death (ref. no)							3.971	0.524 – 30.078	0.182
SWM Between Errors (ref. preserved)[a]	1.087	0.337 – 3.510	0.889	1.000	0.628 – 1.590	0.999	1.477	0.233 – 9.385	0.679
SWM Strategy (6–8 boxes) (ref. preserved)[a]	1.053	0.308 – 3.601	0.934	1.251	0.790 – 1.981	0.339	0.914	0.159 – 5.242	0.920
OTS Problems Solved on First Choice (ref. preserved)[a]	1.508	0.543 – 4.189	0.431	1.298	0.820 – 2.056	0.266	8.810	1.616 – 47.134	**0.011**
OTS Median Latency to First Choice (ref. preserved)[a]	0.300	0.066 – 1.355	0.118	0.498	0.222 – 1.115	0.090	0.131	0.005 – 3.156	0.210
SST Stop Signal Reaction Time (ref. preserved)[a]	1.024	0.664 – 1.578	0.914	1.229	0.783 – 1.930	0.370	1.341	0.669 – 2.689	0.408
CGT Delay Aversion Total (ref. preserved)[a]	3.722	1.216 – 11.400	**0.021**	1.556	1.025 – 2.362	**0.038**	1.204	0.268 – 5.415	0.809
CGT Decision Making Quality Total Merged (ref. preserved)[a]	1.106	0.408 – 3.000	0.843	0.880	0.529 – 1.470	0.623	0.786	0.148 – 4.186	0.778
CGT Risk Adjustment Merged (ref. preserved)[a]	0.575	0.210 – 1.574	0.281	0.881	0.546 – 1.423	0.605	1.210	0.201 – 7.268	0.836
Subject-level random intercept[b]	0.260	0.002 – 43.24		0.371	0.133 – 1.034		0.952	0.007 – 130.368	

EF: executive function; MDD: major depressive disorder; IDS-SR30: Inventory of Depressive Symptomatology-Self Rated; SWM: Spatial Working Memory; OTS: One Touch Stockings of Cambridge; SST: Stop Signal Task; CGT: Cambridge Gambling Task; OR: odds ratio; CI: confidence interval; IRR: incidence-rate ratio.

[a] Time-varying variable.

[b] Standard deviation and 95% CI is reported.

[c] Absence of suicidal ideation or suicide attempt is the reference group.

Statistically significant results ($p < 0.05$) are highlighted in bold.

prevalence of suicidal ideation was an unexpected finding (Phillips and Hempstead, 2017). However, none of these sociodemographic or clinical variables counteracted the influence of executive dysfunction on suicide outcomes. Furthermore, our results point to cognitive impairment being at least partially independent of depression severity, as the prevalence of EF impairments remained relatively stable despite changes in depressive symptoms, suggesting that cognitive impairment in MDD patients is a disease-dependent rather than state-dependent trait (Reppermund et al., 2009).

As clinical implications, our results point to the existence of difficulties in impulse control as a longitudinal correlate of suicidal ideation in patients with MDD. If confirmed in future longitudinal studies with larger samples, it would be of great help for the rapid identification of depressed subjects at high risk for taking the decision to suicide and thus a candidate transdiagnostic factor for suicide prevention (Lalovic et al., 2022). Our results also support that MDD patients with suicidality might benefit from cognitive remediation interventions focused on improving executive dysfunction (Legemaat et al., 2021; Vicent-Gil et al., 2022).

This study is not without limitations. First, the lack of a healthy control group limits the generalizability of our results regarding the profile and prevalence of cognitive impairment. In addition, we did not assess all cognitive domains. For data on the longitudinal association of cognitive domains other than EF with suicidal behavior, see (Gorlyn et al. (2015) and Lan et al. (2020)). Not having used a measure of intelligence quotient is another limitation of the study. Instead, education was used as a proxy for intelligence quotient (Deary and Johnson, 2010). Moreover, all cognitive variables were standardized and demographically corrected to remove the effects of age, sex, and education (see data pre-processing at SM). Another limitation is that neither the role of attention deficit/hyperactivity disorder on executive functioning (Brown, 2009), nor its relationship with suicide risk (Brown et al., 2022), was controlled for. Therefore, diagnostic interviews that include assessment of this disorder are recommended in future research on this topic (i.e., MINI-Plus). The inclusion of patients with recurrent episodes is another limitation since the initial design only considered the inclusion of patients with a first episode. However, as we did with education, all mixed-effects models were controlled for these variables, which turned out to be non-significant, except for a single significant effect of higher education on suicidal ideation that requires further examination in future studies. The severity of depressive symptoms was assessed using a self-rated measure. It is well known that the patient's perception of the severity of depression does not always coincide with that of the clinician (Baune and Christensen, 2019). Therefore, the diagnosis of MDD was always confirmed by the MINI administered at each follow-up by an experienced psychiatrist or psychologist. As for treatments, only the number of patients who were on antidepressant treatment but not on other pharmacological (e.g., benzodiazepines, stimulants) or psychotherapeutic treatments was recorded, so we cannot determine its specific effect in this study. Doses of psychotropic drugs were also not recorded. Yet, the longitudinal design, which allows to establish sustained relationships between EF impairments and suicide outcomes, and the statistical analysis based on mixed-effects models, which deals with missing data, unbalanced groups, and multiple repeated measures at once, are strengths that lend value to the study. Future studies using complementary statistical analyses (e.g., survival models) are encouraged. Finally, it should be noted that this study has a relatively small sample size, so generalization of these results to other adult MDD patients different from those in our study sample requires caution. Studies with larger samples that allow a more exhaustive analysis of the relationship between EF and suicidality, controlling for specific comorbid diagnoses, are also desirable.

In summary, this is the first longitudinal study to demonstrate that, whereas poor decision making, increased risk taking and difficulties in impulse control are risk factors for higher prevalence of suicidal ideation and greater severity of suicidal ideation in adult patients with MDD, impaired spatial planning and working memory are presumptive risk factors for suicide attempts. Among these deficits, impaired risk-taking and cognitive inhibition appear to be the main neurocognitive

markers for increased suicide risk in depressed patients, so clinicians should be especially attentive to dysfunctions in these domains of EF. Although the present study overcomes some of the limitations of previous research, further longitudinal studies are needed to confirm our results in larger samples of participants, providing more detailed insight into the temporal progression from suicidal ideation to attempt and how EF performance may change along this continuum.

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Ethical standards

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.

Authorship and contributorship

MR and MG are the principal investigators and developed the original study idea and study design. PRS, ARLA, VCS and AC performed the study evaluations. PRS and JJM performed the statistical analysis. PRS and GNV drafted the first version of the manuscript. All authors contributed to the interpretation of the data, critically reviewed the article for important intellectual content, approved the final version for publication, and were sufficiently involved in the work to take public responsibility for appropriate portions of the content.

Declaration of Competing Interest

MR received research funding from Lundbeck and Janssen. The other authors have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115235.

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