

Research Article

Cite this article: Barlati S, Nibbio G, Bellomo A, Carpinello B, Colombo C, De Giorgi S, Deste G, Maina G, Martinotti G, Tortorella A, Di Salvo G, Luciano M, Pinna F, Ventriglio A, Fiorillo A (2025).and Vita A the CogRemMDD Study Group (2025).

Effectiveness of cognitive remediation in subjects with major depressive disorder: A multicenter randomized controlled study in a real-world setting. *European Psychiatry*, **68**(1), e106, 1–8

<https://doi.org/10.1192/j.eurpsy.2025.10073>

Received: 08 May 2025

Revised: 02 July 2025

Accepted: 09 July 2025

Keywords:

cognition; cognitive rehabilitation; cognitive remediation; cognitive training; depression; RCT

Corresponding author:

Gabriele Nibbio;









Email: gabriele.nibbio@gmail.com

Members of the CogRemMDD Study Group include: Nicola Necchini, Irene Calzavara-Pinton, Daniela Zardini (Department of Clinical and Experimental Sciences, University of Brescia); Fabiana Ricci, Chiara Villani, Laura De Masi (Department of Clinical and Experimental Medicine, University of Foggia); Luca Marras, Pasquale Paribello, Federico Suprani (Department of Medical Sciences and Public Health, University of Cagliari); Paola Calò, Tiziana De Donatis (Department of Mental Health, ASL Lecce); Elena Teobaldi, Matteo Bianco, Gabriele Aschiero (Department of Neurosciences Rita Levi Montalcini, University of Torino); Maria Chiara Alessi, Francesco Di Carlo (Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti); Giulia Menculini (Department of Psychiatry, University of Perugia); Bianca Della Rocca, Matteo Di Vincenzo, Vincenzo Giallonardo (Department of Psychiatry, University of Campania "L.Vanvitelli", Naples).

© The Author(s), 2025. Published by Cambridge University Press on behalf of European Psychiatric Association. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.



Effectiveness of cognitive remediation in subjects with major depressive disorder: A multicenter randomized controlled study in a real-world setting

Stefano Barlati^{1,2} , Gabriele Nibbio², Antonello Bellomo³ , Bernardo Carpinello⁴ , Cristina Colombo⁵, Serafino De Giorgi⁶, Giacomo Deste^{2,7} , Giuseppe Maina⁸ , Giovanni Martinotti⁹, Alfonso Tortorella¹⁰, Gabriele Di Salvo⁸, Mario Luciano¹¹ , Federica Pinna⁴, Antonio Ventriglio³ , Andrea Fiorillo¹¹  and Antonio Vita^{1,2} the CogRemMDD Study Group

¹Department of Mental Health and Addiction Services, ASST Spedali Civili of Brescia, Brescia, Italy; ²Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; ³Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; ⁴Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; ⁵Department of Clinical Neurosciences, University Vita-Salute San Raffaele, Milan, Italy; ⁶Department of Mental Health, ASL Lecce, Lecce, Italy; ⁷Department of Mental Health and Addiction Services, ASST Valcamonica, Esine, Italy; ⁸Department of Neurosciences Rita Levi Montalcini, University of Torino, Turin, Italy; ⁹Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy; ¹⁰Department of Psychiatry, University of Perugia, Perugia, Italy and ¹¹Department of Psychiatry, University of Campania "L.Vanvitelli", Naples, Italy

Abstract

Background. Cognitive impairment represents a central component of major depressive disorder (MDD), affecting a large proportion of people living with MDD and showing a consistent negative impact on social, interpersonal, and occupational functioning and subjective quality of life. Cognitive remediation (CR) is a training-based psychosocial intervention targeting cognitive performance and psychosocial functioning that has shown consistent evidence of effectiveness in individuals with schizophrenia and that could provide significant benefits also in people with MDD: this study aimed to assess the effects of a computerized CR intervention in adults living with MDD.

Methods. Participants recruited in this single blind multicentric randomized controlled trial were allocated to receive a computerized CR intervention delivered by an active and trained therapist or to an active control condition (computer games – CG). Outcomes were measured with validated instruments by blind assessors and included cognitive performance, depressive symptoms, and psychosocial functioning. Outcomes were assessed using mixed models for repeated measures, considering baseline and end-of-treatment scores.

Results. Hundred and one participants (CR=52 and CG=49) were included and 81 (CR=45 and CG=36) completed the study. CR produced superior results in clinician-rated depressive symptoms ($p=0.023$, $d=0.42$), global clinical severity ($p=0.025$, $d=0.39$), subjective depressive symptoms ($p=0.005$, $d=0.45$), working memory performance ($p=0.004$, $d=0.34$), executive functions/cognitive flexibility ($p=0.020$, $d=0.43$), and subjective cognitive impairment ($p=0.006$, $d=0.48$).

Conclusions. CR represents an effective intervention in MDD, improving clinical outcomes and cognitive performance in a clinician-rated and in a subjective manner, which should be more consistently implemented in clinical practice and included in MDD treatment recommendations.

Introduction**Background**

Major depressive disorder (MDD) represents one of the most common mental health conditions on a global level, showing a lifetime prevalence of over 20% in high-income countries and interesting more than 300 million people worldwide [1–3]. It also represents an essential source of disability, producing a significant socio-economic burden that extends well beyond direct healthcare costs [4].

Cognitive impairment represents a central component of MDD [5–7]. Despite the high level of heterogeneity of clinical presentations of the disorder, cognitive impairment affects a large proportion of people with MDD, often reaching moderate levels of severity and emerging from the first depressive episode [8–10]. This impairment frequently persists after the remission of the

affective episode and appears to increase in severity over time with relapses and with age [11, 12], involves both “hot” and “cold” cognitive functions [13–15] and appears to be composed of state, trait, and scar elements [5, 16, 17]. Processing speed appears to be the most heavily interested domain, showing also a state-dependent effect during affective episodes, but attention, memory, and executive functions are also involved [6, 18, 19].

Cognitive deficits in MDD represent one of the core determinants of impairment in social, interpersonal, and occupational functioning and also have a significant negative impact on subjective quality of life [20–24]. As such, they are becoming a treatment target of increasing importance and interest [2].

Cognitive remediation (CR) is a training-based psychosocial intervention targeting cognitive performance to provide significant and durable improvement in psychosocial functioning [25]. Based on the structured repetition of cognitive exercises and the development of novel strategies with the help of an active and trained therapist [26], CR interventions have been shown to provide substantial positive effects on cognitive performance and on psychosocial functioning in people living with schizophrenia [27–31] which are durable over time [32]. As such, it currently represents the psychosocial intervention with the highest level of recommendation in the European Psychiatric Association guidance for the treatment of cognitive impairment in schizophrenia [33].

CR interventions appear as a promising treatment also in MDD: recently, four meta-analyses have specifically investigated this topic [34–37]. The first meta-analysis included 8 studies and 268 adults with MDD and reported positive treatment effects on most cognitive domains [37]. A meta-analysis included 19 studies for a total of 944 participants with MDD or clinically relevant and depressive symptoms and included both a superiority and a noninferiority analysis: CR emerged as effective in treating depressive symptoms and noninferior to standard interventions for depression [36]. Another meta-analysis included studies on individuals with affective disorders for a total of 22 randomized controlled trials, 4 of which of individuals with bipolar disorder, and 993 participants: it reported small to moderate positive treatment effects on cognitive performance and depressive symptoms [34]. Finally, another meta-analysis included only MDD studies and included 21 trials and 978 participants: significant positive effects were observed on all outcomes, medium-sized on cognitive performance, and small-sized in depressive symptoms and daily functioning [35].

While the results of these works converged in many aspects and showed that CR can represent an effective intervention in MDD, they also highlighted the current limitations in the available evidence: the certainty in the evidence assessed by Legamaat et al. with the GRADE procedure was very low for depressive symptoms and daily functioning, and low for cognitive performance [35].

Besides the high level of heterogeneity in participants’ characteristics, interventions, and measures included in the trials, most available studies included only small samples and were conducted in a single research center. Moreover, subjective experiences of participants and patient-reported outcomes measures, which are becoming increasingly important in a regulatory and in a treatment personalization perspective [38], were seldom considered in available trials.

In this perspective, a large multicentric randomized controlled trial, adopting standardized and validated tools, including patient-reported outcomes, could offer valuable insights into cognitive, depressive, and psychosocial outcomes in MDD from both scientific and clinical perspectives.

Aims

The aims of the present single blind, multicentric randomized controlled trial were to assess the effects of a computerized CR intervention delivered by an active and trained therapist compared to an active control condition (computer games) in adults living with MDD undergoing a Major Depressive Episode (MDE) on cognitive performance, depressive symptoms, and psychosocial functioning. The main research hypothesis was that CR could provide significant improvements in all these outcomes and that the positive effects would be observed in both external, investigator-rated measures and in subjective, participant-reported measures.

Methods

Study design and participants

The present trial included nine different centers for the recruitment of participants: I) Department of Mental Health and Addiction Services, ASST Spedali Civili di Brescia and Department of Clinical and Experimental Sciences, University of Brescia, which also acted as the coordinating center; II) Department of Psychiatry, University of Campania Luigi Vanvitelli, Naples; III) Department of Clinical and Experimental Medicine, University of Foggia; IV) Department of Medical Sciences and Public Health, Psychiatry Section, University of Cagliari; V) Department of Clinical Neurosciences, IRCCS San Raffaele, Milan; VI) Department of Mental Health, ASL Lecce; VII) AOU San Luigi Gonzaga, Orbassano and Department of Neurosciences, University of Turin; VIII) Ospedale Santa Maria della Misericordia and Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, University of Perugia; IX) Department of Neurosciences, Imaging and Clinical Sciences, “Gabriele D’Annunzio” University of Chieti-Pescara.

Centralized training for the delivery of the CR and the control intervention and for the administration and rating of all outcome measures for researchers of all participating centers took place before the start of the study. Regularly scheduled online meetings were held during the course of the study between the coordinating center and all participating centers to assess and resolve potential issues.

Participants were consecutively recruited in each center with the following inclusion criteria: I) diagnosis of MDD according to DSM-5 criteria [39] confirmed with the Structured Clinical Interview for DSM-5- Clinical Version (SCID-5-CV) [40]; II) age between 18 and 60 years; III) clinical diagnosis of current MDE of mild or moderate severity according to DSM-5 criteria; IV) education of at least 8 years; V) consent to participate in the study, attested by a signed written informed consent form.

Exclusion criteria were: I) history of neurological disorders or severe traumatic head injury; II) diagnosis of intellectual disability; III) history of manic or hypomanic episodes, schizophrenia spectrum disorders or other psychotic disorders; IV) MDE with psychotic features and/or treatment resistance; V) history of alcohol or substance abuse in the previous 6 months; VI) participation in any type of CR intervention in the previous 6 months; VII) concurring pharmacological treatment with mood stabilizers, and first or second generation antipsychotics (benzodiazepines or Z-drugs low dose treatments were accepted); VIII) pregnancy.

Both outpatients and inpatients in psychiatric rehabilitation settings were considered for inclusion, as long as they met all inclusion criteria and no exclusion criteria. Participants were consecutively enrolled in each center from the study start (April 2021)

to the recruitment of the targeted number of participants for each center, based on the results of a power analysis conducted prior to the start of the study.

All individuals who were considered for enrollment received a detailed explanation of the study aims and procedures. The subject agreed to participate in the study, provided explicit consent, and signed a dedicated written informed consent form.

The study was approved by the Local Ethical Committee (registration code NP 3173, approved April 29, 2020) of the coordinating center and of other participating centers and conducted in accordance with the Code of Ethics of the World Medical Association and the Declaration of Helsinki.

All necessary precautions were adopted to maintain patients' anonymity and data confidentiality.

Participants were considered as drop-outs if they suspended antidepressant pharmacological treatment for more than 5 days and expressed intention of discontinuing it or if they did not participate in the active or control interventions for 2 consecutive sessions and expressed intention of discontinuing it.

Central randomization using a random number table was carried out in order to allocate participants to the CR intervention group or to the control condition. The randomization was performed by a researcher who was not involved in the delivery of the interventions, in the assessment of participants and in the data analysis.

Interventions

Cognitive remediation intervention

The CR intervention (CR group) was delivered with a computerized approach, using the Cogpack program Version 6.0 (Marker Software®, Mannheim, Germany). The program is composed of several cognitive exercises, including domain-specific exercises as well as non-domain-specific exercises focusing on different domains at once. It also includes exercises that focus on language and calculation skills. The exercises can be adapted for individual participants, with the software automatically setting the difficulty level on the basis of the participant's performance during the session.

The exercises were delivered with the assistance and feedback of dedicated therapists who were specifically trained to deliver the intervention for the present study. Therapists were trained in centralized seminars that included lectures and practical exercises and were supported throughout the duration of the study with regularly scheduled online meetings.

Therapists had an active role in the delivery of the cognitive exercises, providing instruction and feedback to participants, closely monitoring their progress, and fostering the development of novel cognitive strategies.

The cognitive exercises were also integrated into a structured rehabilitation program that included discussion sessions dedicated to the development of cognitive strategies, with the aim of improving the transfer of cognitive gains into real-world functioning.

The CR intervention was administered two times a week, in 45-minute sessions, for 12 weeks and a total of 24 sessions. Missed sessions that were not related to study dropout were individually rescheduled.

Control intervention – computer games

The control intervention, included to assess the role of placebo and nonspecific effects, consisted of the use of computer games (CG group). Available games were “Minesweeper,” “Solitary” and “Pinball,” according to the participant's choice. Games were played

in a setting that included the presence of the therapist, but in this instance, the therapist did not play any active role, and no discussion session on cognitive strategies was provided.

The control intervention was also scheduled two times a week, in 45-min sessions, for a duration of 12 weeks and a total of 24 sessions.

At the conclusion of the study and of the dedicated assessments, participants allocated to the control group were invited to receive the CR intervention.

Measures

All participants were assessed at baseline (T0) and at the conclusion of the intervention (T1) with validated measures of cognitive performance, clinical symptoms, and psychosocial functioning.

Assessors were specifically trained to conduct the assessment and were kept blind as regard to the group allocation of participants for the whole duration of the study. Participants were explained and explicitly reminded not to disclose their group allocation to assessors.

Performance-based cognitive measures included the California Verbal Learning Test (CVLT) [41], measuring the domain of verbal learning and memory; the Digit Symbol Substitution Test (DSST) [42] measuring mostly processing speed; Trail Making Test A (TMT-A) and B (TMT-B), and B-A (TMT-B-A) [43] measuring processing speed, working memory, and executive functions/cognitive flexibility, respectively. Participant-rated measures included the Perceived Deficits Questionnaire – Depression 5 items (PDQ-D-5) to assess subjective cognitive dysfunction in people with depression [44].

Clinical severity measures included the Montgomery-Åsberg Depression Rating Scale (MADRS) [45] and the Clinical Global Impression – Severity scale (CGI-S) [46] for clinician-rated measures and the Beck Depression Inventory, Second Edition (BDI-II) [47] for participant-rated measures. Real-world psychosocial functioning was measured with the Personal and Social Performance scale (PSP) [48].

The inter-rater reliability was evaluated for all measures and for all assessors of each participating center after the centralized training using Interclass Correlation Coefficient (ICC): good to excellent agreement between raters was observed for all measures (ICC ranging from 0.62 to 0.91).

Statistical analyses

All individuals recruited in the study and randomized to one of the treatment arms (CR group or CG group) who completed the initial assessment were included in the analyses according to their allocation, regardless of their completion of the study, to implement an Intention-To-Treat (ITT) approach.

Baseline socio-demographic (age, gender, years of education) and clinical characteristics were compared between groups using *t*-tests for continuous variables and χ^2 tests (or Fisher's Exact test where appropriate) for categorical variables to identify potential differences: variables that emerged as significantly different were introduced as covariates in the outcome analyses to avoid potential confounding factors.

Drop-out rates were compared between the intervention groups to identify potential sources of bias. Baseline values for all outcome measures were also compared between study completers and dropouts.

Outcomes were assessed using mixed models for repeated measures (MMRM), considering baseline (T0) and end-of-treatment

(T1) scores and group allocation (CR or CG) to implement an ITT approach. Statistically significant Time x Group interactions were considered as indicating a significant treatment effect. Simple effects for each treatment arm were also investigated.

p -Values <0.05 were considered significant. Analyses were performed using Jamovi version 2.2.5.

Between-group effect sizes were calculated as Cohen's d , considering both baseline and end-of-treatment values and baseline standard deviations, and taking into account group allocation and size [49].

Statistical analyses were carried out maintaining blinding as regard to participants' group allocation to avoid potential sources of bias.

Results

A total of 142 individuals were screened, and 101 participants were allocated to the CR group ($n = 52$) or to the CG group ($n = 49$). A total of 81 participants, 45 in the CR group and 36 in the CG group, completed the study. The complete CONSORT Flow Diagram of the study is reported in Figure 1.

Baseline socio-demographic and clinical characteristics of the total sample and between-groups comparisons are reported in Table 1. No significant between-groups differences were observed for any baseline socio-demographic or clinical characteristic.

Comparisons between study completers and dropouts are reported in Supplementary Table S1. No significant between-group differences in dropout rates were observed ($\chi^2 = 2.713$, $p = 0.100$). No differences were observed between completers and dropouts regarding baseline variables, except for psychosocial functioning as measured by the PSP ($t = 2.296$, $p = 0.024$).

Study outcomes are reported in Table 2. The CR intervention produced significantly superior results, compared to the CG control condition, in clinician-rated depressive symptoms as measured by the MADRS ($p = 0.023$, $d = 0.42$) and the CGI-S ($p = 0.025$, $d = 0.39$) and in subjective depressive symptoms as measured by the BDI-II ($p = 0.005$, $d = 0.45$). The CR intervention also produced significantly superior results in the working memory domain as measured by the TMT-B test ($p = 0.004$, $d = 0.34$), in the executive functions/cognitive flexibility domain with a moderate effect size, as measured by the TMT-B-A ($p = 0.020$, $d = 0.43$), and in subjective cognitive impairment as measured by the PDQ-5 ($p = 0.006$, $d = 0.48$). No significant treatment effects were observed as regards the verbal

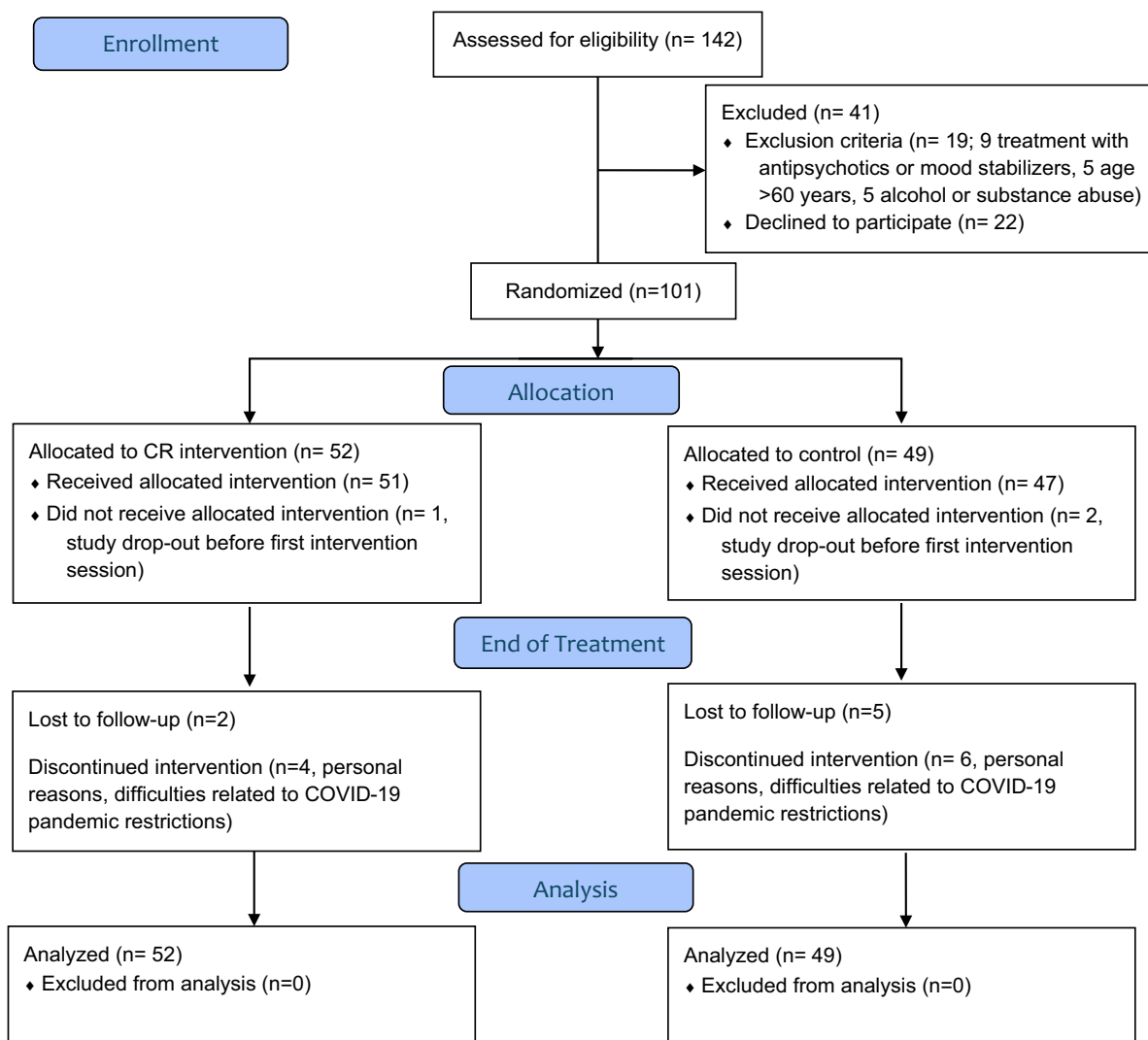


Figure 1. CONSORT flow diagram.

Table 1. Sample characteristics and baseline comparisons

Variable	Total sample (n = 101) mean (± SD); n (%)	Cognitive remediation group (n = 52) mean (± SD); n (%)	Control condition – computer games group (n = 49) mean (± SD); n (%)	t-test / χ^2 -Fisher's exact test	p-Value
Age					
(years)	38.68(±11.69)	39.40(±11.29)	37.92(±12.17)	0.636	0.526
Gender					
Female	34 (33.7%)	18 (34.6%)	16 (32.7%)	0.044	0.835
Male	67 (66.3%)	34 (65.4%)	33 (67.3%)		
Education					
(years)	13.25(±3.39)	13.13(±3.19)	13.37(±3.62)	–0.343	0.732
Age of onset					
(years)	29.98(±12.23)	30.88(±15.50)	29.02(±13.01)	0.764	0.447
Severity of current MDE					
Mild	47 (46.5%)	21 (40.4%)	26 (53.1%)	1.629	0.202
Moderate	54 (53.5%)	31 (59.6%)	23 (46.9%)		
Duration of current MDE (months)					
	9.93(±8.71)	9.43(±8.81)	10.45(±8.66)	–0.582	0.562
Alcohol abuse (lifetime)					
Yes	4 (4.0%)	3 (5.8%)	1 (2.0%)	–	0.618
No	97 (96.0%)	49 (94.2%)	48 (98.0%)		
Substance abuse (lifetime)					
Yes	7 (6.9%)	4 (7.7%)	3 (6.1%)	–	1.000
No	94 (93.1%)	48 (92.3%)	46 (93.9%)		
Pharmacological treatment (molecule)					
SSRI	57 (56.4%)	29 (55.8%)	28 (57.1%)	0.801	0.849
SNRI	20 (19.8%)	9 (17.3%)	11 (22.4%)		
VOR	17 (16.8%)	10 (19.2%)	7 (14.3%)		
Other ^a	7 (6.9%)	4 (7.7%)	3 (6.1%)		

Abbreviations: MDE, major depressive episode; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor; VOR, vortioxetine.

^aOther: amitriptyline, bupropione, clomipramine, trazodone.

memory domain as measured by the CVLT, the processing speed domain as measured by the DSST and the TMT-A, and in real-world psychosocial functioning as measured by the PSP.

Discussion

The present multicentric randomized controlled trial aimed to assess the effects of a CR intervention in people living with MDD undergoing a MDE.

The CR intervention showed a good feasibility profile, with a dropout rate of 13.5%: this is in line with that of other evidence-based psychosocial interventions for MDD [50, 51], as well as with that of CR interventions delivered to individuals with other diagnoses, such as Schizophrenia Spectrum Disorders [52].

The CR intervention produced significant improvements, compared to the CG control intervention, in several outcomes of interest. In particular, a larger reduction in the severity of depressive symptoms, both measured by raters and measured by the participants themselves, was observed in the CR group. The

observation that CR produces significant, small-to-moderate-sized improvements in depressive symptoms is in line with the results of previous, smaller studies and of recent meta-analyses [34, 35]. The fact that this improvement is also recognized by participants, as attested by the scores of self-reported instruments, represents an encouraging finding, further confirming that CR can represent an effective intervention to treat this domain.

As regards the effects on cognitive performance, significantly small-to-moderate-sized positive effects were observed in the working memory and executive functions domains. On the contrary, no significant effect was observed in the processing speed and verbal memory domain. Again, these findings are mostly in line with those reported in the most recent meta-analytic investigation, where a positive effect was observed in the working memory and executive functions, but not in the processing speed, attention, or visual memory domains [34]. It might well be that CR interventions produce in people living with MDD undergoing a MDE improvements that are more evident in some cognitive domains, and are not capable of producing significant improvements in other domains,

Table 2. Study outcomes (mixed model repeated measures)

Variable	Cognitive remediation group T0 mean (\pm SD)	Cognitive remediation group T1 mean (\pm SD)	Control condition – computer games group T0 mean (\pm SD)	Control condition – computer games group T1 mean (\pm SD)	Cognitive remediation group Time effect <i>p</i> -Value	Control condition – computer games group Time effect <i>p</i> -value	Time x group F	Time x group <i>p</i> -value	Effect size Cohen's <i>d</i>
MADRS									
(score)	22.10 (\pm 12.23)	14.04 (\pm 10.72)	18.94 (\pm 10.18)	15.75 (\pm 10.39)	<0.001	0.140	5.326	0.023	0.42
CGI-S									
(score)	3.42 (\pm 0.99)	2.70 (\pm 1.03)	3.26 (\pm 0.92)	2.92 (\pm 0.93)	<0.001	0.070	5.221	0.025	0.39
BDI-II									
(score)	25.10 (\pm 11.93)	15.18 (\pm 11.58)	19.04 (\pm 11.54)	14.50 (\pm 10.86)	<0.001	0.035	8.180	0.005	0.45
CVLT									
(correct answers)	47.04 (\pm 12.65)	52.13 (\pm 18.33)	47.53 (\pm 12.41)	52.89 (\pm 14.02)	0.029	0.051	0.0004	0.982	0.02
DSST									
(correct answers)	45.29 (\pm 13.19)	49.91 (\pm 14.72)	48.48 (\pm 13.79)	48.17 (\pm 13.77)	0.015	0.644	1.745	0.190	0.36
TMT-A									
(seconds)	42.82 (\pm 20.88)	39.54 (\pm 21.61)	39.59 (\pm 16.79)	35.27 (\pm 11.36)	0.115	0.282	0.082	0.774	0.05
TMT-B									
(seconds)	101.20 (\pm 67.99)	80.55 (\pm 47.96)	83.12 (\pm 39.05)	82.17 (\pm 40.46)	<0.001	0.600	8.748	0.004	0.34
TMT-B-A									
(seconds)	58.37 (\pm 57.15)	40.06 (\pm 37.52)	45.57 (\pm 31.91)	48.13 (\pm 33.57)	0.006	0.509	5.687	0.020	0.43
PDQ-5									
(score)	9.13 (\pm 4.95)	5.98 (\pm 4.70)	6.63 (\pm 4.49)	5.81 (\pm 4.52)	<0.001	0.376	7.830	0.006	0.48
PSP									
(score)	60.67 (\pm 18.17)	69.00 (\pm 21.05)	63.51 (\pm 17.26)	73.20 (\pm 12.99)	<0.001	0.006	0.228	0.635	0.07

Abbreviations: BDI-II, Beck Depression Inventory, Second Edition; CGI-S, Clinical Global Impression - Severity scale; CVLT, California Verbal Learning Test; DSST, Digit Symbol Substitution Test; MADRS, Montgomery-Åsberg Depression Rating Scale; PDQ-5, Perceived Deficits Questionnaire – Depression 5 items; PSP, Personal and Social Performance scale; TMT, Trail Making Test. Bold font highlights significant *p*-values ($p < 0.05$).

contrary to what can be observed in the context of CR in Schizophrenia Spectrum Disorders [29, 30]. Developing CR interventions that are specifically designed to also improve cognitive domains such as processing speed, which are among those that are more heavily interested in MDD [6, 18, 19], might represent an interesting perspective for future research.

However, considering the heterogeneity and the prevalence of cognitive impairment in depression and the substantial negative impact that it produces on the daily lives of people with MDD, where it represents one of the main predictors of functional disability [53–56], even providing small improvements in selected domains could represent a substantial benefit for participants.

As regards subjective cognitive deficits, in the present study CR produced significant, small-to-moderate-sized improvements compared to the control condition. This is an interesting and novel finding: in fact, in a recent meta-analytic investigation, a small positive effect on this outcome was observed, but the analysis did not reach statistical significance [34]; this might be due to the small number of included studies ($n = 4$) and the small sample size of each included work. Again, this finding is very encouraging, attesting that CR interventions can provide improvements that are perceived and are considered meaningful for participants: in a patient-centered and person-first approach [38], this outcome is of utmost relevance.

Conversely, no significant improvement was observed in real-world psychosocial functioning. This is a somewhat unexpected finding that could be due to different reasons. First and foremost, the lack of a follow-up observation could largely explain this result: in fact, the transfer of cognitive and clinical improvements to psychosocial functioning usually requires more time to be observed, and in samples of subjects with Schizophrenia Spectrum Disorders, longer follow-up observations are related to increased psychosocial functioning improvements [32]. Moreover, it should also be pointed out that participants who dropped out of the study showed lower baseline psychosocial functioning: this issue could have a negative impact on the results observed for this specific outcome. Finally, it should also be highlighted that part of the present study took place during the COVID-19 pandemic and this issue, which had an enormous impact on the lives of all people and in particular on those of people with mental health conditions and their daily functioning [57, 58], could have negatively impacted the transfer of cognitive gains into real world functional outcomes due to the peculiar context of the pandemic itself, with limited opportunities for novel personal interactions and developments. In any case, to better explore the impact of CR interventions on the psychosocial functioning of people with MDD, future studies should include consistent follow-up observation periods after the conclusion of the active treatment phase.

Strengths of the present study include its multicentric nature and the consequent sample size, which allows for more reliable results compared to previous individual studies, and the inclusion of participant-rated measures for both clinical and cognitive outcomes, which is becoming an increasingly important element also from a regulatory perspective [59].

A limitation of the present work is the lack of follow-up observations, which could have allowed a better evaluation of treatment impact on functional outcomes and to assess the durability of positive effects. Another limitation is the lack of direct and specific assessment of participants' real-world outcomes: while psychosocial functioning represents an outcome of the present work and was assessed with a validated scale, instruments such as the Specific Level of Functioning [60] could allow a more nuanced and detailed evaluation of participants' functioning.

Future perspectives include the development of CR interventions tailored specifically for the characteristics of individuals living with MDD, both during MDEs and during remission phases, the inclusion of follow-up observations even for long periods of time, the inclusion of specific measures of real-world functional outcomes, and the use of novel technologies, such as telemedicine and virtual reality to help deliver evidence-based interventions. In a clinical perspective, a wider dissemination of CR intervention in real-world, day-to-day mental health services could represent an important asset to help treat essential elements of MDD, such as cognitive impairment, providing also improvements that are perceived and appreciated directly by participants [2].

In conclusion, the results of the present work highlight that CR is an effective intervention in people with MDD, capable of improving clinical outcomes and cognitive performance both in a clinician-rated and in a subjective manner. In this perspective, CR should be considered more consistently in MDD treatment recommendations and guidelines as an evidence-based intervention and should be delivered in a more widespread manner in mental healthcare and rehabilitation services.

Supplementary material. The supplementary material for this article can be found at <http://doi.org/10.1192/j.eurpsy.2025.10073>.

Data availability statement. Data from the present study is available upon reasonable request to the Corresponding Author.

Acknowledgements. All authors who contributed to this paper are listed as authors. No professional medical writer was involved in any portion of the preparation of the manuscript.

Financial support. The study was promoted and conducted as an independent study partially supported by Lundbeck Italia.

Competing interests. The authors declare none.

References

- [1] Hasin DS, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry* 2018;75:336–46. <https://doi.org/10.1001/jamapsychiatry.2017.4602>.
- [2] Maj M, Stein DJ, Parker G, Zimmerman M, Fava GA, De Hert M, et al. The clinical characterization of the adult patient with depression aimed at personalization of management. *World Psychiatry* 2020;19:269–93. <https://doi.org/10.1002/wps.20771>.
- [3] Moreno-Agostino D, Wu Y-T, Daskalopoulou C, Hasan MT, Huisman M, Prina M. Global trends in the prevalence and incidence of depression: a systematic review and meta-analysis. *J Affect Disord* 2021;281:235–43. <https://doi.org/10.1016/j.jad.2020.12.035>.
- [4] Greenberg P, Chitnis A, Louie D, Suthoff E, Chen S-Y, Maitland J, et al. The economic burden of adults with major depressive disorder in the United States (2019). *Adv Ther*. 2023;40:4460–79. <https://doi.org/10.1007/s12325-023-02622-x>.
- [5] Barlati S, Lisoni J, Nibbio G, Baldacci G, Cicale A, Ferrarin LC, et al. Current evidence and theories in understanding the relationship between cognition and depression in childhood and adolescence: a narrative review. *Diagnostics*. 2022;12:2525. <https://doi.org/10.3390/diagnostics12102525>.
- [6] Hammar Å, Ronold EH, Rekkedal GÅ. Cognitive impairment and neurocognitive profiles in major depression—a clinical perspective. *Front Psych*. 2022;13:764374. <https://doi.org/10.3389/fpsy.2022.764374>.
- [7] Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med* 2014;44:2029–40. <https://doi.org/10.1017/S0033291713002535>.
- [8] Ahern E, Semkowska M. Cognitive functioning in the first-episode of major depressive disorder: a systematic review and meta-analysis. *Neuropsychology*. 2017;31:52–72. <https://doi.org/10.1037/neu0000319>.
- [9] Tran T, Milanovic M, Holshausen K, Bowie CR. What is normal cognition in depression? Prevalence and functional correlates of normative versus idiographic cognitive impairment. *Neuropsychology*. 2021;35:33–41. <https://doi.org/10.1037/neu0000717>.
- [10] Varghese S, Frey BN, Schneider MA, Kapczynski F, de Azevedo Cardoso T. Functional and cognitive impairment in the first episode of depression: a systematic review. *Acta Psychiatr Scand* 2022;145:156–85. <https://doi.org/10.1111/acps.13385>.
- [11] Dotson VM, McClintock SM, Verhaeghen P, Kim JU, Draheim AA, Szymkowitz SM, et al. Depression and cognitive control across the lifespan: a systematic review and meta-analysis. *Neuropsychol Rev* 2020;30:461–76. <https://doi.org/10.1007/s11065-020-09436-6>.
- [12] Semkowska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. *Lancet Psychiatry* 2019;6:851–61. [https://doi.org/10.1016/S2215-0366\(19\)30291-3](https://doi.org/10.1016/S2215-0366(19)30291-3).
- [13] Dam V, Stenbæk DS, Köhler-Forsberg K, Ip C, Ozenne B, Sahakian B, et al. Hot and cold cognitive disturbances in antidepressant-free patients with major depressive disorder: a NeuroPharm study. *Psychol Med* 2021;51:2347–56.
- [14] Nord C, Halahakoon D, Lally N, Limbachya T, Pilling S, Roiser J. The neural basis of hot and cold cognition in depressed patients, unaffected relatives, and low-risk healthy controls: An fMRI investigation. *J Affect Disord* 2020;274:389–98.
- [15] Salehinejad MA, Ghanavati E, Rashid MHA, Nitsche MA. Hot and cold executive functions in the brain: a prefrontal-cingular network. *Brain Neurosci Adv*. 2021;5 23982128211007769. <https://doi.org/10.1177/23982128211007769>.
- [16] Allott K, Fisher CA, Amminger GP, Goodall J, Hetrick S. Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain Behav*. 2016;6:e00527.
- [17] Ronold EH, Schmid MT, Oedegaard KJ, Hammar Å. A longitudinal 5-year follow-up study of cognitive function after first episode major depressive disorder: exploring state, scar and trait effects. *Front Psychiatr* 2020;11. <https://doi.org/10.3389/fpsy.2020.575867>.
- [18] Morey-Nase C, Phillips LJ, Bryce S, Hetrick S, Wright AL, Caruana E, et al. Subjective experiences of neurocognitive functioning in young people with major depression. *BMC Psychiatr*. 2019;19:209. <https://doi.org/10.1186/s12888-019-2197-1>.
- [19] Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull*. 2013;139:81–132. <https://doi.org/10.1037/a0028727>.
- [20] Årdal G, Lund A, Hammar Å. Health-related quality of life in recurrent major depressive disorder—a 10-year follow-up study. *Nord J Psychiatr* 2013;67:339–43. <https://doi.org/10.3109/08039488.2012.746730>.
- [21] Clark M, DiBenedetti D, Perez V. Cognitive dysfunction and work productivity in major depressive disorder. *Expert Rev Pharmacoecon Outcomes Res* 2016;16:455–63. <https://doi.org/10.1080/14737167.2016.1195688>.
- [22] Gupta M, Holshausen K, Best MW, Jokic R, Milev R, Bernard T, et al. Relationships among neurocognition, symptoms, and functioning in

- treatment-resistant depression. *Arch Clin Neuropsychol* 2013;28:272–81. <https://doi.org/10.1093/arclin/act002>.
- [23] Sumiyoshi T, Watanabe K, Noto S, Sakamoto S, Moriguchi Y, Hammer-Helmich L, et al. Relationship of subjective cognitive impairment with psychosocial function and relapse of depressive symptoms in patients with major depressive disorder: analysis of longitudinal data from PERFORM-J. *Neuropsychiatr Dis Treat* 2021;17:945–55. <https://doi.org/10.2147/NDT.S288108>.
- [24] Woo YS, Rosenblat JD, Kakar R, Bahk W-M, McIntyre RS. Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. *Clin Psychopharmacol Neurosci*. 2016;14: 1–16. <https://doi.org/10.9758/cpn.2016.14.1.1>.
- [25] Wykes T, Bowie CR, Cella M. Thinking about the future of cognitive remediation therapy revisited: what is left to solve before patients have access? *Schizophr Bull*. 2024;sbae075. <https://doi.org/10.1093/schbul/sbae075>.
- [26] Bowie CR, Bell MD, Fiszdon JM, Johannesen JK, Lindenmayer J-P, SR MG, et al. Cognitive remediation for schizophrenia: an expert working group white paper on core techniques. *Schizophr Res*. 2020;215:49–53. <https://doi.org/10.1016/j.schres.2019.10.047>.
- [27] Barlati S, Nibbio G, Vita A. Evidence-based psychosocial interventions in schizophrenia: a critical review. *Curr Opin Psychiatry*. 2024;37:131–9. <https://doi.org/10.1097/YCO.0000000000000925>.
- [28] Kambaitz-Ilankovic L, Betz LT, Dominke C, Haas SS, Subramaniam K, Fisher M, et al. Multi-outcome meta-analysis (MOMA) of cognitive remediation in schizophrenia: revisiting the relevance of human coaching and elucidating interplay between multiple outcomes. *Neurosci Biobehav Rev*. 2019;107:828–45. <https://doi.org/10.1016/j.neubiorev.2019.09.031>.
- [29] Lejeune JA, Northrop A, Kurtz MM. A meta-analysis of cognitive remediation for schizophrenia: efficacy and the role of participant and treatment factors. *Schizophr Bull*. 2021;47:997–1006. <https://doi.org/10.1093/schbul/sbab022>.
- [30] Vita A, Barlati S, Ceraso A, Nibbio G, Ariu C, Deste G, et al. Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatr* 2021;78:848–58. <https://doi.org/10.1001/jamapsychiatry.2021.0620>.
- [31] Yeo H, Yoon S, Lee J, Kurtz MM, Choi K. A meta-analysis of the effects of social-cognitive training in schizophrenia: the role of treatment characteristics and study quality. *Br J Clin Psychol*. 2022;61:37–57. <https://doi.org/10.1111/bjc.12320>.
- [32] Vita A, Barlati S, Ceraso A, Nibbio G, Durante F, Facchi M, et al. Durability of effects of cognitive remediation on cognition and psychosocial functioning in schizophrenia: a systematic review and meta-analysis of randomized clinical trials. *AJP* 2024;181:520–31. <https://doi.org/10.1176/appi.ajp.20230396>.
- [33] Vita A, Gaebel W, Mucci A, Sachs G, Barlati S, Giordano GM, et al. European Psychiatric Association guidance on treatment of cognitive impairment in schizophrenia. *Eur Psychiatry*. 2022;65:e57 <https://doi.org/10.1192/j.eurpsy.2022.2315>.
- [34] Goldberg Z, Kuslak B, Kurtz MM. A meta-analytic investigation of cognitive remediation for mood disorders: efficacy and the role of study quality, sample and treatment factors. *J Affect Disord*. 2023;330:74–82. <https://doi.org/10.1016/j.jad.2023.02.137>.
- [35] Legemaat AM, Semkovska M, Brouwer M, Geurtsen GJ, Burger H, Denys D, et al. Effectiveness of cognitive remediation in depression: a meta-analysis. *Psychol Med* 2022;52:4146–61. <https://doi.org/10.1017/S0033291721001100>.
- [36] Sociali A, Borgi M, Pettorosso M, Di Carlo F, Di Natale C, Tambelli A, et al. What role for cognitive remediation in the treatment of depressive symptoms? A superiority and noninferiority meta-analysis for clinicians. *Depress Anxiety*. 2022;39:586–606. <https://doi.org/10.1002/da.23263>.
- [37] Théron A, Pezzoli P, Abbas M, Howard A, Bowie CR, Guimond S. The efficacy of cognitive remediation in depression: a systematic literature review and meta-analysis. *J Affect Disord* 2021;284:238–46. <https://doi.org/10.1016/j.jad.2021.02.009>.
- [38] Correll CU, Ismail Z, McIntyre RS, Rafeyan R, Thase ME. Patient functioning, life engagement, and treatment goals in major depressive disorder. *J Clin Psychiatry*. 2022;83:42627. <https://doi.org/10.4088/JCP.LU21112AH3>.
- [39] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th edn. (DSM-5). Washington, DC: American Psychiatric Association; 2013.
- [40] First MB, Williams JB, Karg RS, Spitzer RL. Structured clinical interview for DSM-5 disorders. Clinician Version (SCID-5-CV) 2015.
- [41] Delis D, Kramer J, Kaplan E, Ober B. CVLT: California verbal learning test-adult version: manual: psychological Corporation 1987.
- [42] Wechsler D. WAIS-R: manual: Wechsler adult intelligence scale-revised. (No Title) 1981.
- [43] Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8:271–6. <https://doi.org/10.2466/pms.1958.8.3.271>.
- [44] Sullivan MJ, Edgley K, Dehoux E. A survey of multiple sclerosis: I. Perceived cognitive problems and compensatory strategy use. *Canad J Rehabil*. 1990;4:99–105.
- [45] Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatr*. 1979;134:382–9. <https://doi.org/10.1192/bjp.134.4.382>.
- [46] Guy W. ECDEU assessment manual for psychopharmacology. US Department of Health, Education, and Welfare, Public Health Service ...; 1976.
- [47] Beck AT, Steer RA, Brown G. Beck depression inventory–II. Psychological Assessment 1996.
- [48] Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV social and occupational functioning assessment scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;101:323–9.
- [49] Morris SB. Estimating effect sizes from pretest-posttest-control group designs. *Organ Res Methods* 2008;11:364–86. <https://doi.org/10.1177/1094428106291059>.
- [50] Cooper AA, Conklin LR. Dropout from individual psychotherapy for major depression: a meta-analysis of randomized clinical trials. *Clin Psychol Rev*. 2015;40:57–65.
- [51] Solomonov N, Barber JP. What we know, what we do not know, and where are we heading? Efficacy and acceptability of psychological interventions for depression. *Epidemiol Psychiatr Sci* 2016;25:301–8. <https://doi.org/10.1017/S2045796015000815>.
- [52] Vita A, Barlati S, Ceraso A, Deste G, Nibbio G, Wykes T. Acceptability of cognitive remediation for schizophrenia: a systematic review and meta-analysis of randomized controlled trials. *Psychol Med* 2023;53:3661–71. <https://doi.org/10.1017/S0033291722000319>.
- [53] McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallagher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety* 2013;30:515–27. <https://doi.org/10.1002/da.22063>.
- [54] Perini G, Cotta Ramusino M, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: recent advances and novel treatments. *Neuropsychiatr Dis Treat* 2019;15:1249–58. <https://doi.org/10.2147/NDT.S199746>.
- [55] Baune BT, Miller R, McAfoose J, Johnson M, Quirk F, Mitchell D. The role of cognitive impairment in general functioning in major depression. *Psychiatry Res* 2010;176:183–9. <https://doi.org/10.1016/j.psychres.2008.12.001>.
- [56] Cambridge OR, Knight MJ, Mills N, Baune BT. The clinical relationship between cognitive impairment and psychosocial functioning in major depressive disorder: a systematic review. *Psychiatry Res* 2018;269:157–71. <https://doi.org/10.1016/j.psychres.2018.08.033>.
- [57] Moreno C, Wykes T, Galderisi S, Nordentoft M, Crossley N, Jones N, et al. How mental health care should change as a consequence of the COVID-19 pandemic. *Lancet Psychiatry*. 2020;7:813–24. [https://doi.org/10.1016/S2215-0366\(20\)30307-2](https://doi.org/10.1016/S2215-0366(20)30307-2).
- [58] Robinson E, Sutin AR, Daly M, Jones A. A systematic review and meta-analysis of longitudinal cohort studies comparing mental health before versus during the COVID-19 pandemic in 2020. *J Affect Disord*. 2022;296: 567–76. <https://doi.org/10.1016/j.jad.2021.09.098>.
- [59] Baandrup L, Rasmussen JØ, Mainz J, Videbech P, Kristensen S. Patient-reported outcome measures in mental health clinical research: a descriptive review in comparison with clinician-rated outcome measures. *Int J Qual Health Care*. 2022;34:ii70–97. <https://doi.org/10.1093/intqhc/mzab001>.
- [60] Schneider LC, Struening EL. SLOF: a behavioral rating scale for assessing the mentally ill. *Social Work Res Abst*. 1983;19:9–21. <https://doi.org/10.1093/swra/19.3.9>.