

Cognitive remediation in schizophrenia: What happens after 10 years?

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ABSTRACT

Cognitive Remediation Therapy (CRT) represents the gold standard treatment for cognitive impairment in schizophrenia, but the permanence of its effects over time have been poorly investigated. Our study aims to evaluate long lasting cognitive and functional effects of CRT together with standard rehabilitation interventions (SRT) in a group of patients diagnosed with schizophrenia, 10 years after the end of the treatment. Forty patients, previously included in a 5-year follow-up study evaluating the effects of CRT combined with SRT, were revalued 10 years after the complete of the intervention. Results revealed that cognitive and functional improvements of combined CRT/SRT interventions are still preserved 10 years after the end of the treatments, with the only exception of psychomotor speed and coordination cognitive subdomain. Moreover, investigating persistence of the influence of SRT, patients that underwent a shorter SRT following CRT (six months vs one year) showed worsened processing speed abilities.

This is the first study confirming that cognitive and functional improvements of joint CRT/SRT interventions are still conserved 10 years after the end of the treatments. Preliminary datas suggest that a longer SRT following CRT may lead to significant benefits, in terms of cognitive gains, in patients affected by schizophrenia.

1. Introduction

Cognitive Remediation Therapy (CRT) represents the gold standard treatment for cognitive impairment in schizophrenia (Garrido et al., 2017; Wykes et al., 2011). It has been demonstrated that CRT is a promoter of neuroplasticity and therefore of structural and functional brain changes (Bosia et al., 2018; Isaac and Januel, 2016; Matsuda et al., 2019; Penadés et al., 2020) that improve cognition and global functioning (Bowie et al., 2020; Seccomandi et al., 2020; Vita et al., 2021).

However, despite the large number of studies focused on CRT effectiveness among patients with schizophrenia, only a few have analyzed its effects over time to better understand the longitudinal course of cognition in this type of patients (Bell et al., 2003; Buonocore et al., 2018; Deste et al., 2015; Fiszdon et al., 2004; Rispaud et al., 2016; Wykes et al., 2007). Notably, different authors showed that CRT, when put together as a bridging intervention with a standard rehabilitation therapy (SRT), leads to significantly greater functional improvements and that these accomplishments might be better maintained over time (Bechi et al., 2019; Buonocore et al., 2018; Cavallaro et al., 2009;

McGurk et al., 2007; Poletti et al., 2010).

Deste found out that the advantages of CRT joint with usual rehabilitation remained significant for both cognitive and functional measures at 1-year follow-up (Deste et al., 2015). Moreover, McGurk showed that even previous non responders to vocational rehabilitation gained benefit from CRT, and these advantages seemed to accelerate over time, even after the end of training (DeTore et al., 2019).

In line with this evidence, we reported a generalization of cognitive gains linked to the quality of life after a combined CRT/SRT intervention (Poletti et al., 2010). In particular, not only the maintenance of cognitive increases persisted after a 1 year of follow-up, but the improvements in daily functioning progressively intensified both at 6-months and 1-year follow-up (Poletti et al., 2010).

Afterwards, we compared if the effects would be better preserved with a 6-month standard rehabilitation therapy (SRT) or a 1-year cognitive-behavioral rehabilitation (SRT+) combined with the CRT training (Buonocore et al., 2018). Our results showed that the cognitive outcome was not significantly different between and within these two groups, indicating the maintenance of cognitive improvements 5 years

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after-interventions in the whole group of patients, regardless of the SRT duration. However, the reinforce in daily functioning may rather require a more extended training in order to be kept over time: in fact, at 5 year follow-up patients treated with a longer SRT showed a significantly higher quality of life (QLS Total score) (Buonocore et al., 2018).

Taken together, evidence from literature points out that an integrated rehabilitative approach (CRT + SRT) seems to be more effective than CRT alone for both cognitive enhancements and general improvements to daily functioning.

As of today, studies on cognitive and functional persistence do not last more than 5 years. Considering the cognitive declines in schizophrenia, it is fundamental to understand how and if the cognitive remediation could be able to prevent the degeneration (Miwa et al., 2020; Zanelli et al., 2019).

Hence, the focus of our study is evaluating the durability of cognitive gains and therefore their generalization to functional areas of a combined CRT/SRT program in a 10-year follow-up among patients with schizophrenia. Afterwards, we considered possible differences concerning the duration of the integrated SRT intervention, assuming that a longer period of SRT (1 year) may lead to a better maintenance of cognitive and functional gains over time.

2. Methods

2.1. Participants

This is a single-center retrospective study that includes 40 patients (24 males and 16 females) diagnosed with schizophrenia according to DSM-5 (American Psychiatric Association, 2013) criteria, previously enrolled in a 5-year follow-up (Buonocore et al., 2018), recruited at the Disease Unit for Psychotic Disorders at IRCCS San Raffaele Scientific Institute, Milan, Italy. To ensure availability, all patients were reached either through their psychiatrist or by telephone. After a complete description of the study, informed consents to participation were collected. The protocol followed the principles of the Declaration of Helsinki and was approved by the local Ethical Committee.

To be included, patients had to satisfy DSM-5 diagnostic criteria for schizophrenia and the following conditions:

- Age between 18 and 65 years;
- Good compliance to rehabilitation program and follow-up (Buonocore et al., 2018);
- Attending to a cognitive-behavioral rehabilitative program consisting of three 1-h sessions a week over the period of 3 months;
- No evidence of substance dependence or abuse, comorbid diagnoses on Axis I or II, epilepsy, any other major neurological illness, perinatal trauma or mental retardation.

2.2. Design

All patients were evaluated through neurocognitive performance and daily functioning 10 years after the end of the integrated treatment CRT+ standard rehabilitation therapy (SRT). The CRT protocol consisted of three sessions of 1 h each of function-specific computer-aided exercises a week (36 sessions) with Cogpack software.

After this combined treatment, which was performed according to a previous research protocol (Cavallaro et al., 2009), patients were observed in natural different settings. Of the 40 enrolled patients, 25 underwent an additional year of SRT in the rehabilitative out service, while the remaining 15 were monitored at the clinic as outpatients. The main reason of the discontinuity of the rehabilitation program was the distance from the location and/or poor autonomy in transfers. Lastly, we compared patients who underwent only the 3 months CRT plus the 6 months SRT protocol (CRT/SRT) with patients who sustained another year of SRT (CRT/SRT+).

2.3. Measures

According to the original protocol (Cavallaro et al., 2009), all patients were assessed for psychopathology through the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987) administered by trained psychiatrists, and for intellectual functioning by the means of the Wechsler Adult Intelligence Scale Revised (Wechsler, 1997), overseen by trained psychologists, before starting the CRT/SRT program. Neurocognitive performances and daily functioning were also measured at baseline (before the treatment), at the end of the treatment, after 5 and 10 years with the following scales:

- The Italian Version of the Brief Assessment of Cognition in Schizophrenia (BACS), a neuropsychological battery, was used in two versions (A and B), before and after rehabilitation programs, so that the results were not influenced by recall (Keefe et al., 2004). The entire battery, consists of the following tests: verbal memory (words recall); working memory (digit sequencing); psychomotor speed and coordination (token motor task); processing speed (symbol coding); verbal fluency (production of words after semantic and literal cue); executive functions (Tower of London). Raw scores of each BACS subtest were adjusted for age and education. From adjusted scores, equivalent scores (ES) were derived, based on normative values for the Italian population (Anselmetti et al., 2008). Equivalent scores are ranked into a 5-point interval scale, in which 0 sets the limit for pathological performance, 1 is considered as a borderline value, 2 and 3 indicate intermediate “normal” performance and 4 is equal or better than the median value. Finally, a global measure of cognitive efficiency (Cognitive Index), was obtained from the equivalent scores mean.
- The Quality of Life Scale (QLS) (Heinrichs et al., 1984), a semi-structured interview balancing subjective questions regarding life satisfaction and objective indicators of social and occupational role functioning.

For this study, all patients were re-tested with both BACS and QLS, administered respectively by trained psychologists and rehabilitation therapists, within the tenth year after the fulfillment of the integrated treatment. Therapists were trained clinical psychologists and rehabilitation therapists, blind to the assessments.

2.4. Statistical analyses

Analysis of variance (ANOVA) and chi square test (for dichotomic variables) were performed on demographic, clinical, neuropsychological, daily functioning and IQ variables to evaluate differences between groups (CRT/SRT vs CRT/SRT+) at baseline.

In order to evaluate the persistence of cognitive improvements by a qualitative point of view, we elaborated a score (0, 1, 2) based on longitudinal change of BACS Equivalent Scores.

In details:

- 0 = “worsening”: a normal level performance at the end of the treatment (with an ES equal or superior of 2) worsened at 10 years follow-up (0 or 1 ES), or a borderline level performance (1 ES) becoming a deficient level at 10-year follow-up (0 ES).
- 1 = “maintenance of deficit”: an impaired cognitive function at the end of the treatment (with an ES of 0 or 1), which persisted, unchanged, at 10 years follow-up.
- 2 = “maintenance of improvement”: the achievement of a “normalized” function at the end of the treatment (with an ES equal or superior of 2), that still results in the average range at 10 years follow-up (Bosia et al., 2017).

To evaluate the maintenance of cognitive improvements, we performed multiple repeated ANOVAs measures entering BACS adjusted

scores, QLS scores as single dependent variables and time as the independent variable factor (using three levels: T0 = end of the treatment, T1 = 5 years follow-up, T2 = 10 years follow up). Fisher LSD post-hoc analysis followed.

In addition, to investigate possible differences due to the diverse persistence of the integrated treatment, we performed repeated ANOVAs measures, entering BACS adjusted scores and QLS subtests as dependent variables, time as fixed factor (factor with three levels: T0 = end of the treatment, T1 = 5 years follow-up, T2 = 10 years follow-up) and treatment group (CRT/SRT vs CRT/SRT+) as categorical independent variable. Fisher LSD post-hoc analysis followed.

G*Power Software version 3.1.7 was used for power analysis. All other analyses were performed with STATISTICA Software for Windows, version 8 (StaSoft Inc., 2007).

3. Results

3.1. Baseline evaluations

Tables 1 and 2 show demographic, clinical characteristics, neuropsychological and functional assessments of the entire sample and stratified by treatment groups, at baseline. No significant differences were observed between the variables measured in the treatment group.

3.2. Persistence of improvements 10 years after the treatment in the whole sample

Repeated measures ANOVA showed no significant changes of BACS and QLS scores over time in the whole sample, indicating longitudinal stability of cognitive and functional growth, except for Psychomotor speed and coordination ($F = 17.79, p \leq 0.0001$).

In order to qualitatively assess the durability of effectiveness of the previous integrated intervention (Buonocore et al., 2018), we focused on the indexes of persistence of improvements based on longitudinal change of BACS Equivalent Scores, as reported in the methods section. In Fig. 1 are reported: the percentages of “maintenance of improvement”, “maintenance of deficit” and “worsening”. The graph highlighted that the great majority of cognitive abilities maintained the improvement achieved after the CRT/SRT intervention 10 years after. Over than 35% of patients held their gains in the cognitive areas.

3.3. Persistence of improvements 10 years after the treatment between treated groups

At last, repeated measures ANOVA were performed to assess the differences in the durability of effectiveness of the integrated treatment in the two groups. The difference between CRT/SRT and CRT/SRT+

Table 1
Demographic and clinical characteristics.

	ALL (N = 40)	CRT/SRT (N = 15)	CRT/SRT+ (N = 25)	ANOVA Chi ²	
	Mean ± SD	Mean ± SD	Mean ± SD	F	p
Gender (males/ females)	24/16	6/9	10/15	4.20	0.12
Age	33.85 ± 9.32	31.86 ± 7.67	35.04 ± 10.14	1.08	0.30
Education (years)	11.80 ± 2.23	11.33 ± 1.98	12.08 ± 2.36	1.04	0.31
Age at onset (years)	23.85 ± 6.34	22.06 ± 4.66	24.92 ± 7.04	1.94	0.17
Duration (years) PANSS	10 ± 7.69	9.8 ± 22	10.12 ± 30	0.02	0.90
Total score	74.05 ± 16.01	72.07 ± 17.64	75.31 ± 15.18	0.34	0.56

SD = standard deviation; CRT = cognitive remediation therapy; SRT = standard rehabilitation therapy; PANSS = Positive and Negative Syndrome Scale.

Table 2
Neuropsychological and daily functioning assessments scores at baseline.

	ALL (N = 40)	CRT/SRT (N = 15)	CRT/ SRT+ (N = 25)	ANOVA	
	Mean ± SD	Mean ± SD	Mean ± SD	F	p
BACS^a					
Verbal memory	35.40 ± 10.93	32.53 ± 10.96	37.12 ± 10.76	1.67	0.20
Working memory	16.05 ± 4.35	15.86 ± 5.04	16.20 ± 4	0.05	0.81
Psychomotor speed and coordination	69.07 ± 15.46	71.60 ± 15.23	67.56 ± 15.71	0.63	0.43
Verbal fluency	35.04 ± 13.26	32.66 ± 14.25	37.04 ± 12.65	1.01	0.31
Processing speed	37.40 ± 11.68	36.66 ± 10.26	37.84 ± 12.64	0.09	0.76
Executive functions	13.20 ± 4.15	12.60 ± 5.13	13.56 ± 3.50	0.49	0.48
Cognitive Index	1.07 ± 0.71	1.06 ± 0.78	1.08 ± 0.67	0.00	0.95
IQ					
Verbal	88.81 ± 13.12	85.91 ± 10.12	90.20 ± 14.32	0.85	0.36
Performance	85.83 ± 13.22	85.16 ± 14.94	86.16 ± 12.63	0.04	0.83
Total	86.27 ± 12.15	83.58 ± 10.46	87.56 ± 12.89	0.86	0.35
QLS					
Total score	49.69 ± 17.36	51.28 ± 17.36	48.80 ± 17.66	0.17	0.67

SD = standard deviation; CRT = cognitive remediation therapy; SRT = standard rehabilitation therapy; BACS = Brief Assessment of Cognition in Schizophrenia; IQ = intelligence quotient; QLS = Quality of Life Scale.

^a BACS cognitive index was calculated as the mean of equivalent scores of each BACS subtest.

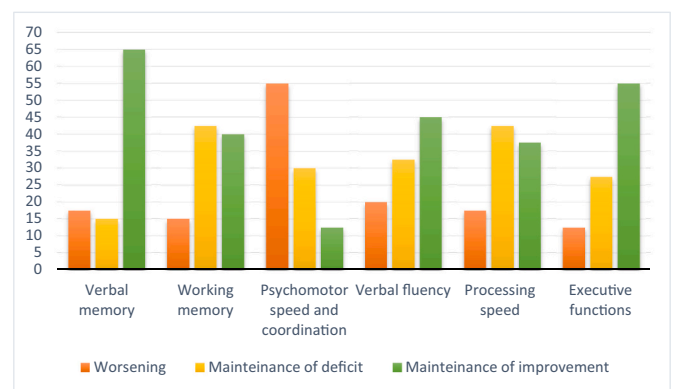


Fig. 1. Proportions of patients that maintained the improvement after treatment stratified by cognitive functions.

group in cognition, assessed by BACS criteria, was analyzed with repeated measures ANOVA and it didn't show any significant time* treatment group interaction on cognitive measures, except for processing speed ($F = 3.59, p = 0.03$), (Table 3).

Precisely, within post-hoc analysis showed a significant decrease in symbol coding performance at 10 years in the CRT/SRT group ($p = 0.01$), while no differences were observed in the CRT/SRT+ group. Moreover, post-hoc analysis showed a significant difference between treated groups on processing speed 10 years after, with higher scores in CRT/SRT+ group, compared to the CRT/SRT group ($p = 0.02$).

Concerning daily functioning, assessed with QLS measures, no significant time * treatment group interaction was observed in QLS, as

Table 3

Neuropsychological and daily functioning assessments scores at the end of the treatment CRT/SRT, after 5 and 10 years, separated according to treatment groups. Repeated Measures ANOVA effects for Time (T) and Time * Treatment group interaction (G * T) are also reported.

	CRT/SRT (N = 15)			CRT/SRT+ (N = 25)			Repeated measures ANOVA			
	End of the treatment	5 years follow-up	10 years follow-up	End of the treatment	5 years follow-up	10 years follow-up	Time * treatment		Time	
							F	p	F	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD				
BACS										
Verbal memory	39.57 ± 10.65	38.60 ± 9.96	36.80 ± 11.66	44.24 ± 13.71	42.50 ± 11.97	41.96 ± 10.27	0.276	0.76	1.055	0.354
Working memory	16.35 ± 4.34	16.86 ± 3.97	15.60 ± 4.28	17.40 ± 4.76	17.87 ± 4.02	17.36 ± 4.16	0.415	0.662	0.715	0.493
Psychomotor speed and coordination	74.71 ± 15.66	59.40 ± 19.36	50.26 ± 17.47	70.56 ± 16.12	62.41 ± 15.35	52.44 ± 17.91	0.45	0.64	17.79	<0.001*
Verbal fluency	36.35 ± 19.04	39.33 ± 13.14	32.46 ± 12.12	43 ± 14.44	43 ± 16.14	40.92 ± 12.18	0.962	0.387	2.003	0.142
Processing speed	41.33 ± 11.59	38.86 ± 8.39	34.80 ± 10.48	39.72 ± 13.31	43.25 ± 10.90	42.16 ± 12.28	3.591	0.032*	1.143	0.324
Executive functions	15.20 ± 4.03	14.33 ± 5.20	14 ± 3.54	15.96 ± 3.74	15.25 ± 3.92	15.52 ± 3.95	0.239	0.788	1.242	0.295
Cognitive Index	1.44 ± 0.71	1.39 ± 1.01	1.1 ± 0.78	1.68 ± 0.89	1.63 ± 0.82	1.7 ± 0.77	2.15	0.124	0.866	0.417
QLS										
Total score	60.84 ± 21.93	50.4 ± 21.01	55.33 ± 21.52	53.69 ± 13.08	55.68 ± 18.94	56.87 ± 21.03	2.191	0.12	1.032	0.362

SD = Standard Deviation; CRT = Cognitive Remediation Therapy; SRT = Standard Rehabilitation Therapy; BACS = Brief Assessment of Cognition in Schizophrenia; QLS = Quality of Life Scale; T0 = after 6 months of CRT/SRT; T1 = 5 years after CRT/SRT completion. BACS cognitive index was calculated as the mean of equivalent scores of each BACS subtest^a.

^a *Statistically significant results.

reported in [Table 3](#).

4. Discussion

In recent years, the effectiveness of CRT in improving cognition has been widely demonstrated (Bosia et al., 2017; Cella et al., 2016; Kurtz et al., 2016; Medalia and Choi, 2009; Vita et al., 2021) but only few studies have evaluated the longitudinal persistence of cognitive and functional improvements over time (Bell et al., 2003; Deste et al., 2015; Fiszdon et al., 2004; Rispaud et al., 2016; Wykes et al., 2007; Zhu et al., 2020).

In this view, this is the first 10 years follow-up research that aims at studying the maintenance of cognitive and functional improvements in patients with schizophrenia.

Results indicated that, regardless of SRT's duration, cognitive and functional increases of combined CRT/SRT interventions are still preserved 10 years after the end of the treatment. Indeed, we reported no significant differences in functional and cognitive areas over time in the whole sample, with the only exception of psychomotor speed and coordination cognitive subdomain. According to literature, this task can be strongly influenced by pharmacological treatment and may rely more on continuous exercise (Buonocore et al., 2018); this possibly explains the divergent trajectory over time. In order to study the persistency of increases, we created qualitative indexes of the maintenance of gains for each BACS subtest. After 10 years, 65% of patients maintained the improvements in verbal memory, 40% in working memory, 45% in verbal fluency, 37.5% in processing speed and 55% in executive functions. Only the subtests psychomotor speed and coordination showed a lower percentage (12.5%). Furthermore, only a limited number of cases showed worsening in cognitive areas. These data confirm that the improvements achieved after the CRT/SRT intervention were conserved in the great majority of cognitive abilities 10 years later.

Given the cognitive deterioration reported in schizophrenia (Fujino et al., 2017; Miwa et al., 2020; Zanelli et al., 2019), the preservation of improvements during time should be considered as a crucial finding.

Moreover, our results highlighted that the highest percentage of patients retained their gains in verbal memory, known as one of the most vulnerable ability to cognitive decline (Zanelli et al., 2019).

These findings emphasize the importance of integrated programs in clinical practice in schizophrenia (Bechi et al., 2019; Buonocore et al., 2018; Cavallaro et al., 2009; McGurk et al., 2007; Poletti et al., 2010) and, cautiously, might show that these types of trainings may slow down the cognitive deterioration and the progressive disability typically reported in patients with chronic mental illness (Bowie et al., 2010; Zanelli et al., 2019). Our data confirm previous studies from literature focused on the persistence of cognitive gains after training in elderly healthy subjects and neurological populations (Ball et al., 2002; Smith et al., 2009; Wolinsky et al., 2016). For example, Rebok et al. (2014) showed improvements in both reasoning and speed of processing at a 10-year follow-up in a volunteer sample of 2832 persons who underwent a cognitive training (Rebok et al., 2014). These data are consistent with another research (Edwards et al., 2017) that demonstrates that sessions of cognitive training over the period of time of 10 years can even reduce the degenerative processes lowering the hazard for dementia. So, these findings demonstrate the durability of effectiveness of cognitive gains after a cognitive rehabilitation.

Moreover, following the results of our previous work (Buonocore et al., 2018), we also aimed to investigate if a different duration of the SRT might influence the longitudinal maintenance of the improvements achieved. Looking at cognition, results showed no differences between and within groups except for the subtest of processing speed, with a better performance of SRT+ group at follow-up. These data, therefore, indicate that the great majority of cognitive effects persist regardless of the duration of SRT.

Anyhow, the better cognitive performance of SRT+ in symbol coding task further supports the importance of an adjunctive year of rehabilitation following CRT. In particular, Dickinson reported that digit symbol coding tasks are, not only useful tools in quantifying the core cognitive impairment in schizophrenia, but are also better discriminators of diagnostic group status, predicting functional status and representing an

index of poor prognosis and functional disability (Dickinson, 2008).

We did not observe significant differences in the remaining cognitive areas. Perhaps a greater continuity of the integrated treatment might affect more the complex functions, such as processing speed, than the simpler ones (Valerio et al., 2021).

With respect to daily functioning, results didn't show a significant difference between CRT/SRT and CRT/SRT+ group. Dissimilarly from our previous results (Buonocore et al., 2018), we did not find significant variations between groups regarding the maintenance of functional improvement. However, different methodological issues could explain this discrepancy. First of all, global functioning is a complex and multi-facets construct. It embraces several complex areas, such as the ability to study, to obtain and maintain a job and to collaborate in everyday housework. Many factors can contribute to dissimilar outcomes in people with serious mental illness, thus it is certainly hard to measure functional changes in a 10-year follow-up without the influence of confounding external variables. At last, in the present study, we used The Quality of Life Scale, focusing on real-world behavior, (Bechi et al., 2017); also functional capacity can be evaluated to have a realistic assessment of the outcome (i.e., UCSD Performance-based Skills Assessment).

In sum, it might be crucial to extend integrated programs in schizophrenia 1-year more utilizing SRT, but this would probably be insufficient to highlight a significant difference in the maintenance of functional gains over a long span of time, as in 10-years. Nonetheless, it may be interesting, as Ball et al. (2002) have already confirmed, to investigate if the effects of a booster training might establish a different outcome (Ball et al., 2002).

Despite our innovative findings, this study also presents some limitations. Firstly, the assignment of the treatment was not randomized, therefore maybe affecting the conclusions about the comparison between interventions. Secondly, the evaluation of the persistence of gains did not consider every variable that might have influenced the outcome. Thus, future studies should include more variables in the analysis and assessment of improvements. Moving forward, the sample size is relatively small, although comparable to previous follow-up studies, and no correction for multiple testing was performed, despite the number of statistical analyses used. Lastly, pharmacological therapy may have changed over time, and tracking these variations during the course of illness should be taken in consideration in future studies.

In conclusion, as far as we know, this is the first study in literature that showed the effectiveness of a CRT/SRT program in schizophrenia at 10-years follow-up, considering the durability of cognitive and functional improvements.

CRedit authorship contribution statement

Conception and design: Mariachiara Buonocore, Marta Bosia, Roberto Cavallaro, Marco Spangaro.

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Critical revision of the article for important intellectual content: All authors.

All authors approved the final version of the article.

Declaration of competing interest

None.

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