Cognitive remediation therapy to enhance cognition and improve recovery in early psychosis: the ECLIPSE research programme including an RCT

Til Wykes,[1*†] Eileen Joyce,[2†] Emese Csipke,[1] Dominic Stringer,[1] Andrew Pickles,[1] Paul McCrone,[3] Matteo Cella,[1] Rumina Taylor,[1] Rose Tinch-Taylor,[1] Janet Boadu,[1] Gregory Aarons,[4] Max Birchwood,[5] Sue Dopson,[6] David Fowler,[7] Kathryn Greenwood,[7] Sonia Johnson,[8] Jesus Perez,[9] Rosa Ritunnano,[5] Andrew Thompson,[10] Rachel Upthegrove,[11] Jon Wilson[12] and Clare Reeder[1]

[1]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[2]Department of Clinical and Motor Neuroscience, UCL Queen Square Institute of Neurology, University College London, London, UK
[3]Institute for Lifecourse Development, Health and Human Sciences, University of Greenwich, London, UK
[4]Child and Adolescent Services Research Center, University of California, San Diego, CA, USA
[5]Warwick Medical School, University of Warwick, Coventry, UK
[6]Saïd Business School, University of Oxford, Oxford, UK
[7]School of Psychology, University of Sussex, Falmer, UK
[8]Department of Psychiatry, University College London, London, UK
[9]Department of Psychiatry, University of Cambridge, Cambridge, UK
[10]Centre for Youth Mental Health, University of Melbourne, Melbourne, VIC, Australia
[11]Institute for Mental Health, University of Birmingham, Birmingham, UK
[12]Norfolk and Suffolk NHS Foundation Trust, Central Norfolk Youth Service, Norwich, UK

[*]Corresponding author til.wykes@kcl.ac.uk

†Joint first authors

Published July 2024
DOI: 10.3310/LMFP9667

Scientific summary

Cognitive remediation therapy to enhance cognition and improve recovery in early psychosis: the ECLIPSE research programme including an RCT

Programme Grants for Applied Research 2024; Vol. 12: No. 4
DOI: 10.3310/LMFP9667

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Cognitive remediation (CR) therapy is a psychological intervention targeting cognitive dysfunction associated with psychosis with the goal of improving functional outcomes. Cognitive remediation can improve cognitive and functional recovery, as well as increasing confidence and motivation. Evidence from the largest meta-analysis demonstrated that these effects are durable.

National Health Service Early Intervention for psychosis services provide care soon after a diagnosis of psychosis to optimise recovery. Embedding CR in those services may confer long-lasting benefits such as improved social relationships and the opportunity to work or take part in further education.

The overarching aim of the Enhancing Cognition and quality of Life in early PSychosiEs (ECLIPSE) research programme was to determine the optimal method of introducing computerised CR therapy (CIRCuiTS™) into NHS Early Intervention Services (EIS) considering improvement in cognitive and social function and cost-effectiveness.

The programme was centred on work package 3 (WP3), a randomised, blinded multiarm multisite controlled trial comparing three CR implementation methods with each other and with routine clinical care [Treatment as Usual (TAU)]. To aid the interpretation of WP3 and bolster our recommendations to the NHS, WP1 included a series of studies investigating: patient and staff satisfaction with CR; preference for the methods of CR delivery; and the influence of team organisational climate.

Although the CR was computerised and can be completed independently, its effects are boosted via learning, practice and feedback supervised by a therapist. WP2 was a series of studies to design and test an online CR therapist training package to use in their individual teams.

Finally, WP4 examined mediators and moderators of the trial results to inform teams about how the clinical features of their individual patients may influence the effect of CR.

In WP3, the CR modalities were: Intensive 1 : 1 therapist supervision; Group supervision with one therapist; and Independent (self-determined with infrequent access to therapist supervision). Participants were recruited from EIS in 12 mental health trusts, linked to 6 universities and serving diverse urban/rural populations. They were clinically stable and presented with a non-affective psychotic episode not < 3 months earlier. All participants were offered 42 hours of CR. Therapy was delivered by a supervised assistant psychologist using the CIRCuiTS software. The primary outcome was achievement of self-determined social goals measured by the Goal Attainment Scale (GAS). Secondary outcomes were changes in cognitive function, general social function, self-esteem and symptoms. An interim analysis was planned so that any treatment arm inferior to the others would be dropped. Assessments were conducted at three time points: baseline, post therapy and 6 months later.

For the primary and secondary outcomes, intention-to-treat analyses estimated treatment effect contrasts for the following: Group versus Intensive; Independent versus TAU; Group + Intensive versus TAU using a linear mixed model with baseline scores, site, period (before and after interim analysis) and baseline missingness as covariates. The average treatment effect per hour of CR on the primary outcome and sensitivity analyses were performed.

The interim analysis used end-point data from 100 participants: TAU (n = 20), Group (n = 33), Independent (n = 22), Intensive (n = 25). The Data Monitoring Committee recommended closing recruitment to the TAU and Independent arms. At the end of the trial, 448 patients consented and 377 were eligible and completed baseline assessment. They were randomised as follows: 134 to Group, 65 to Independent, 112 to Intensive and 66 to TAU.

Post therapy, there was no statistical difference in GAS scores between the Group and Intensive arms [mean difference 0.737; standard error (SE) = 1.652; p = 0.655; lower confidence interval (CI) = −2.50 to upper CI = 3.975], or in the Independent arm compared with TAU (mean difference 0.695; SE = 2.448;

p = 0.777; lower CI = –4.104 to upper CI = 5.493). There was a significant difference between the combined Group and Intensive sample versus TAU post therapy (mean difference 5.734; SE = 1.958; *p* = 0.003; lower CI = 1.898 to upper CI = 9.571).

Post-therapy analyses of global cognition (composite score from several broad-ranging neuropsychological tests) demonstrated no difference between the Group and Intensive arms (mean difference 0.192; SE = 0.499; *p* = 0.699; lower CI = −0.785 to upper CI = 1.170), but there was a significant difference between the combined Group and Intensive conditions versus TAU at post therapy (mean difference 1.479; SE = 0.553; *p* = 0.008; lower CI = 0.395 to upper CI = 2.564). There was also a trend for significance between Independent and TAU (mean difference 1.348; SE = 0.701; *p* = 0.054; lower CI = −0.026 to upper CI = 2.722).

There were no other secondary outcome differences for measures of social function (Social and Occupational Functioning Assessment Scale and time use survey), negative symptoms (Clinical Assessment Interview for Negative Symptoms) and self-esteem (Rosenberg scale) at post therapy and no differences at 6 months for any measure.

Ninety-six adverse events (AEs) were reported for 59 individuals with 60 classified as serious adverse events (SAEs) for 44 participants. The rates of AEs and SAEs were similar across arms. Two participants died, both in the Intensive CR arm, but neither were judged as related to the study intervention.

Work package 3 also included a cost-effective analysis using quality-adjusted life-years (QALYs) as the outcome. QALYs were derived from the EuroQol-5 Dimensions (baseline to 6 months). Service use was measured by the Client Service Receipt Inventory and combined with unit cost information (Personal Social Services Research Unit) to calculate costs. Intervention costs were calculated from therapist training, supervision and access to CIRCuiTS. Differences in costs were not significant (Group vs. Intensive, £26,383 per QALY; Group vs. TAU, £4306 per QALY; Intensive vs. TAU, £3170 per QALY). Group versus TAU and Intensive versus TAU had significantly higher QALYs than TAU, suggesting that Group and Intensive CR provided more benefit compared with TAU. There were no significant differences in costs and outcomes for GAS.

Work package 3 summary. CR provided in Intensive and Group modalities significantly enabled participants to achieve their self-determined goals to a greater extent than standard care alone. Global cognition was also significantly improved by Intensive and Group modalities compared with standard care. Group and Intensive modalities were indistinguishable. There was an indication that CR used independently may lead to improved global cognition compared with standard care. Group and Intensive CR were not different with respect to QALYs, and both conferred significant benefit compared with standard care and their cost–benefit for QALY improvement was well below the National Institute for Health and Care Excellence (NICE) threshold for adopting the intervention to NHS services.

To assess CR acceptability, a new satisfaction scale was developed with service users, representative of trial participants and EIS staff in focus groups using thematic analysis (WP1, Study 1). These were validated (WP1, Study 2) with a survey sent to participants and site teams at the end of the trial. Test–retest analysis showed good reliability; concurrent reliability using the Working Alliance Inventory and validity for the service user scale. The investigation of differences in the different CR approaches (WP1, Study 2) demonstrated that mean differences in satisfaction score were in favour of Group CR over Intensive CR and Independent CR and in favour of Intensive CR over Independent CR, but these differences were not statistically different.

Focus groups conducted with staff and service users assessed service user and staff views of implementation using thematic analysis (WP1, Study 3). There was strong preference for regular open-ended 1 : 1 sessions with options for drop-in sessions.

Organisational climate was measured in two ways. A qualitative study involving semistructured interviews with staff with thematic analysis (WP1, Study 4) indicated that consideration of local conditions and organisational microclimates mediates the successful implementation of new

interventions and is needed in addition to generic, context-free variables such as resources before new interventions can be introduced. A quantitative survey (WP1, Study 5) with staff in the participating sites used a set of validated scales assessing team climate, leadership and team attitude to evidence-based practice (before and after CR implementation). We tested whether leaders affect the climate for use of CR and whether that then influences staff attitudes to CR. Before the introduction of CR, that model was supported. After staff had experience of CR, it was not a significant model. This may be because staff experienced the patient benefit and so the effect of leaders was reduced. If we take the two sets of results together, then improving the organisational climate through flexible leadership and increasing the resources for the intervention will enhance its adoption. Experience of beneficial interventions can reduce the effects of leadership and bodes well for continued adoption.

In WP2, an e-learning CR programme based on previous training materials was further developed through focus groups with mental health clinicians from a range of specialities. It includes multimedia presentations (film, video and short exercises) (Study 6). In Study 7, the acceptability and feasibility of this package were tested with volunteers from eight mental health trusts. Completion of training took longer than expected, partly explained by constraints during the COVID-19 pandemic. Feedback from the participants was positive and their suggestions for what would have helped them complete the training more quickly will be used to refine the training programme.

Following completion of the trial, mediators and moderators of the effects were investigated in WP4. The assumption was made that variation in the intention-to-treat estimates across arms was derived principally from the variation in the time-on-task achieved in each arm. This was tested using analysis of covariance, and a significant effect was found for time-on-task increasing the GAS by 0.187 (95% CI 0.062 to 0.312; $p = 0.003$) for each hour of therapy. There were no significant difference in the effects of time-on-task between the Group and Intensive arms (Wald: 1df $p = 0.753$) and no difference between these pooled therapist-assisted and independently undertaken treatment effects (Wald: 1df $p = 0.630$) when time-on-task was considered.

We tested a model that cognitive improvement (using the post-therapy global cognitive score) mediated the effect of CR time-on-task on Goal Attainment. The model, including baseline variables, fitted well [root mean square error of approximation = 0.00; Tucker Lewis index = 1.012^2; (27df) $p = 0.668$] and showed that the mediated path from time-on-task to cognition and cognition to functional outcome was small and non-significant (Coeff = 0.014, $p = 0.248$, 95% CI −0.009 to 0.037). Baseline global symptoms did not moderate the effect of time-on-task on cognition ($p = 0.098$). However, negative symptoms significantly moderated the effect of improved cognition on goal attainment ($p = 0.016$). Participants with high negative symptoms spent on average an hour more on CR tasks than those with low negative symptoms. The mediation effect of change in cognitive score on the change in Goal Attainment was estimated for high and low negative symptom groups. Larger changes in cognition were associated with larger changes in the GAS score overall, but this was not evident in the high negative symptom group, suggesting that negative symptoms can interfere with mobilising improvements in general cognition to achieve a desired functional outcome.

The **ECLIPSE** programme overall provides valuable evidence of the sort of factors to consider specifically with the introduction of CIRCuiTS into EIS. It also provides insights for introducing cognitive interventions in general, as well as novel interventions in all services. We need to understand the team climate, influence the leaders and provide evidence of benefits. We were not able to differentiate between the two types of therapy (Group and Intensive); both improved personal goals and were cost-effective. The cost of improving by one QALY was lower than the threshold for the NICE, and so there is now ample evidence that it should be more generally available. As the therapy needs trained therapists, the inclusion of an e-learning programme will boost large-scale roll-out. We do not know if everyone improves, but there is an indication that those with higher negative symptoms benefit less from the cognitive improvements. This will be investigated further, but the result suggests that therapy adaptations may be required, including increasing the number of sessions and a more integrated transfer of cognitive skills into everyday life.

Study registration

This study is registered as ISRCTN14678860 https://doi.org/10.1186/ISRCTN14678860.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research Programme (NIHR award ref: RP-PG-0612-20002) and is published in full in Programme Grants for Applied Research; Vol. 12, No. 4. See the NIHR funding and Awards website for further award information.

Programme Grants for Applied Research

ISSN 2050-4330 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

Programme Grants for Applied Research (PGfAR) was launched in 2013 and is indexed by Europe PMC, NCBI Bookshelf, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and Scopus® (Elsevier, Amsterdam, Netherlands).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full PGfAR archive is freely available to view online at www.journalslibrary.nihr.ac.uk/pgfar.

Criteria for inclusion in the *Programme Grants for Applied Research* journal

Manuscripts are published in *Programme Grants for Applied Research* (PGfAR) if (1) they have resulted from work for the PGfAR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Programme Grants for Applied Research programme

The Programme Grants for Applied Research (PGfAR) programme, part of the National Institute for Health and Care Research (NIHR), was established in 2006 to fund collaborative, multidisciplinary programmes of applied research to solve health and social care challenges. Findings are expected to provide evidence that lead to clear and identifiable patient benefits, in the relatively near future.

PGfAR is researcher led and does not specify topics for research; however, the research must be in an area of priority or need for the NHS and the social care sector of the Department of Health and Social Care, with particular emphasis on health and social care areas that cause significant burden, where other research funders may not be focused, or where insufficient funding is available.

The programme is managed by the NIHR Central Commissioning Facility (CCF) with strategic input from the Programme Director. For more information about the PGfAR programme please visit the website: https://www.nihr.ac.uk/explore-nihr/funding-programmes/programme-grants-for-applied-research.htm

This article

The research reported in this issue of the journal was funded by PGfAR as award number RP-PG-0612-20002. The contractual start date was in December 2014. The draft manuscript began editorial review in September 2021 and was accepted for publication in October 2023. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, CCF, PGfAR or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the PGfAR programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).