**Suppl Methods. Additional information on the cognitive remediation intervention (CIRCuiTS).**

Participants in the intervention arm received a 12-week course of therapist-led cognitive remediation (CR) with focus on strategy use, metacognition, and transfer of cognitive practice to daily life activities using the online CR software ‘Computerised Interactive Remediation of Cognition – Interactive Training for Schizophrenia’ (CIRCuiTS; [www.circuitstherapy.com](http://www.circuitstherapy.com)). CIRCuiTS is a manualized CR approach (Reeder & Wykes, 2010), developed according to the basic principles of CR (e.g., errorless learning, scaffolding, positive feedback; Wykes & Reeder, 2005), and has been validated for people with schizophrenia (Reeder et al., 2017). Therapy delivery comprised one-on-one sessions, either in person or remotely (i.e., telephone or video), and supplementary individual homework sessions, according to the availability and the needs of the participants. The target for therapy engagement was 2-3 hourly sessions per week aiming for a total of 30-40 sessions over 12 weeks. Following evidence from a feasibility study in people with schizophrenia (Reeder et al., 2016), it was decided that 20 hours of CIRCuiTS would be the minimum cut-off for treatment completion.

CIRCuiTS is a CR approach using two components: massed practice of cognitive tasks and training in strategy use and metacognitive processing. The software uses the graphical representation of a village as a virtual environment where participants can practice 36 different cognitive tasks, each one with at least 12 gradually increasing levels of difficulty. Progress to higher difficulty levels depends on the accuracy scores achieved, with progression occurring only when the 80% threshold is achieved. This is to facilitate errorless learning and to maintain treatment engagement and high levels of positive feedback for the participant. Cognitive tasks are either abstract or exercises. Abstract tasks are simpler, targeting specific cognitive functions, such as speed of processing (e.g., finding the exit on a maze route), while exercises are designed as more complex ecological tasks emulating real-life activities, such as social interactions, travelling, shopping or work, implicating multiple cognitive functions (e.g., planning the calendar of a working day). Exercises take place in different locations within the CIRCuiTS village (e.g., a train journey initiates at the train station) which provides a social context for task practice. This allows participants to consider the transfer of strategies and metacognitive processes from the software to real-life activities.

CIRCuiTS prompts strategy use for all cognitive tasks and promotes the use of metacognitive competencies in several ways, such as prompting clients to estimate the level of difficulty and the completion time for each task before beginning the task. Although the software provides incentives for increasing the client’s awareness around their own cognitive functioning, the role of the therapist is critical for the metacognitive elements of the therapy. Therapists support participants to select and apply strategies, identify strengths and shortcomings in their own cognitive functioning, and set real-life cogSMART goals (i.e., specific, measurable, attainable, realistic, and timely goals that are related to cognitive improvement) which are reviewed throughout the therapy. Goals and expectations for goal achievement are formulated after considering the metacognitive competencies of the participant (i.e., metacognitive knowledge and regulation), as well as non-cognitive factors (e.g., procrastinating, anxiety, fatigue or sleeping difficulties) which may affect the outcome of a cognitive goal (Cella et al., 2015). Therapists also facilitate the transfer of cognitive gains and new learning to daily life functioning through examples, role-playing, and in vivo practicing. CR was delivered by postgraduate psychologists with supervision from an experienced clinical psychologist. All therapists attended training in the theoretical framework of CIRCuiTS and the delivery of CR using CIRCuiTS. Supervision was provided in group or individual sessions throughout the 12-week intervention period.

CIRCuiTS was feasible to deliver to people with BD and was well accepted by study participants, with 80% (n=32) of them meeting the protocol target for therapy engagement (>20 therapy hours). Overall, participants in the CR group completed on average 25.1 sessions (SD = 11.4) over the course of 12 weeks, while treatment completers attended 29.8 sessions on average (SD = 6.1). The high engagement rate suggested that it was appropriate to further explore the treatment mechanisms of this therapist-led CR delivered through CIRCuiTS. Participants did not receive any compensation for undertaking therapy.

**References for supplementary methods**

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**Suppl Table 1. Estimated treatment effects (CR versus TAU) for cognitive and functional outcomes at weeks 13 and 25.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **Week 13** |  | **Week 25** |
| **Adjusted mean difference (95% CI)** | ***F*-statistic** | ***p*** | ***d*** | **Adjusted mean difference (95% CI)** | ***F*-statistic** | ***p*** | ***d*** |
| *Cognitive outcomes* |
|  Composite score | 0.45 (0.30, 0.61) | 34.562 | <0.001 | 0.71 |  | 0.55 (0.34, 0.76) | 27.034 | <0.001 | 0.87 |
|  Hotel test | 0.64 (0.30, 0.98) | 14.341 | <0.001 | 0.58 | 0.60 (0.11, 1.09) | 5.981 | 0.02 | 0.54 |
|  VPA2 | 0.41 (0.12, 0.69) | 8.138 | 0.006 | 0.37 | 0.65 (0.30, 0.99) | 13.875 | <0.001 | 0.58 |
|  Coding | 0.33 (0.10, 0.57) | 8.191 | 0.007 | 0.46 | 0.36 (0.14, 0.59) | 10.344 | 0.002 | 0.50 |
|  Digit span | 0.36 (0.13, 0.59) | 9.995 | 0.002 | 0.50 | 0.54 (0.25, 0.84) | 13.384 | <0.001 | 0.75 |
| *Functional outcomes*  |
|  FAST | -4.7 (-2.6, -6.9) | 18.921 | <0.001 | 0.48 |  | -6.3 (-3.5, -9.0) | 20.985 | <0.001 | 0.64 |
|  GAS | 13.2 (9.3, 17.2) | 44.926 | <0.001 | 3.14 | 8.1 (4.2, 12.1) | 17.060 | <0.001 | 1.92 |
| *Notes:* CR: Cognitive remediation; FAST: Functional Assessment Short Test; GAS: Goal Attainment Scale; TAU: Treatment-as-usual; VPA2: Verbal Paired Associates – delayed free recall; *d* = Cohen’s *d* effect size (mean difference between groups divided by pooled baseline standard deviation). |

**Suppl Table 2. Standardized direct, indirect and total effects for models testing cognition (week 13) as a mediator of treatment effect (CR versus TAU) on functional outcomes (week 25).**

|  |  |  |
| --- | --- | --- |
| **Outcome: FAST total score – week 25**  |  | **Outcome: GAS total score – week 25** |
| **Mediation models** | ***beta* coefficient (95%CI)** | ***pa*** | **% of effect mediated** | **Mediation models** | ***beta* coefficient (95%CI)** | ***pa*** | **% of effect mediated** |
| **Tx 🡪 Comp 🡪 FAST** |  | **Tx 🡪 Comp 🡪 GAS** |
| Direct effect | -0.43 (-0.77, -0.08) | 0.02 | 35% |  | Direct effect | 0.63 (0.14, 1.12) | 0.01 | 23% |
| Indirect effect | -0.23 (-0.51. -0.04) | 0.04 | Indirect effect | 0.19 (-0.18, 0.52) | 0.21 |
| Total effect | -0.66 (-0.94, -0.37) | <0.001 | Total effect | 0.82 (0.42, 1.22) | <0.001 |
| **Tx 🡪 ExF 🡪 FAST** |  | **Tx 🡪 ExF 🡪 GAS** |
| Direct effect | -0.64 (-0.92, -0.35) | <0.001 | 3% |  | Direct effect | 0.71 (0.27, 1.63) | <0.01 | 12% |
| Indirect effect | -0.02 (-0.16, 0.14) | 0.82 | Indirect effect | 0.10 (-0.13, 0.29) | 0.33 |
| Total effect | -0.66 (-0.95, -0.36) | <0.001 | Total effect | 0.82 (0.42, 1.21) | <0.001 |
| **Tx 🡪 VM 🡪 FAST** |  |  |  |  | **Tx 🡪 VM 🡪 GAS** |
| Direct effect | -0.60 (-0.91, -0.29) | <0.001 | 9% |  | Direct effect | 0.78 (0.38, 1.19) | <0.001 | 5% |
| Indirect effect | -0.06 (-0.21, 0.08) | 0.31 | Indirect effect | 0.04 (-0.16, 0.23) | 0.61 |
| Total effect | -0.66 (-0.96, -0.37) | <0.001 | Total effect | 0.82 (0.40, 1.25) | <0.001 |
| **Tx 🡪 PrSp 🡪 FAST** |  | **Tx 🡪 PrSp 🡪 GAS** |
| Direct effect | -0.55 (-0.85, -0.26) | <0.01 | 14% |  | Direct effect | 0.74 (0.31, 1.17) | <0.01 | 10% |
| Indirect effect | -0.09 (-0.24, 0.01) | 0.16 | Indirect effect | 0.08 (-0.07, 0.26) | 0.38 |
| Total effect | -0.64 (-0.92, -0.36) | <0.001 | Total effect | 0.82 (0.42, 1.21) | <0.001 |
| **Tx 🡪 WM 🡪 FAST** |  | **Tx 🡪 WM 🡪 GAS** |
| Direct effect | -0.57 (-0.88, -0.27) | <0.001 | 12% |  | Direct effect | 0.74 (0.31, 1.16) | <0.01 | 11% |
| Indirect effect | -0.08 (-0.22, 0.03) | 0.23 | Indirect effect | 0.09 (-0.03, 0.29) | 0.25 |
| Total effect | -0.65 (-0.94, -0.36) | <0.001 | Total effect | 0.83 (0. 43, 1.23) | <0.001 |
| *Notes:* Comp: Global cognitive composite score; ExF: Executive functioning; FAST: Functional Assessment Short Test; GAS: Goal Attainment Scale; PrSp: Processing speed; Tx: Treatment group (CR: Cognitive Remediation / TAU: Treatment-as-usual); VM: Verbal memory; WM: Working memory.a *p* values for indirect effects are based on the Sobel test for mediation effects (Preacher & Leonardelli, 2001). |

**Suppl Table 3. Interaction effects and estimates for the effect of treatment (CR versus TAU) on functional outcomes (week 25) at different levels of cognitive moderators (week 13).**

|  |  |  |  |
| --- | --- | --- | --- |
| **Moderation models** | **Outcome: FAST total score – week 25** |  | **Outcome: GAS total score – week 25** |
| **Interaction *beta* coefficient (95% CI)** Tx effect estimate (95% CI) | ***p*** | **Interaction *beta* coefficient (95% CI)**Tx effect estimate (95% CI) | ***p*** |
| ***Tx \* Composite score***  | **β = 0.16 (-0.35, 0.64)** | **0.49** |  | **β = 0.78 (0.08, 1.55)** | **0.03** |
|  Low normative level | -7.22 (-11.2, -3.25) | <0.001 | 2.85 (-2.92, 8.62) | 0.33 |
|  Average normative level | -6.28 (-9.18, -3.37) | <0.001 | 7.40 (3.26, 11.6) | <0.001 |
|  High normative level | -5.33 (-9.37, -1.29) | 0.01 | 11.9 (6.10, 17.8) | <0.001 |
| ***Tx \* Hotel test***  | **β = 0.19 (-0.18, 0.52)** | **0.25** |  | **β = 0.24 (-0.23, 0.75)** | **0.34** |
|  Low normative level | -9.25 (-13.3, -5.20) | <0.001 | 6.05 (0.06, 12.1) | 0.05 |
|  Average normative level | -7.62 (-10.4, -4.80) | <0.001 | 8.08 (3.84, 12.3) | <0.001 |
|  High normative level | -5.98 (-9.56, -2.10) | <0.01 | 10.1 (4.07, 16.2) | <0.001 |
| ***Tx \* VPA2***  | **β = -0.06 (-0.36, 0.23)** | **0.67** |  | **β = 0.36 (-0.09, 0.85)** | **0.09** |
|  Low normative level | -6.11 (-10.1, -2.21) | <0.01 | 4.61 (-1.22, 10.4) | 0.12 |
|  Average normative level | -6.69 (-9.48, -3.91) | <0.001 | 8.24 (4.14, 12.3) | <0.001 |
|  High normative level | - 7.28 (-11.3, -3.30) | <0.001 | 11.8 (5.97, 17.8) | <0.001 |
| ***Tx \* Coding***  | **β = 0.13 (-0.24, 0.45)** | **0.46** |  | **β = 0.40 (-0.15, 0.81)** | **0.13** |
|  Low normative level | -7.42 (-11.1, -3.77) | <0.001 | 4.81 (-0.81, 10.4) | 0.09 |
|  Average normative level | -6.42 (-9.08, -3.76) | <0.001 | 7.92 (3.88, 11.9) | <0.001 |
|  High normative level | -5.42 (-9.23, -1.61) | <0.01 | 11.1 (5.27, 16.8) | <0.001 |
| ***Tx \* Digit span***  | **β = 0.29 (-0.15, 0.65)** | **0.14** |  | **β = 0.44 (-0.18, 0.93)** | **0.14** |
|  Low normative level | -8.61 (-12.2, -5.01) | <0.001 | 5.25 (-0.26, 10.8) | 0.06 |
|  Average normative level | -6.64 (-9.31, -3.99) | <0.001 | 8.20 (4.22, 12.2) | <0.001 |
|  High normative level | -4.68 (-8.52, -0.83) | 0.02 | 11.2 (5.51, 16.8) | <0.001 |
| *Notes:* CR: Cognitive remediation; FAST: Functional Assessment Short Test; GAS: Goal Attainment Scale; TAU: Treatment-as-usual; Tx: Treatment group (CR / TAU); VPA2: Verbal Paired Associates – delayed free recall; |

**Suppl Figure 1. Unadjusted means (95% CI) of individual cognitive domains across time-points (\* *p* < 0.05).**



**Suppl Figure 2. Mediation model for the effect of CR on psychosocial functioning through cognition.**

Model included age, years of education, depressive symptoms at week 25, and baseline measures of both the mediator and the outcome as covariates. CR: Cognitive remediation; FAST: Functioning assessment short test; TAU: Treatment-as-usual.

FAST
week 25

CR vs. TAU

Global cognition
week 13

a = 0.77
(*p*<0.001)

b = -0.30
 (*p*=0.03)

Direct effect: CR vs TAU c’ = -0.43 (*p*=0.02)

Total effect: CR vs TAU c = -0.66 (*p*<0.001)

Indirect effect:

a\*b = -0.23, 95% CI [-0.51, -0.04], *p*=0.04

 **R2 = .82**

**Suppl Figure 3. Treatment effect on goal attainment at study end moderated by the level of post-treatment performance in individual cognitive domains (\* *p* < 0.05).**





