

Group Cognitive Remediation Therapy Prior to Behavioral Weight Loss Treatment for Adults with Severe Obesity: A Randomized Clinical Trial (CRT Study)

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Abstract

Objective: Individuals with obesity show executive dysfunctions which have been implicated in weight management failure. Initial evidence suggests that cognitive remediation therapy (CRT) conducted after behavioral weight loss (BWL) treatment improves weight loss and executive function, but efficacy for CRT conducted before BWL treatment is unknown. This study investigated whether group CRT in adults with class II or III obesity (body mass index, $BMI \geq 35 \text{ kg/m}^2$) improves weight loss, executive function, weight management behavior, and mental and physical health in real world group BWL treatment. **Method:** In this prospective single-center, assessor-blind trial (DRKS00009333), 270 adults with class II and III obesity (age 44.5 ± 12.8 years, $BMI 45.6 \pm 6.9 \text{ kg/m}^2$, 68.9% women) were randomized to CRT with 8 group sessions over 2 months versus no treatment control, followed by routine BWL treatment of up to 12 months for both groups. Primary outcome was percent weight change at 6 months. Secondary outcomes included executive functions, weight management behaviors, and mental and physical health. **Results:** In intent-to-treat analyses, overall weight loss after 6 months was 1.2% (95% CI: -2.0% to -0.4%, $p=.002$). The difference between arms was 0.4% (95% CI: -1.1% to 1.8%, $p=.629$, Cohen's $d=0.09$) after 6 months and 0.3% (95% CI: -1.5% to 2.2%, $p=.721$, Cohen's $d=0.01$) after 12 months. Improvements in most secondary outcomes including executive functions were seen at most timepoints, however, without differences between arms. **Conclusions:** Group CRT versus no treatment prior to real world BWL treatment in adults with class II and III obesity does not improve weight loss.

Keywords: obesity; treatment; cognitive remediation therapy; behavioral weight loss treatment; adults

Public Health Significance Statement

- Individuals with obesity show executive dysfunctions which have been implicated in weight management failure. Initial evidence suggests that cognitive remediation therapy (CRT) after behavioral weight loss (BWL) treatment improves weight loss, but efficacy of CRT before BWL treatment remains unclear.
- This randomized clinical trial in 270 adults with severe obesity demonstrated that group CRT when compared to no treatment did not improve weight loss in routine BWL treatment after 6 months, nor after 12 months, and executive dysfunctions were not significantly improved.
- In adults with severe obesity, group CRT prior to real world BWL treatment is not suited for improving weight loss.

1 **Group Cognitive Remediation Therapy Prior to Behavioral Weight Loss**

2 **Treatment for Adults with Severe Obesity: A Randomized Clinical Trial (CRT Study)**

3 Obesity, an excessive fat accumulation presenting a risk for health (body mass index,
4 BMI \geq 30 kg/m²; World Health Organization [WHO], 2021) has reached pandemic proportions
5 (NCD Risk Factor Collaboration, 2017). Of greatest concern is the rapidly growing prevalence of
6 higher grades of obesity (i.e., class II BMI \geq 35-39.9 kg/m² or class III BMI \geq 40 kg/m²; Williamson
7 et al., 2020; Hales et al., 2018). With increasing BMI, obesity is a major risk factor of non-
8 communicable diseases (e.g., coronary heart diseases, type 2 diabetes mellitus; WHO, 2021) and
9 premature mortality (Flegal et al., 2013), is linked to mental disorders (e.g., depression, eating
10 disorders) and social disadvantages (Lin et al., 2013), all contributing to substantial quality of life
11 impairment. For the past decades, multicomponent behavioral weight loss (BWL) treatment,
12 including behavioral interventions for dietary change and increased physical activity, has been the
13 standard intervention for obesity (Bray et al., 2016). Meta-analytically, BWL treatment leads to
14 additional weight loss of 2.4 kg over 12-18 months when compared to controls (LeBlanc et al.,
15 2018), while for higher grades of obesity, weight loss has been found to be highly variable
16 (Bauer et al., 2020; Hassan et al., 2016). Generally, weight loss is associated with clinically
17 meaningful health benefits (Jensen et al., 2013). In the long term, however, many patients regain a
18 majority of weight initially lost (Diabetes Prevention Program Research Group, 2015). Given
19 these modest results, efficacy improvement is imperative.

20 Recently, weight loss failure has been linked to detriments in executive function, which
21 encompasses multiple higher cognitive capacities enabling forethought and the regulation of
22 complex goal-oriented behavior (Shallice, 1988; Studd & Benson, 1986), and thus self-regulation
23 (Hofmann et al., 2012). Indeed, individuals with obesity versus normal weight present with a
24 range of executive dysfunctions (e.g., in inhibition, cognitive flexibility, working memory,
25 planning, decision-making, and verbal fluency; Emery & Levine, 2017; Favieri et al., 2019; Yang

1 et al., 2018), that have been found to underlie lesser weight management behaviors (e.g., low
2 dietary quality; Dohle et al., 2018). Plausibly, low inhibitory control (Manasse et al., 2017; Galio
3 et al., 2016), cognitive flexibility (Dassen et al., 2018), and working memory (Veronese et al., 2017)
4 were associated with less weight loss in BWL treatment. Experimental cognitive trainings, mostly
5 targeting single executive functions with repeatedly applied computerized, reaction time-based
6 neurocognitive training tasks, have shown some promise, particularly with focus on food-
7 related inhibitory control (Yang et al., 2019; Forcano et al., 2018). Whereas working memory
8 trainings and attention bias modification trainings were mostly unsuccessful for weight loss,
9 four out of the available six food-specific response inhibition studies pointed to short-term,
10 but not longer-term weight loss effects (Yang et al., 2019; Forcano et al., 2018), although this
11 has not been consistently found in obesity (Stice et al., 2017; Verbeke et al., 2018; Du et al.,
12 2021).

13 Little is known about the effects of cognitive remediation therapy (CRT), a more
14 comprehensive rehabilitative approach for the restitution of executive functions through
15 cognitive training and their compensation in a psychotherapeutic format (Barlati et al., 2013).
16 CRT was originally developed for patients with brain lesions (Luria, 1972) and adapted to
17 mental disorders, including depression (Bowie et al., 2013), attention deficit/hyperactivity
18 disorder (Stevenson et al., 2002), and anorexia nervosa (Hagan et al., 2020), classically using
19 paper-and-pencil tasks. In the first open randomized-controlled trial (RCT) in 80 adults with
20 obesity, individual CRT following a brief group BWL intervention led to a greater weight loss
21 at 3-month follow-up than the BWL intervention alone (Raman, Hay et al., 2018), although
22 this effect was not maintained over 12-month follow-up (Raman, Smith et al., 2018). The
23 CRT-related greater improvement in cognitive flexibility significantly predicted higher weight
24 loss and improvement of weight management behavior (Allom et al., 2018). Given these
25 promising results, CRT warrants further investigation when conducted prior to BWL and

1 especially in group format with its greater disseminability, acceptability, and cost-
2 effectiveness because of a possible combination with BWL treatment, commonly delivered in
3 a group format. In other health conditions, previous CRT applications in group format had
4 received empirical support (e.g., Hagan et al., 2020). Further, CRT studies including those
5 with pretreatment administration had suggested motivational effects. Thus, CRT in severe
6 obesity could enhance motivation, including attendance and retention in BWL treatment,
7 known to be critical for weight loss (e.g., Stubbs et al., 2011).

8 This study sought to evaluate the efficacy of group CRT as a preparatory adjunct to
9 real world group BWL treatment versus BWL treatment alone in patients with class II or III
10 obesity. It was hypothesized that patients receiving CRT versus those not receiving CRT
11 would show (1) higher weight loss after 6 months of BWL treatment (6-month follow-up); (2)
12 greater improvements in executive function, weight management behaviors, mental and
13 physical health, and higher adherence to a weight loss regimen at posttreatment and at 6- and
14 12-month follow-up; and (3) larger amounts of weight loss at 12-month follow-up.

15 **Methods**

16 **Study Design and Procedure**

17 The CRT study is a single-center, assessor-blinded, randomized, two-armed parallel-
18 group superiority study, evaluating the efficacy of CRT (experimental condition) versus no
19 treatment (control condition) prior to BWL treatment. The study was registered prior to
20 implementation in the German Clinical Trials Register, <https://www.drks.de>; Identifier:
21 DRKS00009333, September 4, 2015 (last update: July 29, 2020). Methodological detail was
22 published during the recruitment phase (Hilbert et al., 2018), and the study protocol is
23 contained in Supplement 1. Ethical approval was granted by the Ethics Committee of the
24 University of Leipzig (256-15-13072015). Written informed consent was obtained by trained
25 staff after the study was fully explained and prior to any intervention.

1 A total of 270 adult patients with class II or III obesity ($BMI \geq 35.0 \text{ kg/m}^2$) seeking
2 BWL treatment were recruited at the Obesity Outpatient Unit, Integrated Research and
3 Treatment Center Adiposity Diseases, Leipzig University Medical Center, between May 2015
4 and July 2019. Main recruitment avenues consisted of informational sessions for treatment-
5 seeking patients, public notices and advertisements, and clinical referrals. Incentives for
6 participation in assessments and travel allowances were offered (200 €). Data analysis was
7 performed after study completion between October 2019 and December 2020. Following
8 enrollment in BWL treatment and after determining eligibility for the CRT study, patients
9 were randomized to 2 months of CRT versus no treatment (Figure 1). After 2 months, patients
10 were scheduled for BWL treatment of up to 12 months. Patients were assessed at pretreatment
11 (t_0), at posttreatment (t_1) after CRT versus no treatment, and at 6- and 12-month follow-up
12 (t_2, t_3), i.e., after 8 and 14 months following randomization.

13 **Participants**

14 Inclusion criteria required age ≥ 18 years, $BMI \geq 35.0 \text{ kg/m}^2$, presentation for BWL
15 treatment, feasible participation in study procedures, and sufficient German language skills.
16 Exclusion criteria encompassed serious somatic and mental conditions (assessed by clinical
17 interview; Beesdo-Baum et al., 2019); physical, mental, or other inability regarding study
18 participation; previous or planned bariatric surgery; use of medication impacting weight or
19 executive functioning; current psychotherapy regarding weight or eating behavior; current
20 participation in other interventional studies; lack of compliance; and pregnancy or lactation.

21 BWL treatment consisted of a routine care multicomponent group plus individual
22 manualized lifestyle intervention at high or low intensity. The high-intensity modularized BWL
23 treatment program offered 6-12 group and up to 6 individual sessions of nutritional counseling;
24 40-48 group exercise sessions; and 10-12 group and up to 6 individual sessions of behavior
25 therapy over one year within a four-year treatment program, financed by the largest public health

1 insurance company in Saxony for its insurants from 08/2014 (Frenzel et al., 2020). Patients with
2 insurance at all other health insurance companies continued to receive a low-intensity
3 intervention, including 8 group sessions and 3 individual sessions of nutritional counseling. In
4 addition to this program, patients were offered to attend 50 group exercise sessions (at external
5 institutions) over one year with health insurance coverage. Both the high- and low-intensity
6 treatments were conducted by registered dietitians, bachelor's or master's level sports scientists,
7 and, for the high-intensity program, master's level clinical psychologists. The high-intensity
8 treatment program was documented to result in a weight loss of 5 kg (95% CI: 3.8 to 6.2 kg) or
9 4.0% (95% CI: 3.1 to 4.9%) over one year (N=243; (Frenzel et al., 2020).

10 **Treatment**

11 CRT was based on the CRT manual for obesity (Smith et al., 2014; Raman, Hay et al.,
12 2018), broadened to address the range of executive dysfunctions in obesity (Yang et al., 2018;
13 Emery & Levine, 2017) and adapted to pre-BWL use and group setting. CRT was delivered in 8
14 weekly, 120-min group sessions with 6–10 patients over 8 weeks prior to BWL treatment. CRT
15 focused on general and weight management-related mental exercises aimed at improving goal-
16 setting, switching attention, inhibition and automatic behavior, decision-making, planning,
17 problem-solving, and flexibility (eTable 1, Supplement 2). Aimed at fostering metacognition
18 and applying new thinking strategies, CRT was not directly focused on weight loss, but
19 related exercises were included. Paper-and-pencil and computerized neuropsychological
20 exercises (Dickhut et al., 2014) were used. From the 27 tasks, 22 tasks were noncomputerized,
21 while five tests were computerized, four of which were reaction time-based. In general, all
22 tasks were applied for 1–3 trials or for at least 10 minutes. Handouts were delivered and
23 homework was given after each session in order to increase real-world application. Treatment
24 was provided by 2 master's level female clinical psychologists with specific training in CRT,

1 and was conducted under regular supervision by AH to ensure fidelity and drift prevention.

2 The control group did not receive treatment before entering BWL treatment.

3 **Randomization and Sample Size Estimation**

4 After pretreatment assessment, patients were centrally randomized by the Clinical Trial
5 Centre Leipzig to ensure allocation concealment. The electronic randomization was stratified by
6 sex and age (≥ 45 years), using blocks of variable length and an allocation ratio of 1:1 between
7 arms.

8 For power calculations, our BWL program was assessed for 200 patients, suggesting that a
9 weight loss of about 5 kg (5.5%) could be expected for control group completers with a 30%
10 dropout rate. We expected the CRT completers to lose 2 kg more on average, according to interim
11 data from the Raman, Hay et al. (2018) study, and have half the dropout rate. Assuming no weight
12 change for dropout patients, and a comparable variance to completers, this translated to a weight
13 loss of $7 \pm 5.5\%$. A *t* test has 80% power at 5% significance level if 120 patients per arm are
14 analyzed. The cluster effect of the group sessions was modeled with an intra-class correlation for
15 BMI at the postcode level of 0.004 (Ukoumunne et al., 1999), requiring about one more group
16 per arm to be enrolled after accounting for dropout. We thus planned on randomizing 130 patients
17 per arm, considering an overall dropout rate of 22%.

18 **Measures**

19 Primary outcome was the % weight change at 6-month follow-up (t_2) compared with
20 pretreatment (t_0), both derived from objectively measured body weight. Secondary outcomes
21 included % weight change from pretreatment at posttreatment (2 months, t_1) and at 12-month
22 follow-up (t_3). Further secondary outcomes (eAppendix, Supplement 2) consisted of: executive
23 function (t_0 , t_1), including decision-making (Iowa Gambling Task, Delay Discounting Task;
24 Bechara et al., 1994; Richards et al., 1999), inhibition (Go/NoGo; Kaiser et al., 2015),
25 cognitive flexibility (Trail Making Test, Wisconsin Card Sorting Test; Rodewald et al., 1993),

1 and problem-solving (Tower of London; Kaller et al., 2015); weight management behaviors
2 (t0–t3), including self-efficacy (Generalized Self-efficacy Scale; Schwarzer & Jerusalem, 1995)
3 and eating behavior (Dutch Eating Behavior Questionnaire; Grunert, 1989); mental health (t0–t3),
4 operationalized as eating disorder psychopathology (Eating Disorder Examination-Questionnaire
5 8; Kliem et al., 2016), general psychopathology (Patient Health Questionnaire-Depression; Gräfe
6 et al., 2004), and quality of life (Impact of Weight on Quality of Life-Lite; Mueller et al., 2011);
7 physical health (t0–t3), for which hip and waist circumference, blood pressure, bioelectrical
8 impedance, and triceps and subscapularis skinfolds were measured; and attendance to BWL
9 sessions and retention as measures of patients' adherence to a weight loss regimen. Expectation
10 and motivation (t0) were rated as 0, not at all, to 10, completely. Likewise, patient evaluation of
11 CRT was assessed at t1. All assessments were conducted by trained assessors, regularly
12 supervised for drift prevention. All assessors conducting posttreatment and follow-up assessments
13 were blinded to randomization and not involved in treatment.

14 **Safety**

15 Adverse events were recorded through self-report assessment of somatic symptoms at
16 each assessment. An independent Data Monitoring and Safety Committee was not deemed
17 necessary as patient safety was not expected to be affected by the intervention not focusing on
18 psychopathology but on executive functioning. Adverse events were monitored upon regular on-
19 site and central monitoring performed by the by the Clinical Trial Centre Leipzig (cf. Hilbert et
20 al., 2018) Rules for premature discontinuation of the trial are specified in the trial protocol
21 (Supplement 1).

22 **Statistical Analysis**

23 All analyses are described in the Statistical Analysis Plan (Supplement 3) and were
24 performed using R (version 3.5.3; RCore Team, 2019), applying two-sided $\alpha < .05$.

1 The primary endpoint, % weight change at 6-month follow-up, was estimated along with
2 95% confidence interval (CI) based on a normal approximation and analyzed using a partially
3 nested mixed-effect model with the stratification variables (sex, age \geq 45 years), randomization
4 arm, and pretreatment weight as fixed effects and the CRT group modeled as a partially nested
5 random effect. Based on the full analysis set, this confirmatory analysis followed the intent-to-
6 treat (ITT) principle. If data on body weight in either arm were missing, multiple imputation was
7 performed with 50 imputations (Buuren, 2012), taking into account body weight (t0, t1, t3) and
8 height, sex, age, BWL program intensity, and attendance. If patients underwent bariatric surgery
9 or became pregnant, all anthropometric measures were set to missing.

10 Sensitivity analyses used (1) linear regression models for both absolute and % weight
11 change with randomization arm, stratification variables, pretreatment weight, and attendance to
12 BWL treatment as covariates; (2) the linear-mixed regression model from the primary analysis in
13 the complete case sample; and (3) a linear model analysis comparing % weight change for
14 patients in the CRT arm with good protocol adherence (PP, per-protocol set) versus control
15 patients, controlling for pretreatment weight. The PP set consisted of CRT patients who attended
16 \geq 5 CRT sessions and provided data for the primary endpoint.

17 Secondary endpoints were analyzed using similar mixed models as for the primary
18 endpoint, taking into account the repeated measures structure of the data, if appropriate. To assess
19 differences between arms at each follow-up, interactions were modeled for randomization arm
20 and time. Furthermore, differences in time were assessed in models without interaction term.
21 Regarding executive functioning, a partially nested mixed-effects model on the absolute
22 difference between posttreatment (t1) and pretreatment (t0) as the dependent variable was
23 conducted, with the stratification variables (sex, age \geq 45 years), randomization arm, and the
24 pretreatment score as fixed effects.

1 For the routine care BWL program, a total of 53.0% of CRT patients (71/134) received the
2 high-intensity BWL program, and a total of 56.6% of control patients (77/136) received the low-
3 intensity program (cf. Participants).

4 **Primary Outcome**

5 The ITT analysis did not show a significant difference between CRT and control in %
6 weight change at 6-month follow-up. CRT patients reduced their pretreatment weight by 0.4%
7 (95% CI: -1.1% to 1.8%, $p=.629$, $d=0.09$) less than control patients. Sensitivity analyses
8 confirmed this nonsignificant result (eAppendix, Supplement 2).

9 **Secondary Outcomes**

10 Regarding secondary outcomes, there were no significant differences between CRT
11 and control in % weight change at posttreatment (0.2%, 95% CI: -0.7% to 1.1%, $p=.588$,
12 $d=0.01$) and at 12-month follow-up (0.3%, 95% CI: -1.5% to 2.2%, $p=.721$, $d=0.01$). Overall,
13 % weight change amounted to -0.4% (95% CI: -1.1% to 0.4%, $\beta=-0.01$) at posttreatment, to -
14 1.2% (95% CI: -2.0% to -0.4%, $\beta=-0.05$) at 6-month follow-up, and to -1.7% (95% CI: -2.6%
15 to -0.8%. $\beta=-0.07$) at 12-month follow-up. Similar results were found for weight loss in kg
16 and BMI (Tables 3 and 4; for raw data see eTable 3, Supplement 2).

17 Regarding further secondary outcomes, no significant differences were seen between
18 randomization arms; however, many of these measures showed significant improvements
19 across arms over time (Tables 2 and 3). Regarding weight management behavior, self-efficacy
20 and external eating improved and restrained eating increased from pretreatment to 12-month
21 follow-up, while emotional eating decreased at 12-month follow-up. Regarding mental health,
22 eating disorder psychopathology improved at posttreatment and 12-month follow-up, while
23 depression did not change. The impact of weight on physical function, self-esteem, and public
24 distress improved from posttreatment to 12-month follow-up, and the impact of weight on
25 sexual function or work improved at 6- and 12-month follow-up or 6-month follow-up only,

1 respectively. Indicators of physical health revealed a lowered waist and hip circumference at
2 6- and 12-month follow-up as well as a decreased systolic and diastolic blood pressure at
3 posttreatment and 12-month follow-up, respectively, whereas skinfolds and bioelectrical
4 impedance analysis did not reveal any significant change.

5 Regarding executive functions, there was no significant differential pre- to
6 posttreatment improvement in CRT versus control (Table 4). Across arms, response inhibition
7 and cognitive flexibility were significantly improved, while decision-making and problem-
8 solving were not significantly changed.

9 Regarding patients' adherence to a weight loss regimen, CRT patients attended a
10 nonsignificantly greater number of BWL sessions than control patients (CRT: median 75%
11 [interquartile range 0, 88] vs. control: 60% [0, 86]; $W=100081.5, p=.124$), and showed a
12 nonsignificantly lower dropout from BWL treatment [i.e., attendance to <50% of sessions; CRT:
13 37%, 50/134 vs. control: 45%, 61/136; $\chi^2(df=1, N=270)=1.3, p=.256, OR=0.73$]. Overall,
14 patients in the CRT arm evaluated CRT at posttreatment as suited for their problems ($M=6.9,$
15 $SD=2.2$) and helpful for their everyday life currently ($M=6.6, SD=2.4$) and in the long term
16 ($M=6.7, SD=2.5$).

17 **Safety**

18 Only one adverse event was reported (a 65-year-old woman randomized to CRT suffered
19 a stroke between posttreatment and 6-month follow-up), considered a serious adverse event not
20 causally related to the intervention.

21 **Weight change by BWL program intensity**

22 In the exploratory analysis of % weight change by BWL program intensity and its
23 interaction with randomization arm, patients in the high-intensity BWL program significantly
24 showed a 2.2% greater weight loss at 6-month follow-up (95% CI: 0.7 to 3.8%, $p=0.005$) and
25 a 3.9% greater weight loss at 12-month follow-up (95% CI: 1.9 to 6.0%, $p<0.001$). No

1 interaction was found between BWL program intensity and randomization arm, i.e., the
2 interaction term for % weight change was 0.8% at 6-month follow-up (95% CI: -2.0 to 3.7%,
3 $p=0.57$) and 1.2% at 12-month follow-up (95% CI: -2.6 to 4.9%, $p=0.54$). Similar results were
4 found for weight change in kg and BMI (see eTable 4, Supplement 2).

5 **Discussion**

6 In this large, well-controlled superiority trial, group CRT conducted prior to real world
7 BWL treatment in adults with class II and class III obesity did not increase weight loss
8 compared to BWL treatment alone. Both randomization arms reduced weight at 6- and 12-
9 month follow-up, and both showed improvements in most indicators of executive function,
10 weight management behaviors, and mental and physical health at most time points. CRT was
11 well-received by patients and safe, but did not differentially improve BWL treatment
12 adherence.

13 The results indicate that group CRT as a pre-BWL adjunct is generally not efficacious
14 for weight loss in adults with $BMI \geq 35$ kg/m². This lack of additive weight loss effects through
15 CRT is not inconsistent with the previous open obesity-related RCT, where 8 sessions of
16 individual CRT following 3 group BWL treatment sessions did not lead to a greater weight
17 loss than BWL intervention alone at 12-month follow-up, but did so at 3-month follow-up
18 (Raman, Hay et al, 2018; Raman, Smith et al., 2018). Rather, if CRT effects exist, their action
19 on weight outcome is likely to be short-lived, and pre-BWL use of CRT in our study may
20 have made weight loss effects more unlikely to detect than post-BWL use. Consistent with
21 this interpretation is that the successful weight loss-oriented experimental trainings on food-
22 related inhibitory control mostly documented short-term weight loss effects only (Yang et al.,
23 2019).

24 Notably, in this study, CRT did not change general executive functions, including
25 response inhibition, cognitive flexibility, decision-making, and problem-solving when

1 compared to the control group. While the previous obesity-related open RCT found
2 differential improvement of post-BWL individual CRT in cognitive flexibility (Raman, Hay
3 et al., 2018), in other health conditions, inconsistent CRT effects on cognitive flexibility were
4 reported (e.g., Hagan et al., 2020). The reasons for the lack of executive function effects of
5 CRT in this study are difficult to pinpoint and may pertain to diverse assessment, intervention,
6 and sample characteristics. Regarding assessment, as opposed to Raman, Hay et al. (2018),
7 we used different tests for CRT than for assessment in order to prevent assessment bias,
8 which may have made changes in executive functions more difficult to occur. Experimental
9 weight loss-focused cognitive trainings on food-related inhibitory control using different
10 (Allom & Mullan, 2015) or the same neuropsychological tests (Lawrence et al., 2015; Stice et
11 al., 2017; Verbeken et al., 2018) for assessment as for intervention did not consistently show a
12 differential learning effect in the intervention versus control condition, suggesting that
13 methodological variations in assessment (as well as sampling and intervention) contribute to
14 instability of training effects. Further, because of a lack of validated disorder-specific
15 executive function tests, we selected validated, general tests of executive function. Given the
16 greater support for the effects of disorder-specific rather than general executive function
17 trainings, for example, targeting inhibitory control (Yang et al., 2019; Forcano et al., 2018), it
18 may be assumed that changes could have been more easily detected using disorder-specific
19 tests.

20 Regarding intervention, as CRT sought to address a range of executive dysfunctions
21 associated with obesity (Table 1; Yang et al., 2018; Emery & Levine, 2017), the interventional
22 focus may have been too broad and nonspecific and relatedly, the number of repeated trials by
23 training tasks may have been too low. This line of interpretation is consistent with previous
24 evidence on interventions with a narrower scope, for example, weight loss-related CRT with a
25 main focus on cognitive flexibility (Raman, Hay et al., 2018) and experimental trainings

1 targeting food-related inhibitory control (Yang et al., 2019; Forcano et al., 2018). In addition,
2 CRT's group versus individual format (Raman, Hay et al., 2018) may have decreased its
3 potency.

4 Further, regarding the sample, normative comparisons of pretreatment results in
5 executive function tests for which normative data were available revealed a small proportion
6 of patients with executive dysfunctions >1 SD above the population mean (response
7 inhibition: 35.5%, 87/245; cognitive flexibility: 2.0%, 5/245; problem-solving: 19.0%,
8 47/247) and clinical levels of executive dysfunctions >2 SD above the mean in a few patients
9 (9.0%, 0%, 1.6%, respectively; Kaiser et al., 2015; Rodewald et al., 2015; Kaller et al., 2015).
10 Thus, the overall low degree of executive dysfunctions may have made improvements in CRT
11 unlikely to occur. However, it is also possible that in our clinic-based sample with severe
12 obesity, metabolic alterations associated with higher grades of obesity may have decreased the
13 capacity to restore executive dysfunctions (Bosia et al., 2018), as opposed to population-based
14 samples with lower overweight status in previous CRT for obesity (Raman, Hay et al., 2018)
15 and weight-loss-inducing cognitive trainings on food-specific inhibitory control (Lawrence et
16 al., 2015; Stice et al., 2017). Consistent with this interpretation, in a clinical sample of youth
17 with obesity, Verbeken et al. (2018) failed to find any effects of experimental food inhibition
18 training on executive function and weight loss.

19 Finally, regardless of CRT, the achieved weight loss through routine BWL treatment
20 of 1.2% at 6-month follow-up and 1.7% at 12-month follow-up may have made effects of
21 CRT unlikely to occur. Notably, weight loss differed by BWL program intensity: Patients in
22 the high-intensity BWL program lost an additional 2.2% at 6-month follow-up and 3.9% at
23 12-month follow-up when compared to those in the low-intensity program, likely related to a
24 greater number of sessions and inclusion of behavior therapy in addition to nutritional
25 counseling and exercise (cf. Participants); however, no interaction was seen with any

1 randomization arm. Importantly, overall weight loss, and especially that in the high-intensity
2 program, was comparable to that seen in other real world treatment settings (Galaviz et al.,
3 2018; Mudaliar et al., 2016; Primack, 2018), but was expectedly somewhat lower than in
4 RCTs for BWL treatment (LeBlanc et al., 2018), likely related to greater barriers to weight
5 loss in real world settings (Delahanty et al., 2019). In general, weight loss through BWL
6 treatment in patients with severe obesity was found to be highly variable (Bauer et al., 2020).

7 Regarding further secondary outcomes displaying nondifferential changes, although
8 weight loss in our study fell below the prespecified threshold of a clinically significant weight
9 loss of >10% (German Obesity Society, 2014), it plausibly co-occurred with improvements in
10 waist and hip circumference and systolic and diastolic blood pressure. In addition, while CRT
11 did not differentially change weight management behavior, inspection of effect sizes
12 suggested slight advantages of CRT versus control in these parameters, which is consistent
13 with executive function training effects on eating behavior (Yang et al., 2019). Finally, while
14 motivation for weight loss was generally high in our study, CRT may have enhanced it.
15 Indeed, CRT was associated with a nonsignificant, but a clinically noteworthy trend of greater
16 adherence to and lower dropout from BWL treatment. Previously, motivational effects of
17 CRT in other health conditions have been documented (Hagan et al., 2020).

18 Strengths and limitations of this study include the well-controlled design with a low
19 risk of selection and detection bias. As in other psychological treatment trials, blinding of
20 patients and therapists was not possible, contributing to a performance bias. Assessment
21 dropout for the primary endpoint was 22.6% (61/270); therefore, ITT analyses, confirmed by
22 sensitivity analyses, served to prevent an attrition bias. To avoid a reporting bias, methods had
23 been published previously (Hilbert et al., 2018). To ensure generalizability, exclusion criteria
24 were kept to a minimum to prevent confounding effects and safety reasons. According to
25 these criteria, 31.3% of eligible volunteers were excluded, while 33.5% declined to

1 participate, leaving 35.2% for inclusion, providing a fair data base for generalization of
2 results. The proportion of patients with a nationality other than German was low, but only fell
3 slightly below the respective proportion in the population in Eastern Germany (Federal
4 Statistical Office, 2019). Related to the real-world treatment setting, BWL treatment had
5 varying intensity levels (cf. Participants), which were controlled for in the analyses and
6 specifically addressed regarding their relevance for weight loss in an exploratory analysis.
7 Although weight loss did not differ by randomization arm, it was lower than expected because
8 a lower than anticipated proportion of patients received high-intensity BWL treatment due to
9 organizational reasons. Finally, although no treatment conditions represent a first-line control
10 in intervention design (Friedman et al., 2015), it needs to be noted that they only control for
11 time and assessment effects, but not for expectancy and demand characteristics, which could
12 be addressed using psychological placebo conditions (e.g., credible treatment controlling for
13 common factors; Zipfel et al., 2020).

14 In sum, the results show that comprehensive group CRT is not efficacious as a
15 preparatory adjunct to group BWL treatment in severe obesity. Potential efficacy in specific
16 patient groups (e.g., those with high levels of executive dysfunctions) should systematically
17 be examined, with consideration of treatment mechanisms (e.g., improvement of executive
18 functions). Whether and under which conditions disorder-specific executive function
19 trainings, for example, on food-specific response inhibition (Yang et al., 2019; Forcano et al.,
20 2018), help to improve executive function and weight loss especially in clinical applications
21 deserves further study.

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1 **Table 1**2 *Baseline Sociodemographic Characteristics and Motivation*

Baseline characteristic	CRT	Control	Total
	(n=134)	(n=136)	(N=270)
	<i>n (%) / M (SD)</i>	<i>n (%) / M (SD)</i>	<i>n (%) / M (SD)</i>
Sex, female	93 (69.4)	93 (68.4)	186 (68.9)
Age, y	44.2 (13.7)	44.8 (12.0)	44.5 (12.8)
Nationality			
German	133 (99.3)	132 (97.8)	265 (98.5)
Other	1 (0.7)	3 (2.2)	4 (1.5)
Education			
≥12 years	37 (27.6)	40 (29.9)	77 (28.7)
<12 years	97 (72.4)	94 (70.1)	191 (71.3)
Body weight, kg	130.8 (26.7)	133.4 (24.6)	132.1 (25.6)
Body mass index, kg/m ²	45.3 (6.9)	45.9 (7.0)	45.6 (6.9)
Weight status			
Obesity Class 1	1 (0.7)	2 (1.5)	3 (1.1)
Obesity Class 2	31 (23.1)	25 (18.4)	56 (20.7)
Obesity Class 3	102 (76.1)	109 (80.1)	211 (78.1)
Therapy expectations: Mindset ^a			
Motivation to change	8.6 (1.7)	8.6 (1.7)	8.6 (1.7)
Readiness to keep change	8.8 (1.7)	8.8 (1.4)	8.8 (1.5)
Confidence to keep change	7.6 (1.8)	7.1 (1.5)	7.4 (1.7)
Therapy expectations: Weight loss-related behaviors ^a			
Motivation to change	8.7 (1.4)	8.7 (1.5)	8.7 (1.4)
Readiness to keep change	8.7 (1.4)	8.6 (1.4)	8.7 (1.4)
Confidence to keep change	7.6 (1.7)	7.3 (1.7)	7.4 (1.7)
Reasons for study participation			
Change mindset only	2 (1.5)	1 (0.7)	3 (1.1)
Weight loss only	30 (22.4)	27 (20.0)	57 (21.2)
Both	102 (76.1)	107 (79.3)	209 (77.7)

3 *Note.* Percentages calculated from valid cases. CRT, cognitive remediation therapy.4 ^aAssessed on a rating scale from 0-10 with higher scores indicating higher expectations.

1 **Table 2**2 *Secondary Outcomes by Intent-to-treat*

Secondary outcome	Pretreatment		Posttreatment		6-month follow-up		12-month follow-up	
	CRT	Control	CRT	Control	CRT	Control	CRT	Control
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Weight loss								
Body weight, kg	130.8 (26.7)	133.4 (24.6)	130.3 (26.5)	132.7 (25.3)	129.4 (26.6)	131.3 (25.1)	128.6 (26.8)	130.7 (26.4)
Body mass index, kg/m ²	45.3 (6.9)	45.9 (7.0)	45.1 (6.8)	45.7 (7.3)	44.8 (6.9)	45.2 (7.4)	44.5 (7.1)	45.0 (7.7)
Weight management behavior								
Generalized Self-Efficacy Scale	29.6 (5.3)	29.4 (5.4)	30.5 (5.8)	30.1 (6.0)	30.8 (6.0)	30.3 (5.8)	31.0 (6.0)	29.7 (6.8)
Dutch Eating Behavior Questionnaire								
Restrained eating	2.8 (0.8)	2.7 (0.8)	2.9 (0.8)	2.9 (0.8)	3.0 (0.8)	3.0 (0.9)	3.0 (0.8)	2.9 (0.9)
External eating	2.8 (0.7)	2.9 (0.8)	2.5 (0.8)	2.8 (0.9)	2.6 (0.8)	2.7 (0.9)	2.5 (0.9)	2.7 (0.9)
Emotional eating	2.3 (0.9)	2.4 (1.1)	2.2 (1.0)	2.4 (1.2)	2.1 (1.1)	2.4 (1.3)	2.1 (1.1)	2.3 (1.3)
Mental health								
Eating Disorder Examination-Questionnaire 8	3.8 (1.0)	3.8 (0.9)	3.7 (1.2)	3.7 (1.1)	3.6 (1.1)	3.8 (1.2)	3.5 (1.3)	3.6 (1.3)
Patient Health Questionnaire-Depression	6.5 (4.2)	6.5 (4.3)	6.2 (4.7)	6.4 (5.7)	6.3 (5.2)	6.4 (6.1)	6.5 (5.6)	6.4 (6.0)
Impact of Weight on Quality of Life-Lite								
Physical function	32.6 (9.4)	32.8 (9.2)	30.6 (10.2)	31.2 (10.8)	29.7 (10.5)	30.1 (10.8)	28.9 (11.1)	31.0 (10.9)
Self-esteem	20.5 (8.2)	20.8 (8.2)	19.1 (8.6)	19.6 (8.5)	17.8 (8.3)	19.0 (8.7)	17.4 (8.5)	19.0 (9.1)
Sexual life	9.1 (5.0)	9.3 (5.3)	9.0 (5.7)	9.2 (6.1)	8.5 (5.6)	8.5 (6.0)	8.4 (6.4)	8.4 (6.0)
Public distress	10.5 (4.3)	11.1 (4.9)	9.8 (4.7)	10.5 (5.3)	9.6 (4.8)	10.9 (5.6)	9.3 (4.7)	10.7 (5.9)
Work	7.9 (3.3)	8.2 (4.0)	7.5 (4.0)	7.9 (4.6)	7.1 (3.8)	7.9 (5.1)	7.0 (3.7)	8.0 (5.0)
Physical health								
Waist circumference, cm	126.3 (16.0)	128.6 (15.8)	126.0 (15.3)	126.3 (18.7)	125.2 (16.8)	125.4 (18.1)	124.4 (16.7)	125.9 (18.6)
Hip circumference, cm	140.1 (14.9)	140.4 (14.4)	139.7 (14.5)	139.3 (18.5)	138.2 (15.5)	138.0 (15.9)	137.4 (17.0)	138.6 (16.8)
Blood pressure systolic, mm Hg	143.5 (20.7)	142.5 (18.5)	140.9 (20.6)	140.2 (19.6)	140.7 (20.4)	141.1 (19.1)	140.1 (20.5)	141.8 (22.0)
Blood pressure diastolic, mm Hg	90.3 (12.9)	89.4 (11.9)	89.2 (11.9)	89.0 (12.6)	89.0 (13.3)	88.4 (12.1)	87.5 (13.7)	88.2 (12.9)
Triceps skinfolds, mm	47.5 (15.3)	45.8 (12.9)	47.0 (12.9)	48.1 (15.4)	47.4 (15.8)	47.0 (15.3)	46.4 (14.9)	46.4 (15.9)
Subscapularis skinfolds, mm	39.7 (12.8)	39.5 (13.1)	40.2 (12.0)	40.8 (15.1)	40.7 (12.9)	40.6 (13.2)	39.7 (13.4)	37.4 (13.4)
Bioelectrical impedance analysis								
Fat mass, %	51.2 (9.1)	51.7 (8.7)	51.6 (9.4)	51.7 (9.4)	51.3 (9.7)	51.0 (9.7)	51.1 (10.0)	50.8 (9.9)
Total body water, %	39.5 (5.4)	39.3 (5.1)	39.2 (5.8)	38.8 (5.5)	39.4 (5.6)	39.3 (5.5)	39.5 (6.2)	39.5 (5.5)

3 *Note.* Observed and imputed values. CRT, cognitive remediation therapy.

1 **Table 3**
 2 *Secondary Outcomes in Intent-to-treat Analyses*

Secondary outcome	Group × Time									Time											
	Posttreatment			6-month follow-up			12-month follow-up			Posttreatment			6-month follow-up			12-month follow-up					
	B	95% CI	p	β	B	95% CI	p	β	B	95% CI	p	β	B	95% CI	p	β	B	95% CI	p	β	
Weight loss																					
Body weight, kg	0.26	.778	0.01	0.72	.459	0.03	0.46	.651	0.02	-0.55	.252	-0.02	-1.76	<.001	-0.07	-2.43	<.001	-0.10			
	-1.56, 2.08			-1.18, 2.62			-1.55, 2.48			-1.48, 0.39			-2.79, -0.73			-3.63, -1.23					
Body mass index, kg/m ²	0.09	.790	0.01	0.23	.489	0.03	0.17	.625	0.03	-0.18	.295	-0.03	-0.59	.001	-0.09	-0.83	<.001	-0.12			
	-0.54, 0.71			-0.43, 0.89			-0.52, 0.87			-0.50, 0.15			-0.95, -0.23			-1.25, -0.41					
Weight management behavior																					
Generalized Self-Efficacy Scale	-0.26	.673	-0.05	-0.32	.617	-0.06	-1.16	.073	-0.22	-0.81	.006	-0.15	-1.07	<.001	-0.20	-0.89	.005	-0.17			
	-1.49, 0.96			-1.55, 0.92			-2.43, 0.11			-1.39, -0.23			-1.67, -0.47			-1.51, -0.27					
Dutch Eating Behavior Questionnaire																					
Restrained eating	-0.02	.802	-0.03	-0.01	.875	-0.02	-0.03	.754	-0.04	0.15	<.001	0.20	0.26	<.001	0.34	0.22	<.001	0.28			
	-0.21, 0.16			-0.20, 0.17			-0.22, 0.16			0.07, 0.24			0.17, 0.35			0.12, 0.31					
External eating	-0.15	.086	-0.20	-0.05	.599	-0.06	-0.15	.106	-0.20	-0.16	<.001	-0.22	-0.19	<.001	-0.26	-0.22	<.001	-0.30			
	-0.32, 0.02			-0.22, 0.13			-0.32, 0.03			-0.25, -0.07			-0.29, -0.10			-0.33, -0.12					
Emotional eating	-0.06	.604	-0.06	-0.08	.493	-0.08	-0.05	.669	-0.05	-0.09	.131	-0.09	-0.11	.116	-0.11	-0.17	.014	-0.17			
	-0.29, 0.17			-0.32, 0.15			-0.28, 0.18			-0.21, 0.03			-0.24, 0.03			-0.31, -0.03					
Mental health																					
Eating Disorder Examination-Questionnaire 8	0.01	.958	0.01	-0.13	.330	-0.14	-0.04	.751	-0.05	-0.13	.033	-0.14	-0.09	.143	-0.10	-0.24	.001	-0.25			
	-0.25, 0.27			-0.40, 0.14			-0.32, 0.23			-0.25, -0.01			-0.22, 0.03			-0.38, -0.10					
Patient Health Questionnaire-Depression	-0.19	.734	-0.05	-0.09	.885	-0.02	0.13	.821	0.03	-0.22	.475	-0.05	-0.16	.629	-0.04	-0.09	.803	-0.02			
	-1.30, 0.91			-1.27, 1.09			-1.03, 1.29			-0.82, 0.38			-0.79, 0.48			-0.76, 0.59					
Impact of Weight on Quality of Life-Lite																					
Physical Function	-0.31	.793	-0.03	-0.18	.880	-0.02	-1.80	.129	-0.20	-1.86	<.001	-0.20	-2.84	<.001	-0.31	-2.79	<.001	-0.30			
	-2.59, 1.98			-2.52, 2.16			-4.13, 0.53			-2.91, -0.80			-3.92, -1.75			-3.95, -1.64					
Self-esteem	-0.20	.817	-0.02	-0.87	.329	-0.11	-1.28	.161	-0.16	-1.37	<.001	-0.17	-2.26	<.001	-0.28	-2.49	<.001	-0.31			
	-1.87, 1.48			-2.61, 0.88			-3.08, 0.51			-2.16, -0.57			-3.08, -1.44			-3.35, -1.63					
Sexual life	0.04	.948	0.01	0.22	.724	0.04	0.14	.829	0.03	-0.12	.700	-0.02	-0.73	.023	-0.15	-0.82	.018	-0.16			
	-1.19, 1.27			-1.02, 1.47			-1.17, 1.45			-0.75, 0.50			-1.37, -0.10			-1.50, -0.14					
Public distress	-0.04	.943	-0.01	-0.71	.192	-0.15	-0.77	.180	-0.17	-0.63	.015	-0.14	-0.58	.032	-0.13	-0.80	.003	-0.17			
	-1.09, 1.02			-1.77, 0.36			-1.90, 0.36			-1.14, -0.13			-1.11, -0.05			-1.32, -0.27					
Work	-0.08	.873	-0.02	-0.48	.321	-0.13	-0.66	.167	-0.18	-0.28	.218	-0.08	-0.49	.049	-0.14	-0.50	.054	-0.14			
	-1.01, 0.86			-1.44, 0.47			-1.60, 0.28			-0.73, 0.17			-0.98, -0.00			-1.01, 0.01					
Physical health																					
Waist circumference, cm	2.01	.190	0.13	2.08	.177	0.13	0.84	.602	0.05	-1.29	.103	-0.08	-2.15	.013	-0.14	-2.28	.013	-0.14			
	-1.00, 5.03			-0.94, 5.11			-2.31, 3.98			-2.85, 0.26			-3.83, -0.47			-4.06, -0.50					
Hip circumference, cm	0.71	.683	0.05	0.53	.768	0.04	-0.86	.652	-0.06	-0.84	.305	-0.06	-2.18	.006	-0.15	-2.33	.007	-0.16			
	-2.70, 4.12			-3.00, 4.05			-4.61, 2.89			-2.44, 0.77			-3.75, -0.62			-4.00, -0.65					

Secondary outcome	Group × Time									Time											
	Posttreatment			6-month follow-up			12-month follow-up			Posttreatment			6-month follow-up			12-month follow-up					
	<i>B</i>	95% CI	<i>p</i>	β	<i>B</i>	95% CI	<i>p</i>	β	<i>B</i>	95% CI	<i>p</i>	β	<i>B</i>	95% CI	<i>p</i>	β	<i>B</i>	95% CI	<i>p</i>	β	
Blood pressure systolic, mm Hg	-0.32	.905	-0.02	-1.34	.627	-0.07	-2.71	.325	-0.14	-2.49	.024	-0.13	-2.13	.062	-0.11	-1.99	.113	-0.10			
	-5.49, 4.86			-6.75, 4.07			-8.12, 2.70			-4.65, -0.33			-4.36, 0.11			-4.46, 0.48					
Blood pressure diastolic, mm Hg	-0.68	.691	-0.06	-0.27	.872	-0.02	-1.55	.391	-0.13	-0.87	.233	-0.07	-1.29	.074	-0.11	-2.06	.009	-0.17			
	-4.06, 2.70			-3.57, 3.02			-5.11, 2.00			-2.31, 0.56			-2.70, 0.13			-3.60, -0.52					
Triceps skinfolds, mm	-0.80	.663	-0.06	-0.13	.943	-0.01	2.00	.294	0.16	0.89	.284	0.07	1.05	.228	0.08	-1.04	.258	-0.08			
	-4.42, 2.82			-3.67, 3.42			-1.74, 5.75			-0.74, 2.51			-0.66, 2.76			-2.86, 0.77					
Subscapularis skinfolds, mm	-2.74	.196	-0.19	-1.28	.558	-0.09	-1.62	.476	-0.11	0.88	.306	0.06	0.56	.546	0.04	-0.24	.803	-0.02			
	-6.89, 1.41			-5.56, 3.01			-6.04, 2.83			-0.81, 2.57			-1.27, 2.40			-2.17, 1.68					
Bioelectrical impedance analysis																					
Fat mass, %	0.46	.545	0.05	0.81	.337	0.09	0.90	.293	0.10	0.23	.534	0.03	-0.26	.479	-0.03	-0.51	.192	-0.06			
	-1.04, 1.97			-0.85, 2.47			-0.78, 2.58			-0.51, 0.98			-0.97, 0.45			-1.27, 0.26					
Total body water, %	0.08	.871	0.01	-0.12	.801	-0.02	-0.23	.630	-0.04	-0.40	.054	-0.08	-0.05	.794	-0.01	0.12	.589	0.02			
	-0.83, 0.98			-1.03, 0.80			-1.17, 0.71			-0.80, 0.01			-0.46, 0.35			-0.32, 0.57					

1 *Note.* Coefficients and *p* values derived from linear mixed models of Group × Time or of Time, respectively. A negative sign indicates greater improvement in

2 the CRT versus control arm or over time versus pretreatment, respectively.

3 Significant *p* values are bolded, $p < .05$.

4

1
2 **Table 4**
3 *Secondary Outcomes of Executive Functioning in Intent-to-treat Analyses*

Executive function	Pretreatment		Posttreatment		Group × Time			Time				
	CRT	Control	CRT	Control	B	95% CI	p	β	B	95% CI	p	β
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>								
Decision-making												
Iowa Gambling Task, total net score	-3.70 (29.69)	-8.08 (31.21)	-1.31 (34.15)	-4.81 (36.98)	1.24	.798	0.04	2.86	.209	0.09		
					-8.28, 10.75			-1.61, 7.33				
Delay Discounting Task, area under the curve	0.46 (0.32)	0.50 (0.31)	0.48 (0.36)	0.48 (0.36)	-0.03	.503	-0.08	0.00	.995	0.00		
					-0.10, 0.05			-0.04, 0.04				
Response inhibition												
Vienna Test System INHIB, n commission errors	10.36 (6.56)	10.82 (7.23)	9.18 (6.67)	10.57 (8.08)	-0.98	.180	-0.14	-0.77	.037	-0.11		
					-2.42, 0.46			-1.49, -0.05				
Cognitive flexibility												
Trail Making Test-B, sec completion	35.19 (17.93)	36.97 (15.79)	33.89 (16.83)	34.80 (15.96)	0.30	.839	0.02	-1.63	.041	-0.10		
					-2.63, 3.24			-3.20, -0.06				
Wisconsin Card Sorting Test, n perseverative errors	20.67 (11.36)	20.83 (11.57)	17.23 (12.10)	17.60 (12.79)	-0.15	.911	-0.01	-3.36	<.001	-0.30		
					-2.82, 2.52			-4.86, -1.85				
Problem-solving												
Tower of London Task, n correct solutions	15.23 (3.27)	14.48 (3.47)	15.55 (3.49)	14.95 (4.14)	-0.12	.765	-0.04	-0.41	.063	-0.12		
					-0.95, 0.70			-0.83, 0.02				

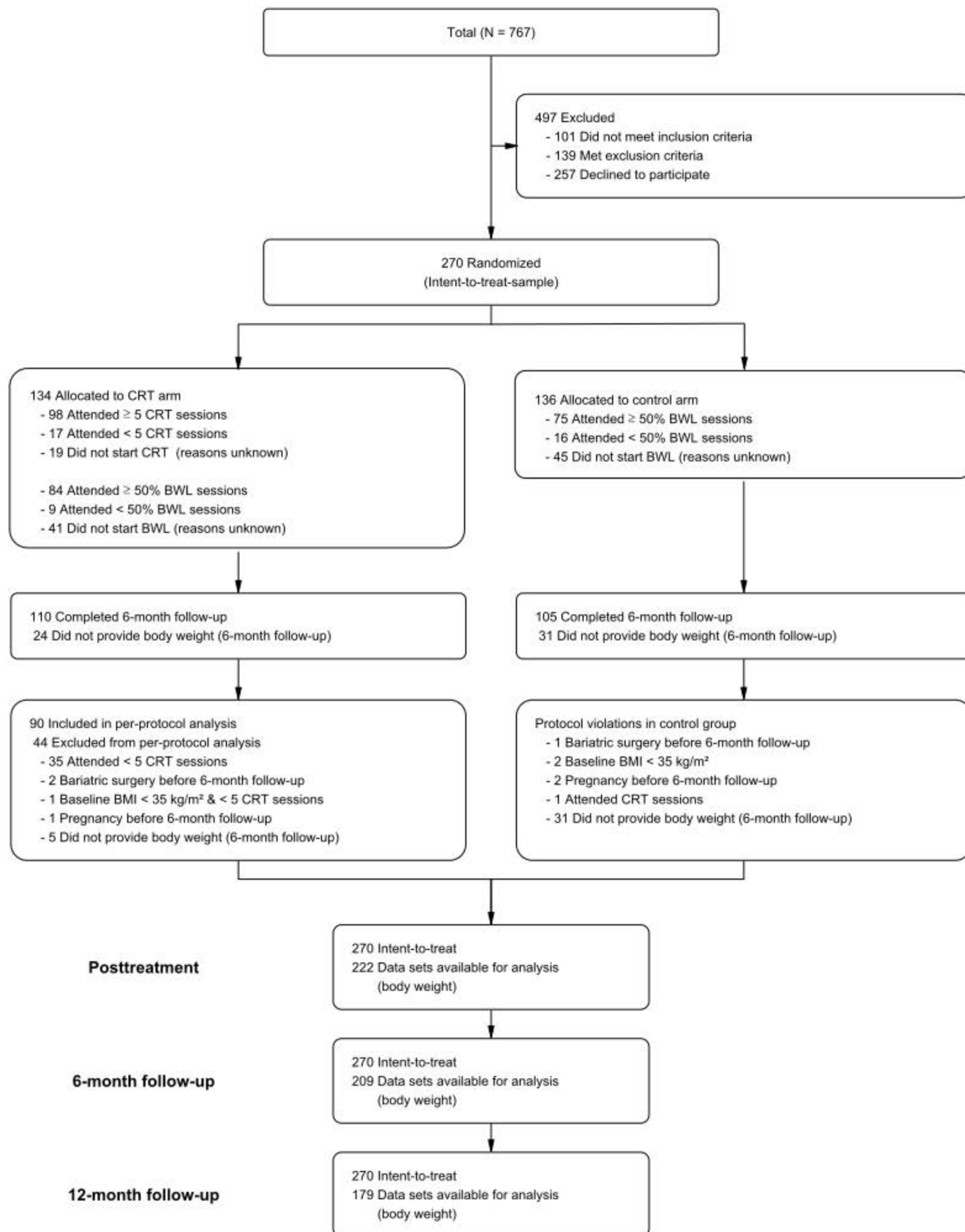
4 *Note.* Coefficients and *p* values derived from linear mixed models of Group × Time or of Time, respectively. A negative sign indicates greater
5 improvement in the CRT versus control arm or over time versus baseline, respectively.
6 Significant *p* values are bolded, *p*<.05.

7

Figure Captions

Figure 1

CONSORT Flow Diagram



Study protocol

Cognitive Remediation Therapy (CRT) for adults with obesity – a randomized-controlled efficacy study

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GENERAL INFORMATION

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Study protocol synopsis

Title of the study:	Cognitive Remediation Therapy (CRT) for adults with obesity – a randomized-controlled efficacy study
Short name of the study:	CRT
Indication:	Obesity (class II and III; body mass index ≥ 35.0 kg/m ²)
Phase of clinical trial:	n. c. (no study according to AMG or MPG)
Primary objective of the study:	Evidence of the efficacy of Cognitive Remediation Therapy (CRT) on weight loss in the treatment of patients with obesity.
Secondary objectives of the study:	Assessment of changes due to CRT in behaviors associated with weight loss, mental and physical health, and adherence to behavioral weight loss treatment.
Study design:	Prospective, randomized-controlled, observer-blinded efficacy study
Study population:	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Patients (age ≥ 18 years) of the IFB Adiposity outpatient clinic with obesity class II or III (BMI ≥ 35.0 kg/m²); - Written informed consent; - Sufficient German language skills; - Possibility of regular participation in the appointments at the IFB study outpatient clinic. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Severe physical disease (e.g. neurological diseases, stroke, head injuries); - Significant psychiatric/psychosomatic comorbidity (e.g. psychotic disorder, current suicidal tendency, current substance dependence, hyperkinetic disorders, intelligence impairment, developmental disorder); - Lack of compliance; - Pregnancy and lactation; participation in other interventional studies; - Ongoing psychotherapy; physical, mental or other inability to participate in required tests (e.g., impaired hearing, vision, or speech); - Use of medications that affect weight or executive functions (e.g., antipsychotics, sedatives, hypnotics); - Previous or planned bariatric surgery.
Number of patients:	Screening (testing of inclusion and exclusion criteria) (n = 600). Randomization (n = 260) Statistical analysis populations n = 260 (intent-to-treat), n = 201 (per-protocol).
Therapy:	The 8-week CRT aims at improving executive function prior to behavioral weight loss treatment. This is intended not only to maximize weight loss, but also to improve behaviors associated with weight loss, participation in behavioral weight loss treatment, and mental and physical health.
Primary endpoint:	Percentage weight change between baseline (t ₀) und 6-month follow-up (t ₂)

Secondary endpoint:	Changes in parameters: (a) executive functions (t0 vs. t1); (b) behavioral indicators of weight loss (t0 vs. t2); (c) compliance with behavioral weight loss treatment; (d) mental health (t0 vs. t2); (e) physical health (t0 vs. t2). In addition, examination of changes in parameters at 12-month follow-up (t3).
Biometry:	<p>The primary question is analyzed using a mixed model. Randomization arm and weight to baseline are considered "fixed effects" and group membership is considered a "random effect." Comparable models will be used at 12-month follow-up (t3), and longitudinal analysis of the data will be performed to determine if the outcome differs between treatment arms.</p> <p>Secondary questions will be analyzed exploratively. Effects will be estimated along with 95% confidence intervals and they will be tested for arm difference. Regression analyses will be used to identify possible predictors of treatment effect.</p>
Schedule:	<p>Follow-up (from beginning of the end of CRT/TAU) per patient: 12 months Duration of intervention per patient (CRT/TAU): 2 months</p> <p>Study related: Start of recruitment: after receipt of all necessary positive votes and completion of preparations (expected September 2015). Recruitment period (12 months) Study duration: 26 months Data cleaning and evaluation: 7 months after Last Patient Out (LPO).</p>

Flow chart

Examination / query	Telephone screening	t0	2 months	t1	t2	t3
		Baseline		t0 + 2 months ^{1,2}	t1 + 6 months ³	t1 + 12 months ³
Written informed consent		●	CRT / TAU			
Inclusion and exclusion criteria	●	4				
Comorbidities	●	●		●	●	●
Concomitant medication	●	●		●	●	●
Medical history		●				
Sociodemography		●				
Physical examination including body height and weight		●		●	●	●
Randomization		●				
Adverse events		●		●	●	●
Executive functions (tests)		●		●		

¹ ± 2 weeks

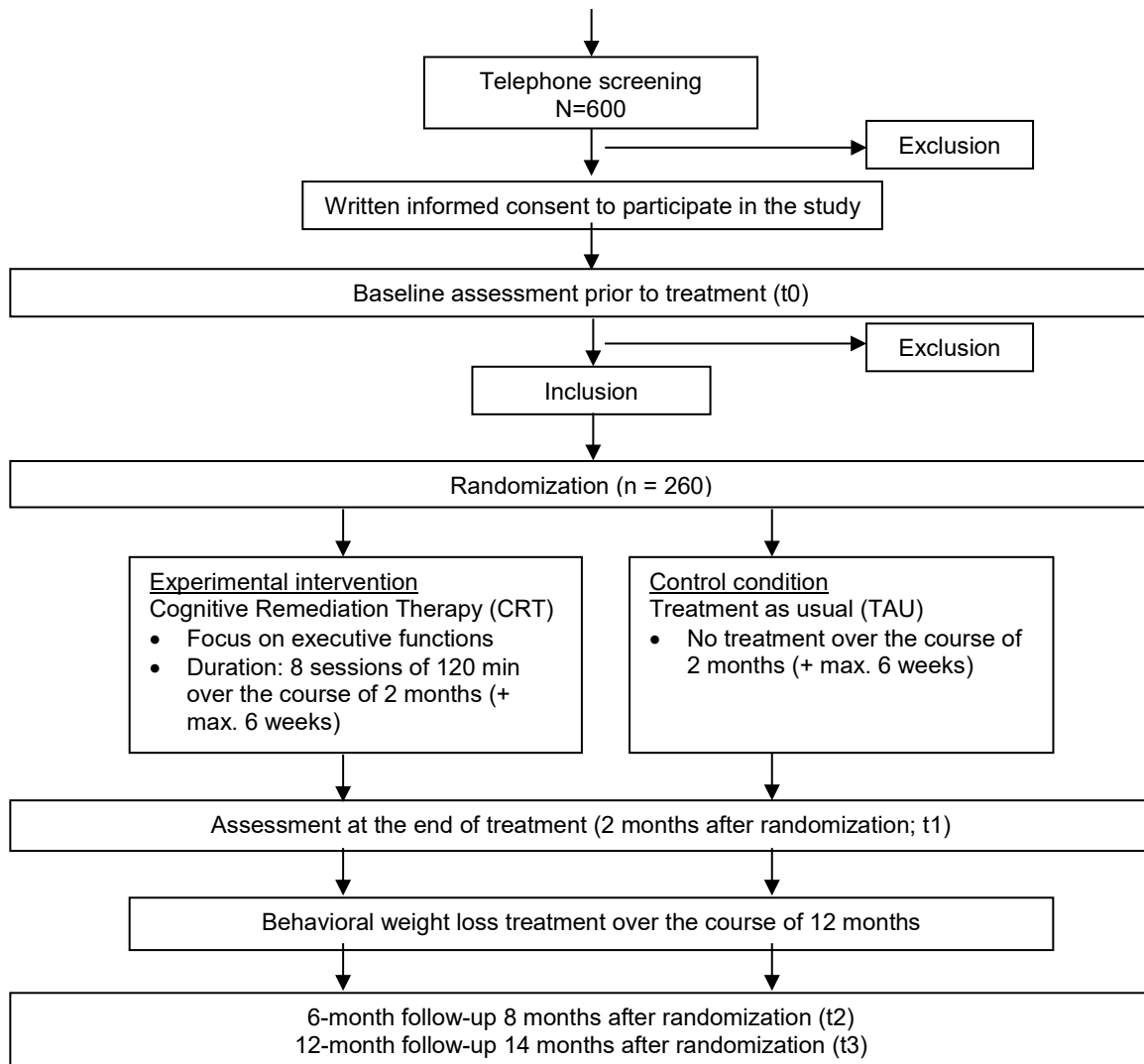
² For the calculation of the date, the treatment date is used, i.e. ideally t0 + 2 months, but if the start of therapy is delayed (e.g., due to the late start of a therapy group), dates are shifted accordingly.

³ ± 4 weeks

⁴ Review/confirmation of inclusion criteria

Examination / query	Telephone screening	t0	2 months	t1	t2	t3
		Baseline		t0 + 2 months ^{1,2}	t1 + 6 months ³	t1 + 12 months ³
Cognitive function (tests)		●				
Behavioral indicators (questionnaires)		●		●	●	●
Mental health (questionnaires)		●		●	●	●

Therapy plan



1 RATIONALE

1.1 Background

In recent decades, prevalence rates of overweight and obesity have increased.¹ Obesity is a risk factor for a number of physical diseases such as type 2 diabetes mellitus or coronary heart disease.² The comorbidities of obesity can be attenuated by even moderate weight loss³ and by long-term weight loss maintenance.⁴ However, only few patients succeed in maintaining the weight reduced in weight loss programs over the long term.⁵ Recent findings suggest that failure in weight reduction is related to difficulties in cognitive processes, particularly executive functions. Executive functions encompass a range of cognitive processes and behavioral skills such as initiation, inhibition, planning, regulation, sequencing, and execution of complex goal-directed behavior. Thus, difficulties in decision making predicted both lower weight loss after behavioral^{6,7} and bariatric^{8,9} weight loss therapy and lower adherence to postoperative recommendations.¹⁰ In general, individuals with obesity showed deficits in executive functions but not in other cognitive aspects such as word fluency, learning, and memory.^{11,12}

The results of a meta-analysis showed moderate to large associations between difficulties in executive functions and high body mass index (BMI, kg/m²).¹³ It can be hypothesized that executive functions provide the basis for many behaviors and cognitions in the context of successful weight management (e.g., self-monitoring, goal setting, physical activity, self-efficacy).¹⁵ Other findings show that weight loss is associated with improvements in executive and attentional functions as well as in memory performance in individuals with obesity.¹⁶

Although the importance of executive functions for weight management has been demonstrated, there are few interventions that aim at improving executive functions in individuals with obesity. CRT was developed to improve basic neurocognitive functions in patients with brain lesions and schizophrenia³⁶ and has already been adapted for other disorders (e.g., depression, attention-deficit/hyperactivity disorder). With respect to eating disorders, CRT adaptations already exist for anorexia nervosa.^{37,38} Two randomized-controlled trials demonstrated that CRT delivered at baseline or during treatment of this eating disorder resulted in more significant improvements in executive function (e.g., flexibility) than cognitive behavioral therapy or non-specific neuropsychological treatment.^{39,40} Both CRT treatment conditions also resulted in improvements in other outcomes (e.g., body weight). Other experimental studies showed that inhibitory control training reduced consumption of high-calorie foods in hedonic eaters and dieters.^{41,42} Executive function training after intensive behavioral weight loss treatment led to improvements in working memory in children with obesity. An unpublished pilot study in adults with obesity showed that as few as 8 sessions of CRT resulted in improvements in executive function and an additional -3.2 kg weight loss at 6-month follow-up.^{43,44} A first randomized-controlled trial testing CRT vs. no CRT in patients with obesity after behavioral weight loss treatment is currently conducted in Australia.⁴⁵

1.2 Rational

1.2.1 Hypothesis and experimental aspects of the clinical trial

The aim of the present study is to test the efficacy of Cognitive Remediation Therapy (CRT) in patients with obesity. The monocenter, randomized-controlled trial will test CRT against a no-treatment control condition (treatment as usual, TAU) in a total of 260 patients with obesity prior to initiation of behavioral weight loss treatment at the IFB Adiposity outpatient clinic. Blinded measurements will be performed at baseline, after the end of treatment, and 6 as well as 12 months after the end of treatment.

It is hypothesized that the weight loss of patients receiving CRT will be greater than that of patients in the TAU group at both 6 and 12 months after the end of treatment. In addition, improvements in

executive function, behavioral indicators of weight loss, and higher compliance with behavioral weight loss treatment are expected in the CRT group compared with the TAU group.

1.3 Risk-benefit estimation

All patients, in CRT and TAU, will be offered individualized behavioral weight loss therapy tailored to their obesity symptoms according to the S3 guidelines. The TAU group will receive no treatment prior to the beginning of the behavioral weight loss program. Since there is no established pre-treatment prior to behavioral weight loss treatment and CRT has not yet been evaluated for this purpose, no treatment is an adequate and justifiable control condition.

The safety and efficacy of CRT has already been demonstrated in comparable studies in which no serious adverse events (SAEs) were reported. However, significant improvement in executive function and weight loss have been demonstrated without worsening psychopathology.^{39,40,43,44}

For the treatment of obesity, analysis of the efficacy of CRT raises the possibility of optimizing the treatment of patients with obesity. Appropriate modification of behavioral weight loss treatment could increase its efficacy or success and, secondarily, could possibly reduce weight regain.

Overall, the anticipated minimal risk is offset by substantial evidence on the efficacy of CRT, which may help to disseminate and optimize the effectiveness of obesity treatment. The minimal risk includes the fact that treatment at the study site involves extensive, psychological diagnostic testing, which is time-consuming for participants and may also lead to mild fatigue.

2 STUDY AIMS

2.1 Primary aim

The primary objective is to demonstrate the efficacy of Cognitive Remediation Therapy (CRT) for the treatment of patients with obesity. The primary outcome measure will be the percentage weight change between baseline (t0) and 6-month follow-up (t2=t1+6 months). In addition, objectively measured body weight at the end of CRT treatment/ TAU (t1) and at 12-month follow-up (t3=t1+12 months) will be used to determine the impact of CRT compared to TAU on weight outcomes (measured as percent weight change compared to baseline).

2.2 Secondary aims

The secondary aims refer on the one hand to the mentioned characteristics of feasibility. On the other hand, the temporal changes of the mentioned mental and physical parameters are of interest.

- (a) Validated tests on executive functions (t0, t1): e.g., Iowa Gambling Task
- (b) Validated tests on behavioral indicators for weight loss (t0 to t3): e.g., physical activity (IPAQ)
- (c) Compliance with behavioral weight loss therapy: presence, attrition
- (d) Validated questionnaires on mental health (t0 to t3): e.g., general psychopathology (PHQ-D)
- (e) Physical health (t0 to t3): Hip and waist circumference, blood pressure, bioelectrical impedance analysis, skinfold thickness

Covariates: Sociodemography (t0 to t3); validated tests on cognitive functions (t0): e.g., vigilance (WAFV of the Vienna Test System)

Predictors (t0, t1): a to e; Sociodemography, weight change, expectations and motivation (visual analogue scales), and compliance with CRT.

3 STUDY DESCRIPTION

3.1 Study design

The study will be conducted as prospective, randomized-controlled, observer-blind efficacy study.

3.2 Personnel and technical requirements for test centers

The study is supervised by Prof. Dr. Dipl.-Psych. Anja Hilbert and managed by other psychologists from the Research Unit of Behavioral Medicine at the University of Leipzig Medical Center. The investigators are experienced in conducting clinical trials and are also trained and instructed in all procedures. The equipment of the study center includes all necessary devices for diagnosis (e.g., BIA, skin fold forceps, etc.).

3.3 Participating centers and number of patients

The study will be conducted in a monocentric manner at the following study site:

University of Leipzig Medical Center
IFB AdiposityDiseases, Behavioral Medicine
Medical Psychology and Medical Sociology
Principal investigator: Prof. Dr. Dipl.-Psych. Anja Hilbert
Philipp-Rosenthal-Str. 27
04103 Leipzig
Germany

The study is expected to enroll 260 patients.

3.4 Expected duration of the study

The maximum duration of the study per patient is 14 months:

- Cognitive Remediation Therapy (CRT) or Treatment as usual (TAU): 2 months
- Behavioral weight loss treatment: 12 months
- Follow-up: 12 months (from end of CRT/TAU)

The total duration of the study is 33 months and is divided as follows:

- Preparation to conduct the trial (study protocol, CRF, etc.): 5 months
- Start of clinical trial: with date of first signed informed consent, planned for September 2015
- Planned end of recruitment phase: 12 months after first-patient-in (FPI)
- Study duration: 26 months (12 months recruitment period, 12 months follow-up from the start of behavioral weight loss treatment, i.e., follow-up will start no earlier than 2 months after the start of recruitment)
- Period for data cleaning and statistical analysis: approx. 7 months

3.5 Termination of the study

3.5.1 Termination of the entire study

The study may be terminated prematurely by the principal investigator in case of

- Serious adverse events
- Unexpected, undesirable risks that lead to consecutive change in the benefit-risk estimation
- Further changes in the benefit-risk estimation
- New findings from other studies
- Insufficient recruitment and follow-up rates

The final decision to terminate the study rests with the head of the study in consultation with the biometrician. When deciding to terminate the study, a decision must be made at the same time on how to deal with patients who may still be on therapy.

4 STUDY POPULATION

4.1 Inclusion criteria

The patients must meet ALL of the following criteria:

- Patient of the IFB AdiposityDiseases outpatient clinic with obesity class II or III (BMI \geq 35.0 kg/m²)
- Planned participation on the behavioral weight loss treatment of the IFB AdiposityDiseases outpatient clinic
- Age \geq 18 years
- Written informed consent has been obtained
- Sufficient knowledge of German
- Possibility of regular participation in the IFB outpatient clinic

4.2 Exclusion criteria

Patients must NOT meet ANY of the following criteria:

- Severe physical disease (e.g., neurological disease, stroke, head injury)
- Significant psychiatric/psychosomatic comorbidity (e.g., psychotic disorder, current suicidality, current substance dependence, hyperkinetic disorders, intelligence impairment, developmental disability)
- Lack of willingness to cooperate (compliance)
- Women during pregnancy and lactation
- Participation in other interventional studies
- Ongoing psychotherapy
- Physical, mental, or other inability to participate in required testing (e.g., impaired hearing, vision, or speech)
- Use of medications affecting weight or executive functions (e.g., antipsychotics, sedatives, hypnotics)
- Previous or planned bariatric surgery

5 INDIVIDUAL COURSE OF THE STUDY

5.1 Patient information and consent

Patients will be informed about the study by the investigators of the Research Unit of Behavioral Medicine of the University of Leipzig Medical Center prior to the baseline assessment (t₀).

Patient consent must also explicitly refer to the collection and processing of health information. Therefore, patients must be explicitly informed about the purpose and scope of the collection and use of personal data, especially health data.

The patient information and consent form must be handwritten, dated and signed by the patient and the investigator. The patient should read the patient information and consent form thoroughly and have an opportunity for questions before he/she signs and dates the forms. The patient cannot be enrolled in the study until the written informed consent form is provided.

The patient information and consent form template is located in the investigator's folder. The 1st original of the informed consent form will remain in the investigator's folder. The patient information and the 2nd original of the informed consent form are given to the patient.

5.2 Withdrawal of consent

Patients may withdraw their consent and discontinue the study at any time and without giving reasons. In such a case, the patient is asked to state the reason for discontinuation, but is informed that he/she does not have to do so. The information when and for what a patient was randomized as well as the time of patient's withdrawal of consent must be retained in the documentation.

The patient must be informed that in the case of withdrawal of consent, the stored data may continue to be used to the extent necessary to ensure that interests of the data subject worthy of protection are not impaired.

5.3 Inclusion in the study

Patients are recruited via the IFB AdiposityDiseases outpatient clinic by means of announcement of the clinical trial in the preliminary talks for behavioral weight loss treatment at the outpatient clinic. If the patient is interested in participating in the clinical trial, he or she can contact the study management by phone or e-mail. In addition, the study team will also contact eligible patients who have previously consented to be contacted for IFB study purposes. With the help of the telephone call or the e-mail contact, the screening is carried out, during which comorbidities and concomitant medication are inquired and inclusion and exclusion criteria are checked.

If the patient meets all inclusion criteria according to the screening and none of the exclusion criteria apply, he/she is invited to an assessment (baseline visit; t₀).

After baseline data collection, the patient can be randomized. For randomization, the randomization form (R) has to be filled out and faxed to the data management of the Clinical Trial Centre (ZKS) Leipzig (fax number: +49 341 97 16 259).

Randomization will be performed on weekdays between 8:00 and 17:00. The Research Unit of Behavioral Medicine will receive the result of the randomization by e-mail as soon as possible (within one hour).

5.3.1 Subsequent detection of violated inclusion and exclusion criteria

Violation of inclusion and exclusion criteria after inclusion of a patient in the clinical trial is generally not a reason for discontinuation of the study for that patient.

If it is subsequently determined that a violation of the inclusion and exclusion criteria already existed at the time of randomization of a patient, the KKS data management will be informed of this as soon as possible. The head of the study decides, if necessary after consultation with the biometrician, how to proceed with the patient. The documentation of the patient will be continued.

5.4 Description of the course of study

Prior to the baseline assessment (t₀), the first step is to provide information and to obtain written informed consent and final review of inclusion and exclusion criteria. Furthermore, the following procedures are performed:

Time	Procedures
t ₀ /baseline	<ul style="list-style-type: none"> • Final review and recording of inclusion and exclusion criteria • Patient information and written informed consent • Randomization • Physical examination <ul style="list-style-type: none"> ○ Body height and weight ○ Hip and waist circumference ○ Blood pressure ○ Bioelectric impedance analysis ○ Skinfold thickness • Comorbidities and concomitant medication • Anamnesis and sociodemography • Validated tests for executive functions <ul style="list-style-type: none"> ○ e.g., Iowa Gambling Task • Validated tests for cognitive functions <ul style="list-style-type: none"> ○ e.g., vigilance (WAFV of the Vienna Test System) • Validated tests for behavioral indicators of weight loss <ul style="list-style-type: none"> ○ e.g., physical activity (IPAQ) • Validated questionnaires for mental health <ul style="list-style-type: none"> ○ e.g., general psychopathology (PHQ-D)

After the end of the baseline assessment and successful randomization, the study treatment (CRT or TAU) is started. CRT takes place in 8 group sessions, each lasting up to 120 minutes, which are scheduled at intervals of about one week. The group size is approximately 6 to 10 patients. The treatment period extends over a duration of 2 months. An overview of the prototypical CRT procedure can be found below:

Sessions	Contents
(1) Introduction	<ul style="list-style-type: none"> - Get to know - Introduction to Cognitive Remediation Therapy
(2) Decision making	<ul style="list-style-type: none"> - Homework discussion - Introduction in decision making - Exercises for decision making in general - Exercises for decision making with regard to "overweight" (i.e., diet, exercise, weight, figure)
(3) Goal setting	<ul style="list-style-type: none"> - Homework discussion - Introduction in goal setting - Exercises for goal setting in general - Exercises for goal setting with regard to "overweight"
(4) Planning	<ul style="list-style-type: none"> - Homework discussion - Introduction in planning - Exercises for planning in general - Exercises for planning with regard to "overweight"
(5) Inhibition	<ul style="list-style-type: none"> - Homework discussion - Introduction in inhibition - Exercises for inhibition in general - Exercises for inhibition with regard to "overweight"
(6) Selective attention and attentional change	<ul style="list-style-type: none"> - Homework discussion - Introduction in selective attention - Exercises for selective attention in general - Exercises for selective attention with regard to "overweight"
(7) Problem solving and flexibility	<ul style="list-style-type: none"> - Homework discussion - Introduction in problem solving and flexibility - Exercises for problem solving and flexibility in general - Exercises for problem solving and flexibility with regard to "overweight"
(8) Reflection und conclusion	<ul style="list-style-type: none"> - Homework discussion - Summary - Feedback - Fare well

At the end of Cognitive Remediation Therapy (CRT) or Treatment as Usual (TAU) [2 months after randomization] the following procedures are performed:

Time	Procedures
t1 (= t0 + 2 months ⁵) ±2 weeks	<ul style="list-style-type: none"> • Physical examination <ul style="list-style-type: none"> ○ Body height and weight ○ Hip and waist circumference ○ Blood pressure ○ Bioelectric impedance analysis ○ Skinfold thickness • Comorbidities and concomitant medication • Sociodemography • Validated tests for executive functions <ul style="list-style-type: none"> ○ e.g., Iowa Gambling Task • Validated tests for behavioral indicators of weight loss <ul style="list-style-type: none"> ○ e.g., physical activity (IPAQ) • Validated questionnaires for mental health <ul style="list-style-type: none"> ○ e.g., general psychopathology (PHQ-D) • Adverse events

5.5 Follow-up

Patients will be asked for follow-up after completion of CRT or TAU. Visits will take place 6 and 12 months after the end of therapy for both therapy groups. The following procedures will be performed:

Time	Procedures
t2 (= t1 + 6 months ^{5,6}) and t3 (=t1 + 12 months ⁶) ±4 weeks each	<ul style="list-style-type: none"> • Physical examination <ul style="list-style-type: none"> ○ Body height and weight ○ Hip and waist circumference ○ Blood pressure ○ Bioelectric impedance analysis ○ Skinfold thickness • Comorbidities and concomitant medication (only for t2) • Sociodemography • Validated tests for behavioral indicators of weight loss <ul style="list-style-type: none"> ○ e.g., physical activity (IPAQ) • Validated questionnaires for mental health <ul style="list-style-type: none"> ○ e.g., general psychopathology (PHQ-D) • Adverse events

5.6 Premature termination of the study intervention or follow-up

Any termination of the study intervention (CRT or TAU) or of the follow-up will be documented by the center caring for the patient with the date (or the most precise possible indication of the time) and, if possible, with an indication of the circumstances and reasons and reported to the KKS - data management.

⁵ For the calculation of the date, the treatment date is used, i.e. optimally t0 + 2 months, but if the start of therapy is delayed (e.g., due to the late start of a therapy group), there is a corresponding shift.

⁶ For the calculation of the date, the treatment date is used, i.e. optimally t0 + 2 months, but if the start of therapy is delayed (e.g., due to the late start of a therapy group), there is a corresponding shift.

5.6.1 Termination of study therapy for individual patients

If, during CRT or the waiting period with the TAU group, reasons arise for individual patients that make further study participation (CRT, waiting period, and/or weight loss treatment) impossible, the patient's participation will be terminated. Possible reasons may include one or more of the following:

- Adverse events (AE) or serious adverse events (SAE) that do not allow further participation in the study. These include: serious medical or psychological problems (e.g., cardiovascular disease, suicidal tendencies, major depression with indication for inpatient psychiatric treatment) that do not permit further treatment with the study intervention, or that result in difficulty interpreting the results and therefore do not permit further participation in the study;
- Psychiatric/psychotherapeutic inpatient treatment longer than one week;
- Inpatient treatment for other reasons of more than two weeks;
- More than 2 outpatient crisis intervention appointments for mental health reasons;
- Unacceptable risk-benefit ratio;
- Lack of patient cooperation or compliance;
- Patient's refusal to continue participation;
- Withdrawal of informed consent.

If study participation is terminated for the CRT or TAU group during the waiting period for the individual patient, the reason will be documented and an attempt will be made to ensure that endpoints can be collected at the scheduled CRT/TAU end. That means procedures of follow-up at t1 will be performed.

5.6.2 Cancellation of follow-up for individual patients

In general, all randomized patients are to be followed up and documented. Follow-up for individual patients will be terminated if the following apply:

- Occurrence of adverse events (AE) or serious adverse events (SAE) e.g., accident or dementia that absolutely prevent the patient from answering questions during follow-up;
- Loss-to-follow-up;
- Patient's refusal to continue participation;
- Withdrawal of informed consent.

6 ADVERSE EVENTS (AE/SAE)

6.1 Adverse and serious adverse events

6.1.1 Definitions

The ICH-GCP Guideline E6 (points 4.11 and 5.17) and the Declaration of Helsinki⁴⁶ put the protection of the study participant in clinical trials first. Therefore, even in the context of clinical trials of treatments and therapies in which the mode of action of drugs and other investigational products is not being investigated, the safety and safety of use must be verified.

Adverse events (AE) are all unfavorable medical occurrences in a patient or clinical research subject to whom an intervention described in the protocol was applied.

These include diseases, signs of disease (including pathological laboratory findings), and symptoms that occur or worsen after the patient's inclusion in the study (usually after the start of the intervention).

Serious adverse events (SAE) are present (definition according to ICH guideline E2A, section IIB) if the events:

- Have resulted in death,
- Are life-threatening,
Note: The term life-threatening, when defined as serious, refers to an event in which the patient was in a life-threatening situation at the time the event occurred; it does not refer to events that hypothetically would have been life-threatening if the event had been more serious.
- Require inpatient medical treatment or require the prolongation of an existing inpatient stay,
- Lead to permanent damage, or
- Represent a congenital deformity or birth defect.

In the CRT study, the following events are also considered serious:

- Psychological decompensation (e.g., acute suicidality, massive self-harm, major depressive episode) with indication for inpatient psychiatric treatment;
- General: inpatient treatment for psychiatric reasons or inpatient treatment for somatic reasons.

An adverse event is additionally defined as **unexpected** if it has not previously been described in the literature in the type or intensity that occurred in relation to the intervention.

6.1.2 Documentation of adverse events (AE)

All AEs will be documented on the provided documentation sheet (CRF page AE) indicating start and end dates and the details: Name/description of AE, date of onset and end, intensity, causality, and outcome documented. AEs are documented in both groups for the period from patient inclusion to the last follow-up date.

All adverse (somatic/psychiatric/psychotherapeutic) events are additionally recorded in a standardized way by questionnaire for all diagnostic sessions. This does not replace the general documentation requirement of AEs on the AE sheet mentioned above. Inpatient treatment of concomitant diseases, such as extreme worsening of psychological symptoms, must be documented as a serious adverse event on the AE sheet (with additional information regarding the definition of serious).

When documenting adverse events, classifications are used, the exact definitions of which can be found in the appendix to the protocol (see chapter 16.1).

6.1.3 Documentation of serious adverse events (SAE)

Serious adverse events are documented on the AE sheet, which includes additional questions on the SAE. Separate documentation on an SAE sheet is not provided.

SAEs are documented for the period from patient inclusion to the time of the last visit for follow-up.

In case of death of a subject, the investigator will provide the responsible ethics committee as well as the study management with all additional information necessary for the fulfillment of their tasks upon request.

For all reports, personal data must be pseudonymized using the data subject's identification code prior to transmission. It must be possible to assign the primary report and all subsequent reports to each other by means of a patient identification number.

6.1.4 Dealing with serious adverse events

Responsibilities of the investigators

Serious adverse events are documented on the AE sheet, which includes additional questions on the SAE, and faxed by the investigator to KKS - data management. The original initially remains with the investigator. The original of the AE sheet, together with the other documentation sheets, is sent to KKS - data management after the final visit (t1) and after the respective visits for follow-up or collected by the monitor. If further information on the SAE is available at a later time, it will also be sent to KKS - data management or collected by the monitor.

For all reports, personal data must be pseudonymized using the data subject's identification code prior to transmission. It must be possible to assign the primary message and all subsequent messages to each other by means of a patient identification number.

6.2 Safety analyses

Each patient will be closely monitored for safety during the course of the study. This includes the recording of adverse and serious adverse events at the final visit (t1) and at each follow-up (t2 and t3). The adverse and serious adverse events that occurred will be analyzed descriptively for final evaluation.

6.3 Comorbidities and concomitant therapies

If extreme deterioration of psychological symptomatology is noted by the therapist during CRT intervention, short-term inpatient treatment should be considered. In particular, attention should be paid to the emergence of suicidal tendencies. If inpatient admission is deemed unnecessary, two outpatient appointments outside of study appointments are allowed for crisis intervention. However, the inpatient or outpatient treatment may not be provided by the therapist. If an inpatient admission for mental health reasons is longer than one week and if more than two outpatient appointments for crisis intervention are made for mental health reasons, the patient is considered to have dropped out of therapy (see Section 5.6.1).

Adjunctive therapies with influence on weight or executive functions are not allowed (see Chapter 4.2).

6.4 Therapeutic measures

If the patient requires treatment due to the adverse event, this must be carried out in accordance with the current state of medical research in order to restore the patient's health. Appropriate equipment and preparations for resuscitation must be available to treat the patient as quickly as possible in an emergency.

The treatment of the AE or SAE must be documented.

General	Regarding the intervention
The measures taken must be documented by the investigator either at the appropriate place in the CRF and/or by additional documentation	<ul style="list-style-type: none"> • Treatment interrupted • Treatment modified • Treatment not interrupted • Unknown • Not applicable

7 BIOMETRIC ASPECTS OF THE STUDY

7.1 Randomization algorithm

Block randomization with variable block length (4 and 6) is implemented electronically - stratified by sex and age (cut-off 45 years). The randomization ratio of the two study arms is 1:1.

7.2 Endpoints of the study

7.2.1 Primary endpoint

The primary endpoint is the percentage change in body weight from baseline (t0) to the 6-month examination (t2).

The percent change in weight at the 2-month examination (t1, immediately after intervention) and at the 12-month examination (t3) are used to provide further information about the effect of the intervention and the longer-term effect of the therapy, respectively.

This endpoint is appropriate because it represents a clinically relevant primary goal of therapy for all patients and obesity is the indication for their enrollment in the IFB. Percent changes are largely independent of baseline BMI in weight loss therapies as opposed to, for example, the often used "excess weight loss" and are therefore biometrically more appropriate for analysis.

7.2.2 Secondary endpoints

In chapter 2.2 secondary objectives and the associated measures are listed as examples.

7.3 Statistical formulation of the study question

H₀: Percent weight change in CRT group = Percent weight change in TAU group

H_A: Percent weight change in CRT group ≠ Percent weight change in TAU group

7.4 Discussion of case numbers

7.4.1 Estimation of the effect sizes

Good estimates for the effects in the control group come from in-house data from over 200 patients. There, after 6 months, a weight loss of 4.4 ± 9 kg is recorded in about 70% of the patients - the remaining 30% stop the program. With an approximately normally distributed initial weight of 125 ± 23 kg, this implies a percentage weight loss of 5 ± 5.5 percentage points, assuming that dropouts have no weight loss on average, but a variance comparable to that of completers.

The expectation for the CRT group is that completers will have a mean weight loss of 2 kg more and that the dropout rate will be "only" 15%. Thus, 7 ± 5.5 percentage points weight loss are expected.

7.4.2 Statistical error sizes

The significance level of 5% is set and the target power is 80%.

Patients will receive CRT/TAU as well as the following potential weight loss options offered at the IFB AdiposityDiseases outpatient clinic based on indication: Individualized nutrition therapy plus nutrition group, Doc Weight group therapy, Mobilis group therapy. These therapy options and participation in them are documented.

Within a treatment group, patients may be more homogeneous than between groups and group membership is considered in the analysis. In case planning, the group effect has been accounted for

with an intra-class correlation coefficient of 0.004, which has been observed as a coefficient for BMI at the postcode level.⁴⁶

7.4.3 Drop-outs

It has already been mentioned above that 30% drop-outs are to be expected in the TAU group and 15% drop-outs in the CRT group. At this point, "drop-out" means any patient who does not provide weight data at t0 and t2.

In obesity research, high drop-out rates are common and data handling is accordingly important. Here, the assumption is made that patients who do not provide data on average do not change from their baseline values, but have a variance in values comparable to those who provide data. This provides an adequate handling of data that should not lead to biased estimates and statistical tests.

7.4.4 Sample size calculation

The sample size calculation was first based on a t test with the data described above (calculated with the software program R): accordingly, 120 patients per arm would be necessary. The cluster effect was then taken into account with the software PASS, which led to an increase in the number of cases (additional group). Thus, 130 patients per arm should be included. The methods already account for expected dropouts, and the t test is expected to be slightly more conservative than the planned mixed model. Thus, a power slightly above 80% can be expected.

7.5 Methods for data analysis

7.5.1 Analysis populations

The analyses are based on the "intent-to-treat" (ITT) principle and the relevant population is all randomized patients. It is expected that a relatively large number of patients will drop out of the weight loss program or not even start. Efforts will be made to obtain weight at the scheduled appointments in these patients as well. If this is not possible, missing data will result. If no further data have been obtained afterwards, an imputation procedure is used in which these values do not differ on average from the baseline values, but have a variance like the existing values.

The per-protocol population consists of patients in the intervention arm who attended at least 4 CRT sessions and provided data on the primary endpoint. Confidence interval estimates are calculated for this population in case the population differs significantly from the ITT population.

7.5.2 Planned analysis methods

The primary question is analyzed using a mixed model. Here, randomization arm and weight to baseline are considered "fixed effects" and group membership is considered a "random effect." Comparable models will be used at 12-month follow-up (t3), and longitudinal analysis of the data will be performed to determine if the outcome differs between treatment arms.

Secondary questions will be analyzed exploratively. Effects will be estimated along with 95% confidence intervals and arm difference will be tested for. Regression analyses will be used to identify possible predictors of treatment effect.

More detailed descriptions for analysis of secondary endpoints will be recorded in a statistical analysis plan prior to analysis.

7.6 Interim analysis

No interim analysis is planned.

7.7 Final analysis

Final analysis is performed after the last visit is completed, the documentation is complete, all queries are answered, and the database is closed.

8 ETHICAL AND REGULATORY REQUIREMENTS

8.1 GCP Declaration

All parties involved in the study (head of the study and contractors of the head of the study, investigators, etc.) undertake to conduct the clinical study in accordance with the requirements of national laws, the requirements of the ICH Guideline for Good Clinical Practice (GCP) E6 of June 1996 and CPMP/ICH/135/95 of September 1997, and to observe the recommendations of the Declaration of Helsinki in its current version.

8.2 Application

In accordance with the requirements of §15 of the professional code of conduct for physicians, the clinical study is submitted to the responsible ethics committee for consultation prior to start.

8.3 Subsequent study protocol changes

Changes to the clinical trial that has received approval from the ethics committee that are likely to

- Impact the safety of subjects, e.g., essential changes in Cognitive Remediation Therapy (CRT),
- Additional data collection or evaluations that require a change in patient information and/or consent,
- Affect the interpretation of the scientific documents on which the trial is based or the scientific validity of the trial results,
- Materially change the manner in which the study is conducted or performed,

May be made only, if such changes have been approved by the ethics committee.

Study protocol changes may be made by the principal investigator and must be communicated in writing to all parties involved in the conduct of the study and documented in the Trial Master File with a date.

9 DOCUMENTATION

9.1 Patient identification list

All patient-related data are recorded in pseudonymized form. For this purpose, a non-speaking pseudonym is used, from which alone the identity of the patient cannot be inferred.

The study personnel maintains a patient identification list in which the patient identification numbers are linked to the full patient name and date of birth of the participants. This list is used for the possibility of later identification of participating persons. It must be kept absolutely confidential, must not leave the study center, and must be archived for at least ten years after the end of the study.

In addition, the participation of the person concerned in the study must be noted in the patient file.

9.2 Case report forms (CRF)

The documentation sheets are created by KKS - data management and printed with an original (no

carbon copy). The KKS - data management receives the original.

All entries on the documentation sheets must be made with a dark ballpoint pen. Corrections are made by drawing a horizontal line across the incorrect entry so that the entry to be corrected remains visible. The correction must be confirmed by initials and the current date by an authorized person of the study center. The use of correction fluids is not permitted.

Signature on the documentation forms for each visit will confirm the accuracy of the information and any corrections. During the course of the study, the CRF sheets are sent to the ZKS Leipzig - KKS - data management at regular intervals (every two months) or, if a visit is scheduled beforehand, collected by the monitor. At the ZKS Leipzig - KKS data entry and analysis take place.

Source documents (source data) are all data available in the patient files.

9.3 Data management

Data management is performed using the study management tool eResearch Network® from OMNICOMM. For the creation of the study database, a CRF specification is prepared by the responsible project manager in collaboration with the biometrician, which serves as the basis for the database programmer to create the database application. Prior to release, the database application is tested for errors and validated. The validation process is documented in writing.

Data collected on the CRFs are entered into the eRT database using input screens. Simple data entry is performed.

The data are checked for completeness, consistency, and plausibility. Queries are submitted promptly in written form to the study center or, if a monitoring visit takes place promptly, by the responsible monitor.

A complete backup of all data is performed on a daily basis. The use of a hierarchical access concept based on roles makes unauthorized access to patient data impossible. The anonymity of the data in the context of evaluations is guaranteed. Every change to the data, e.g. due to the incorporation of answered queries, is documented in the database via an automatic audit trail.

9.4 Archiving

All relevant study documents (Trial Master File), electronically recorded data, originals of all CRFs, and the final report will be retained at the study center for at least 10 years after completion of the study.

Furthermore, the investigator's folder, the patient identification list, the signed informed consent forms, all CRFs, and the patient files will be kept at the study center for at least 10 years after completion of the study.

10 MONITORING OF THE CLINICAL STUDY

10.1 Access to source data

Due to legal regulations to ensure data quality and to monitor study conduct at the center, investigators are obliged to guarantee authorized third parties access to patient records (source data). These include monitors, auditors, and other agents of the client. These persons are obliged to maintain confidentiality.

10.2 Monitoring

On-site monitoring by staff of the ZKS Leipzig - KKS will be performed to monitor the study site. An initiation visit to the IFB AdiposityDiseases, Behavioral Medicine Research Unit, University of Leipzig Medical Center, is planned prior the start of the study. During the course of the study, the study center will be visited regularly, with the frequency of visits depending on the study phase (treatment or follow-up period) and recruitment performance. During these monitoring visits, the existence and correct informed consent of all study participants will be verified. Study-relevant documents are checked and updated if necessary.

The exact planning and execution of the monitoring is based on the SOPs of the ZKS Leipzig - KKS available for this purpose and will be described in more detail in a monitoring manual yet to be prepared.

To perform the monitoring, the investigators will allow access to the study premises and access to the files of all study participants to ensure a complete source data comparison.

In addition to on-site monitoring, study data are reviewed for consistency and plausibility at regular intervals as part of central monitoring. As part of this statistical monitoring, the occurrence of AEs or SAEs is also investigated and evaluated in terms of type and frequency.

10.3 Independent monitoring of the study

As no vulnerable groups will be included and treated in this study, and as no invasive or burdensome investigations will be performed as part of the intervention, an independent data monitoring committee will not be established.

The safety of the study intervention as well as the integrity and validity of the data collected and the conduct of the clinical trial will be reviewed on a regular basis as part of the statistical monitoring to ensure the safety of the study participants.

11 DATA PROTECTION AND CONFIDENTIALITY

As part of the study, personal data and data on treatment and the course of the disease (medical findings, types of treatment, prescribed medication, etc.) are collected from the study participants. These data are stored and analyzed electronically in pseudonymized form (i.e., without direct reference to the patient's name) using an identification number.

Since direct patient contact by the study center is necessary during the course of the study, the patients' full name and address/telephone number will be collected and stored with their prior written consent. These data are kept and stored separately from the study data. Inference is possible here via the patient ID.

Data processing takes place in the study center of the ZKS Leipzig - KKS. With the help of a security concept, protection against unauthorized access and data loss is ensured here, among other things, and care is taken to ensure that the provisions of the Data Protection Act are complied with. The study data are protected against unauthorized access and only study employees are allowed to access them. These employees are bound to secrecy.

In the event of a withdrawal of consent by the patient, the extent to which the stored data are still required is checked. Data that are no longer required will be deleted immediately. The personal data collected will be deleted/anonymized after completion of all study-related projects, but at the latest after 10 years, unless this conflicts with legal, statutory, or contractual retention periods.

Declaration on data protection

The provisions of the Data Protection Act are observed during data entry, processing, and evaluation, which takes place at the ZKS Leipzig - KKS. Only employees of the study have access to all study data. These persons are bound to secrecy. The data are protected against unauthorized access

12 ADMINISTRATIVE REGULATIONS

12.1 Execution of the study according to the study protocol

The clinical trial presented herein is planned, conducted, and evaluated in accordance with the requirements of ICH-GCP and applicable regulatory requirements.

Protocol violations are all deviations from the instructions and procedures described in this protocol. These include:

- Missing examinations or performing them at the wrong time, e.g., failure to observe the minimum number of 4 treatment sessions
- Lack of compliance
- Intake of unauthorized concomitant medications (see chapter 4.2)
- Violation of inclusion or exclusion criteria
- Psychotherapeutic treatment parallel to participation in the study:
 - o Inpatient treatment of more than one week or
 - o More than two outpatient appointments for crisis intervention
- Inpatient treatment for other reasons for more than two weeks

Once a participant has been enrolled in the study, it is the responsibility of the investigator to avoid protocol violations in order to keep the patient/participant in the study.

Serious protocol violations will be reported immediately to the head of the study. All protocol violations will be documented and discussed with the responsible biometrician prior to statistical analysis of the study.

The investigator must ensure that all data collected are documented according to the protocol. Minor deviations are certainly unavoidable in everyday work, but must be documented with a justification.

12.2 Financing and insurance

The study is financed by the funding program of the German Federal Ministry of Education and Research (BMBF). Patient insurance for the study is waived, as there is no administration of investigational medication or use of medical devices. It is a psychotherapeutic intervention. Patient and accident insurance is not required for psychotherapeutic studies.

12.3 Publication agreements and registration

The study is to be published in internationally recognized journals. The head of the study, Prof. Dr. Dipl.-Psych. Anja Hilbert, will make every effort to ensure publication regardless of the outcome of the study.

"First author" is the head of the study Prof. Dr. Dipl.-Psych. Anja Hilbert. Further authors are medical or psychological staff members of the University of Leipzig Medical Center as well as the biometrician

responsible for the biometrics at the IFB Data Center. The respective publication guidelines are to be followed.

Authors are required to mention the IFB AdiposityDiseases in the author line. For institutional attribution, the wording "University of Leipzig Medical Center, IFB AdiposityDiseases" should be used.

In all publications, the BMBF is to be indicated in the acknowledgement as follows: "The study was funded by the Federal Ministry of Education and Research (BMBF), FKZ: 01EO1001."

For abstracts that can be cited, the sponsor and the IFB AdiposityDiseases must be referred to analogously. On posters, the logo of the IFB AdiposityDiseases and the BMBF must also be used.

The study will be registered in a publicly accessible study registry, e.g., the German Clinical Trials Registry Freiburg (www.germanctr.de), before recruitment begins.

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14 SIGNATURES FOR THE STUDY PROTOCOL

Confirmation of the study protocol

The study protocol is hereby confirmed in its final version:

Head of the study

Date

Signature

Biometrician:

Date

Signature

15 RECOGNITION OF THE STUDY PROTOCOL

I hereby confirm that I have read and understood the present study protocol and accept it in all its parts. I undertake to ensure that the patients brought into the trial by my center are treated, observed, and documented in accordance with the provisions of this protocol. I undertake to ensure that all persons involved in the clinical trial are informed about the contents of the study protocol.

Date:

Signature of the principal investigator:

Address of the test center (stamp):

16 APPENDIX

16.1 Classification of adverse events

16.1.1 Severity

The severity of an adverse event is assessed according to the definitions in chapter 6.1.1.

16.1.2 Assessment of intensity

The intensity is evaluated according to CTCAE V3.0

	Mild event
Mild adverse event	<ul style="list-style-type: none"> • No specific medical intervention necessary, • Only asymptomatic laboratory results or X-ray findings, • Low medical relevance
	Moderate event
Moderate adverse event	<ul style="list-style-type: none"> • Minimal medical intervention required or intervention locally limited, • Only non-invasive measures (e.g., wraps) necessary
	Serious and undesirable adverse event
Serious and undesirable adverse event	<ul style="list-style-type: none"> • Significant symptoms requiring hospitalization or invasive interventions, • E.g., transfusions, elective interventional radiology procedures, therapeutic endoscopy or surgery.
	Life-threatening or disabling adverse event
Life-threatening or disabling adverse event	<ul style="list-style-type: none"> • Aggravated by acute, life-threatening complications of the metabolism or circulatory system, e.g., circulatory collapse, hemorrhage, sepsis • Life-threatening physiological consequences, <p>Need for intensive care, immediate invasive, interventional, or radiological measures, therapeutic endoscopy or surgery</p>
Death related to adverse event	Death as a result of AE

16.1.3 Assessment of the causal relationship

The investigator must evaluate whether, in his/her opinion, the occurrence of the adverse event is causally related to investigational therapy/intervention. The classification given below must be used for this purpose. Each adverse event must be documented, even if no relationship to the investigational therapy/intervention can be identified.

- Possible
- Not possible

The association is assessed as **possible** if one of the following criteria according to WHO-UMC is fulfilled:

- Plausible temporal relationship, and cannot be explained by comorbidities or other products
- Justified temporal relationship, and explanation by comorbidities or other products unlikely
- Justified temporal relationship, but explanation by other products or comorbidities possible
- Further information necessary to make an accurate assessment
- Assessment not possible because information is insufficient or contradictory

The association is assessed as **not possible** if the following criterion according to WHO-UMC is fulfilled:

- Temporal connection makes the causal relationship unlikely, and other product or comorbidities provide plausible explanations

16.1.4 Expected / unexpected

An adverse event is additionally defined as **unexpected** if it has not previously been described in the literature in the type or intensity that occurred in relation to the intervention.

16.1.5 Outcome of the adverse event

The outcome of an adverse event is classified as follows:

- Restored
- Improvement
- Not yet restored
- Restored with consequential damages
- Fatal outcome*
- Unknown outcome

*Caution: The death of a patient is not in itself an event, but its outcome. The event that led to the patient's death must be fully documented and reported, even if the death occurred only four weeks after the end of the study therapy and regardless of whether there is a connection with the therapy or not.

16.2 Abbreviations

AE	Adverse event
BMBF	Federal Ministry of Education and Research
BMI	Body mass index
CRF	Case report forms
CRT	Cognitive Remediation Therapy
FKZ	Funding code
GCP	Good Clinical Practice
GCP-V	GCP Regulation
ICH	International Conference on Harmonisation
IFB	Integrated Research and Treatment Center
KKS	Centre for Clinical Trials
SAE	Serious adverse event
TAU	Treatment as usual

Supplement 2

Hilbert, A., Neuhaus, P., Köhler, N., Petroff, D., Hay, P., & Hübner, C. Group cognitive remediation therapy prior to behavioral weight loss treatment for adults with severe obesity: A randomized clinical trial (CRT Study). *Journal of Consulting and Clinical Psychology*.

eAppendix. Supplementary information

eTable 1. Cognitive remediation therapy: therapeutic sessions, topics, and exercises

eTable 2. Baseline sociodemographic and clinical characteristics in the per protocol (PP) set of patients randomized to cognitive remediation therapy

eTable 3. Raw, nonimputed data on secondary outcomes in the intent-to-treat sample

eTable 4. Exploratory analyses of weight change by group and behavioral weight loss (BWL) treatment intensity in intent-to-treat analyses

eReferences

eAppendix. Supplementary Information

1. Study Protocol

Revisions Made to the Published Study Protocol

- Omission of the secondary outcome variable physical activity as assessed through the International Physical Activity Questionnaire (IPAQ) because of non-interpretable data.

Study Protocol Publication

Hilbert, A., Blume, M., Petroff, D., Neuhaus, P., Smith, E., Hay, P. J., & Hübner, C. (2018). Group cognitive remediation therapy for adults with obesity prior to behavioural weight loss treatment: study protocol for a randomised controlled superiority study (CRT study). *BMJ Open*, 8(9), e022616. doi: 10.1136/bmjopen-2018-022616

2. Measures

Primary Outcome

Percent weight change (t0–t2). Based on participants' objectively measured weight, % weight change was computed by subtracting t0 weight from t2 weight and dividing it by t0 weight, i.e. $(t_0 - t_2)/t_0 \times 100$. Negative values are thus indicative of weight loss, while positive values are indicative of weight gain.

Secondary Outcomes

Iowa Gambling Task (IGT; t0–t1). To evaluate decision-making in complex and uncertain situations, a computerized version of the IGT was used (Bechara et al., 1994). The goal was to win the highest possible amount of virtual money when drawing 100 times a card from four possible card decks (A, B, C, D). Each of these card decks were associated with different amounts of wins and losses: Decks A and B involved long-term total losses (unfavorable decks), whereas decks C and D involved long-term total wins (favorable decks). The total net score was determined as an indicator of IGT performance, by subtracting the total number of unfavorable decisions from the total number of favorable decisions.

Delay Discounting Task (DDT; t0–t1). A computerized version of the DDT served to determine impulsive decision-making (Richards et al., 1999). In the DDT, participants are instructed to choose between two possible amounts of money at different time delays. A choice between a standard amount (10 EUR) at different time delays (0, 2, 30, 180, and 365 days) and a variable amount (0-10 EUR) without delay is offered. For each of the five temporal delays, an indifference point is calculated where the immediate reward and the delayed reward are the same in regards to their subjective value. Performance in the DDT was determined using the area under the curve (AUC) for the five indifference points. With a range from 0-1, larger AUC values are indicative of lower discounting of delayed rewards, i.e. less impulsive decision-making.

Go/No Go (t0–t1). To determine inhibitory control, the computerized version of the visual Go/NoGo paradigm in the Vienna Test System was used (Kaiser et al., 2015). In the Go/NoGo task, the participant has to distinguish between stimuli requiring a rapid response and those requiring inhibition. Therefore, a total of 250 stimuli were randomly presented, requiring a total of 202 responses and 48 inhibitions upon presentation of triangles or circles, respectively. Inhibitory capacity was determined by the number of commission errors (i.e., false positive responses to a NoGo trial), with more commission errors indicating decreased inhibitory control.

Trail Making Test – Part B (TMT-B; t0–t1). Cognitive flexibility was assessed with the TMT-B, provided by the Vienna Test System (Rodewald et al., 2015). In this test, the numbers 1-13 and letters A-L must be clicked alternately and in ascending order as quickly as possible. As main outcome the processing time was determined, with shorter times indicating better cognitive flexibility.

Wisconsin Card Sorting Test (WCST; t0–t1). Cognitive flexibility was determined using the computerized version of the WCST (Heaton et al., 1993). In the WCST, 128 cards are sorted according to three possible rules (e.g., shape, color, or number). These rules are unknown to the participant and can only be inferred from feedback

provided. The rule was changed suddenly and without warning after ten consecutive and correctly sorted cards, requiring cognitive flexibility of the participant in the identification of and adaptation to these changes. Outcome variable was the number of perseverative errors, representing the tendency to persevere on the previous rule.

Tower of London (TOL; t0–t1). To determine planning capability for qualitatively different problems, the computerized version of the TOL in the Vienna Test System was used (Kaller et al., 2015). Three differently colored balls on three rods with different capacities (one, two, or three balls) have to be transferred from an initial state to a target state. Several rules have to be followed, for example, not keeping a ball in the hand between moves and not placing it on the table. Constantly, the difficulty and the number of optimal moves to solve the problem is increased. Planning ability was determined based on the number of four to six move tasks solved in the specified minimum number of moves required. Higher values are indicative of better planning ability.

Generalized Self-Efficacy Scale (GSES; t0–t3). The 10-item GSES measures participants' global confidence of coping with demanding situations based on the own competence (Schwarzer & Jerusalem, 1995). Items are scored on a 4-point scale ranging from 1=*not at all true* to 4=*exactly true*. Participants' total sum scores were computed, with higher scores indicating greater generalized self-efficacy. The GSES has good validity and adequate reliability. Internal consistency in this study's sample was $\alpha=.91$.

Dutch Eating Behavior Questionnaire (DEBQ; t0–t3). To assess participants' non-normative eating behavior, the German adaptation (Grunert, 1989) of the DEBQ was used. It consists of the subscales restrained eating, emotional eating, and external eating, each with ten items rated on a 5-point Likert scale ranging from 1=*never* to 5=*very often*. Mean subscale scores were computed, with higher scores indicating more frequent non-normative eating behavior. Good validity and adequate reliability of the DEBQ were demonstrated. Internal consistencies in this study's sample were $\alpha=.88$ (restrained eating), $\alpha=.93$ (emotional eating), and $\alpha=.89$ (external eating), respectively.

Eating Disorder Examination-Questionnaire 8 (EDE-Q8; t0–t3). The EDE-Q8 served for assessment of participants' global eating disorder psychopathology (Kliem et al., 2016). Based on eight items rated on a 7-point Likert scale from 0=*not present* to 6=*present every day or in extreme form*, the global mean score was computed, with higher scores indicating greater global eating disorder psychopathology. The EDE-Q8 has shown good validity and excellent reliability. Internal consistency in this study's sample was $\alpha=.69$.

Patient Health Questionnaire-Depression (PHQ-D; t0–t3). The PHQ-D is the short form of the German version of the PRIME MD screening for depressive and anxiety disorder symptoms over the last two and four weeks, respectively (Gräfe et al., 2004). Using its nine depression items (PHQ-9), scored on a 4-point scale from 0=*not at all* to 3=*nearly every day*, a sum score was computed with higher scores indicating more severe depression. Internal consistency for the PHQ-9 in this study's sample was $\alpha=.80$.

Impact of Weight on Quality of Life – Lite (IWQOL-Lite; t0–t3). The IWQOL-Lite measures quality of life in obesity during the last week in five domains (physical function, self-esteem, sexual life, public distress, work; Mueller et al., 2011). The 31 items were rated on a 5-point Likert scale from 1=*never true* to 5=*always true*. Sum scores for each subscale were computed, with higher scores indicating poorer quality of life. The IWQOL-Lite has shown good validity and excellent reliability. Internal consistencies in this study's sample were $\alpha=.78$ –.94.

Anthropometric measures (t0–t3). As indicators for physical health, hip and waist circumference (cm), blood pressure (mm Hg), triceps and subscapularis skinfolds (mm) were measured and – based on bioelectrical impedance analysis – patients' body fat mass and total body water (%) were determined.

3. Sensitivity Analyses

Sensitivity analyses confirmed the intent-to-treat analyses on the primary endpoint % weight change at 6-month follow-up: Linear regression models showed a very slightly lower percent and absolute change in body weight in the CRT than control arm, where the difference was not significant (0.3%, 95% CI: -1.2% to 1.7%, $p=.713$; 0.4 kg, 95% CI: -1.5 kg to 2.3 kg, $p=.691$). Similarly, in the complete case sample, patients in the CRT arm reduced their pretreatment weight by 1.0% (95% CI: -0.5% to 2.5%, $p=.177$, Cohen's $d=0.09$) less than patients in the control arm. In the per protocol sample, patients in the CRT arm with good protocol adherence reduced their pretreatment weight nonsignificantly less than patients in the control arm ($\beta=0.11\%$, 95% CI: -1.56% to 1.78%, $p=.895$, Cohen's $d=0.00$).

eTable 1*Cognitive Remediation Therapy: Therapeutic Sessions, Topics, and Exercises*

Sessions	Content
(1) Introduction	<ul style="list-style-type: none"> - Getting to know each other - Introduction to cognitive remediation therapy - Handwriting task^a - Homework: creating a personal mind map on “my overweight”^b
(2) Goal-setting	<ul style="list-style-type: none"> - Discussion of homework - Introduction to goal-setting - General tasks regarding goal-setting: complex figure task^b (drawing complex figures from description only and creating a description of a complex figure for blinded drawing); reflection - Weight management-related tasks regarding goal-setting: SMART goal analysis^c of eating or exercise behavior; guided imaginative relaxation "my present and future life from the bird's eye view"; reflection - Homework: finalizing the SMART goal analysis^c; complex figure task^b
(3) Selective attention and switching attention	<ul style="list-style-type: none"> - Discussion of homework - Introduction to attention and switching attention - General tasks regarding selective attention and switching attention: illusions task^b; computerized Simon task and task switching^d; reflection - Weight management-related tasks regarding attentional processes: Stroop task with food (based on ^b); switching attention task with food and exercise (based on ^b); reflection - Homework: illusions task^b; hidden object picture^e; creating a reward list
(4) Automatisms and inhibition	<ul style="list-style-type: none"> - Discussion of homework - Introduction to automatic behavior and inhibition - General tasks regarding automatisms and inhibition: random generation task^b (generating letters in random order without two letters appearing in sequence); computerized inhibition task and stop-signal task^d; reflection - Weight management-related tasks regarding automatisms and inhibition: identifying automatisms in eating and exercise behavior; reflection - Homework: inhibiting automatisms in eating or exercise behavior
(5) Decision-making	<ul style="list-style-type: none"> - Discussion of homework - Introduction to decision-making - Weight management-related tasks regarding decision-making: food cue exposure; identifying short- and long-term pros and cons of cue-dependent, automatic versus planned eating and exercise behavior; reflection - Homework: finalizing the identification of short- and long-term pros and cons of inhibiting automatisms in eating or exercise behavior
(6) Planning	<ul style="list-style-type: none"> - Discussion of homework - Introduction to planning - General tasks regarding planning: how to task (based on ^b); computerized frustration tolerance task (Box World^f); reflection - Weight management-related tasks regarding planning: using the how to task for eating or exercise behavior change planning; reflection - Homework: realizing the planned behavior change and rewarding

Sessions	Content
(7) Problem-solving	<ul style="list-style-type: none"> - Discussion of homework - Introduction to problem-solving - General tasks regarding problem-solving: applying the problem-solving scheme^g to a general problem; reflection - Weight management-related tasks regarding problem-solving: Map task in combination with prioritizing task (based on ^a; organizing a day with eating- and exercise-related problem-solving; reflection - Homework: applying the problem-solving scheme to eating or exercise behavior change
(8) Conclusion	<ul style="list-style-type: none"> - Discussion of homework - Conclusion - Feedback - Farewell

Note. SMART = specific, measurable, attainable, reasonable, and time-bound (Doran, 1981). ^aTchanturia et al. (2010). ^bRaman et al. (2018). ^cDoran (1981). ^dDickhut et al. (2014). ^eBrainDen.com (n.d.). ^fBox world website (n.d.). ^gFunke (2011).

eTable 2

Baseline Sociodemographic Characteristics and Motivation in the Per Protocol (PP) Set of Patients Randomized to Cognitive Remediation Therapy Versus Patients Randomized to the Control Group

Baseline characteristic	PP	Control	<i>p</i>
	(<i>n</i> =90)	(<i>n</i> =136)	
	<i>n</i> (%) / <i>M</i> (<i>SD</i>)	<i>n</i> (%) / <i>M</i> (<i>SD</i>)	
Sex, female	62 (68.9)	93 (68.4)	1.000
Age, y	44.6 (14.2)	44.8 (12.0)	.887
Nationality			
German	89 (98.9)	132 (97.8)	.918
Other	1 (1.1)	3 (2.2)	
Education			.996
≥12 years	26 (28.9)	40 (29.9)	
<12 years	64 (71.1)	94 (70.1)	
Body weight, kg	131.2 (27.7)	133.4 (24.6)	.532
Body mass index, kg/m ²	45.5 (7.1)	45.9 (7.0)	.660
Weight status			.414
Obesity Class 1	0 (0)	2 (1.5)	
Obesity Class 2	20 (22.2)	25 (18.4)	
Obesity Class 3	70 (77.8)	109 (80.1)	
Therapy expectations: Mindset ^a			
Motivation to change	8.8 (1.5)	8.6 (1.7)	.353
Readiness to keep change	8.8 (1.7)	8.8 (1.4)	.980
Confidence to keep change	7.5 (1.8)	7.1 (1.5)	.124
Therapy expectations: Weight management behavior ^a			
Motivation to change	8.8 (1.4)	8.7 (1.5)	.459
Readiness to keep change	8.8 (1.4)	8.6 (1.4)	.360
Confidence to keep change	7.6 (1.9)	7.3 (1.7)	.165
Reasons for study participation			.636
Change mindset only	2 (2.2)	1 (0.7)	
Weight loss only	18 (20.0)	27 (20.0)	
Both	70 (77.8)	107 (79.3)	

Note. Percentages calculated from valid cases. ^aAssessed on a rating scale from 0–10 with higher scores indicating higher expectations. Welch's *t* test for continuous variables, Fisher's exact test for categorical variables. Significant *p* values are bolded, *p*<.05.

eTable 3*Raw, Nonimputed Data on Secondary Outcomes in the Intent-to-treat Sample*

Secondary outcome	Pretreatment		Posttreatment		6-month follow-up		12-month follow-up	
	CRT	Control	CRT	Control	CRT	Control	CRT	Control
	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>
Weight change								
Body weight, kg	134; 130.8 (26.7)	136; 133.4 (24.6)	118; 130.6 (26.4)	104; 131.6 (25.5)	107; 128.0 (26.9)	102; 130.0 (25.2)	90; 124.0 (24.2)	89; 129.6 (26.9)
Body mass index, kg/m ²	134; 45.3 (6.9)	136; 45.9 (7.0)	118; 45.2 (6.7)	104; 45.1 (7.2)	107; 44.6 (6.9)	102; 44.3 (7.1)	90; 43.3 (6.1)	89; 43.8 (7.0)
Weight management behavior								
Generalized Self-Efficacy Scale	134; 29.6 (5.3)	135; 29.4 (5.4)	119; 30.7 (5.4)	113; 30.2 (5.6)	115; 31.0 (5.6)	109; 30.4 (5.3)	106; 31.4 (5.3)	104; 29.8 (6.4)
Dutch Eating Behavior Questionnaire								
Restrained eating	134; 2.8 (0.8)	135; 2.7 (0.8)	120; 3.0 (0.7)	113; 2.9 (0.8)	116; 3.1 (0.7)	109; 3.0 (0.8)	107; 3.0 (0.8)	103; 2.9 (0.8)
External eating	134; 2.8 (0.7)	135; 2.9 (0.8)	120; 2.5 (0.7)	113; 2.8 (0.8)	116; 2.5 (0.8)	109; 2.7 (0.8)	107; 2.4 (0.8)	103; 2.7 (0.8)
Emotional eating	134; 2.3 (0.9)	135; 2.4 (1.1)	120; 2.2 (0.9)	113; 2.4 (1.1)	116; 2.1 (1.0)	109; 2.4 (1.1)	107; 2.1 (0.9)	103; 2.3 (1.1)
Mental health								
Eating Disorder Examination-Questionnaire 8	134; 3.8 (1.0)	135; 3.8 (0.9)	119; 3.6 (1.2)	113; 3.6 (1.1)	116; 3.6 (1.1)	109; 3.8 (1.1)	107; 3.5 (1.2)	104; 3.5 (1.1)
Patient Health Questionnaire-Depression	134; 6.5 (4.2)	135; 6.5 (4.3)	118; 6.1 (4.3)	113; 6.2 (5.2)	114; 6.2 (4.6)	109; 6.2 (5.2)	106; 6.3 (4.7)	103; 6.1 (5.2)
Impact of Weight on Quality of Life-Lite								
Physical function	133; 32.6 (9.4)	135; 32.9 (9.2)	120; 30.6 (9.9)	113; 31.2 (10.1)	116; 29.4 (9.8)	108; 29.6 (10.0)	107; 28.2 (9.9)	104; 31.0 (10.2)
Self-esteem	133; 20.5 (8.1)	135; 20.8 (8.2)	120; 19.1 (8.0)	113; 19.4 (8.2)	116; 17.5 (7.6)	108; 18.7 (8.0)	107; 17.0 (7.5)	104; 18.6 (8.2)
Sexual life	129; 9.1 (4.9)	131; 9.3 (5.2)	116; 9.0 (5.2)	109; 9.2 (5.4)	113; 8.4 (5.0)	106; 8.3 (5.2)	100; 8.0 (5.0)	102; 8.3 (5.3)
Public distress	134; 10.5 (4.3)	135; 11.1 (4.9)	119; 9.7 (4.3)	112; 10.4 (4.7)	115; 9.4 (4.2)	108; 10.9 (5.3)	107; 9.0 (4.1)	104; 10.7 (5.3)
Work	133; 7.9 (3.3)	135; 8.1 (4.0)	119; 7.4 (3.5)	112; 7.8 (4.0)	115; 6.9 (3.2)	109; 7.8 (4.3)	107; 6.7 (2.8)	104; 7.9 (4.2)

Secondary outcome	Pretreatment		Posttreatment		6-month follow-up		12-month follow-up	
	CRT	Control	CRT	Control	CRT	Control	CRT	Control
	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>	<i>N; M (SD)</i>
Physical health								
Waist circumference, cm	134; 126.3 (16.0)	136; 128.6 (15.8)	119; 125.8 (14.2)	105; 126.7 (17.1)	106; 124.7 (15.0)	102; 126.0 (16.6)	91; 123.7 (14.4)	89; 126.8 (16.1)
Hip circumference, cm	134; 140.1 (14.9)	135; 140.4 (14.3)	119; 139.5 (13.4)	105; 138.8 (17.4)	106; 137.8 (13.9)	102; 137.2 (14.3)	91; 136.1 (14.6)	89; 137.8 (14.6)
Blood pressure systolic, mm Hg	128; 143.6 (20.7)	129; 142.6 (17.9)	116; 140.9 (19.7)	100; 139.9 (17.0)	103; 141.0 (18.3)	99; 141.0 (16.5)	90; 139.5 (17.1)	87; 142.4 (19.1)
Blood pressure diastolic, mm Hg	128; 90.4 (12.8)	129; 89.5 (11.5)	116; 89.1 (11.0)	100; 88.7 (10.2)	103; 88.8 (12.6)	99; 88.1 (10.5)	90; 86.7 (11.4)	87; 87.6 (10.9)
Triceps skinfolds, mm	134; 47.5 (15.3)	134; 45.8 (12.8)	119; 46.7 (12.3)	104; 48.2 (14.5)	107; 47.0 (14.5)	101; 46.8 (13.0)	91; 45.8 (12.1)	89; 46.1 (12.5)
Subscapularis skinfolds, mm	134; 39.7 (12.8)	136; 39.5 (13.1)	119; 40.2 (10.8)	104; 40.7 (14.3)	107; 40.8 (11.3)	101; 40.6 (11.8)	91; 39.3 (10.7)	89; 35.5 (9.8)
Bioelectrical impedance analysis								
Fat mass, %	131; 51.2 (9.0)	131; 51.6 (8.6)	117; 51.6 (9.0)	102; 51.2 (8.7)	106; 51.1 (9.1)	100; 50.0 (9.2)	90; 50.4 (9.3)	88; 49.1 (8.8)
Total body water, %	131; 39.5 (5.3)	131; 39.3 (5.0)	117; 39.2 (5.7)	102; 39.0 (5.2)	106; 39.4 (5.2)	100; 39.8 (5.3)	90; 39.9 (5.9)	88; 40.4 (5.0)
Executive functioning								
Iowa Gambling Task, total net score	134; -3.70 (29.69)	135; -8.06 (31.05)	119; -0.12 (32.42)	107; -4.26 (33.80)	-	-	-	-
Delay Discounting Task, area under the curve	132; 0.46 (0.32)	136; 0.50 (0.31)	118; 0.49 (0.34)	107; 0.50 (0.32)	-	-	-	-
Vienna Test System INHIB, n commission errors	131; 10.39 (6.54)	132; 10.87 (7.12)	118; 8.83 (5.89)	106; 10.46 (7.74)	-	-	-	-
Trail Making Test-B, sec completion	131; 35.09 (17.71)	132; 36.90 (15.50)	118; 33.83 (15.75)	106; 34.91 (14.52)	-	-	-	-
Wisconsin Card Sorting Test, n perseverative errors	132; 20.71 (11.27)	134; 20.81 (11.49)	118; 16.85 (11.36)	107; 17.32 (11.74)	-	-	-	-
Tower of London Task, n correct solutions	131; 15.24 (3.22)	131; 14.46 (3.41)	118; 15.68 (3.16)	106; 14.99 (3.79)	-	-	-	-

eTable 4

Exploratory Analyses of Weight Change by Group and Behavioral Weight Loss (BWL) Treatment Intensity in Intent-to-treat Analyses

Weight change	6-month follow-up						12-month follow-up					
	Group × BWL program intensity			BWL program intensity			Group × BWL program intensity			BWL program intensity		
	<i>B</i> 95% CI	<i>p</i>	β	<i>B</i> 95% CI	<i>p</i>	β	<i>B</i> 95% CI	<i>p</i>	β	<i>B</i> 95% CI	<i>p</i>	β
Weight change, %	0.83	0.568	0.03	-2.21	0.005	-0.09	1.15	0.542	0.04	-3.93	<0.001	-0.15
	-2.02, 3.67			-3.76, -0.67			-2.56, 4.86			-5.97, -1.90		
Weight change, kg	1.22	0.523	0.05	-2.80	0.007	-0.11	1.38	0.584	0.05	-5.22	<0.001	-0.20
	-2.54, 4.99			-4.81, -0.79			-3.59, 6.35			-7.86, -2.58		
Weight change, BMI	0.45	0.500	0.06	-0.92	0.010	-0.13	0.48	0.582	0.07	-1.72	<0.001	-0.25
	-0.86, 1.75			-1.61, -0.22			-1.23, 2.19			-2.64, -0.80		

Note. Coefficients and *p* values derived from linear mixed models of Group × BWL program intensity or of BWL program intensity, respectively. Negative estimates indicate greater weight loss (in patients enrolled in the high-intensity BWL program). Significant *p* values are bolded, $p < .05$.

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Statistical Analysis Plan (SAP)
- Final Analysis -
Cognitive Remediation Therapy (CRT)
A randomized, controlled clinical trial

Principal Investigator

Biometry / Project management

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Coordinating investigator

Biometrician

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1 Introduction

The purpose of this document is to provide a detailed elaboration of the statistical analysis described in the protocol, including detailed procedures for the confirmatory analysis of the primary and secondary endpoints and other variables.

The Statistical Analysis Plan (SAP) assumes familiarity with the Study Protocol. If in doubt, the study protocol formulation takes precedence.

The SAP is based on the planned analysis specification as written in the study protocol, section 7 “Biometrical Aspects” and on those described in a published paper on the protocol. If there are discrepancies between the two, the published version takes precedence.

The software environment for statistical computing R (version $\geq 3.5.3$) will be used for statistical analyses (R Core Team 2019). Multiple imputation will be performed using the `mice` package (version $\geq 3.4.0$) (Buuren 2012; Buuren and Groothuis-Oudshoorn 2018).

2 Endpoints and further variables

2.1 Primary endpoint

Primary endpoint is the percent weight change at 6-month follow-up (t2) compared with pre-treatment (t0), both derived from objectively measured body weight (variable AGEW).

2.2 Secondary endpoints

- Percent weight change between baseline (t0) and post-CRT-treatment (t1) and 12-month follow-up (t3), derived from objectively measured body weight, will be evaluated in order to inform about treatment effects on early weight loss and on weight loss maintenance.
- Executive functioning (t0, t1), assessed through:
 - Vienna Test System (VTS) (Response Inhibition, Tower of London, Trail Making Test)
 - Iowa Gambling Task (IGT)
 - Delay Discounting and Probability (DDP)
 - Wisconsin Card Sorting Test (WCST)
- Weight loss related behaviour (t0 – t3)
 - Self-efficacy (GSES)
 - Eating behaviour (DEBQ)
 - Physical activity (IPAQ)
- Adherence to a weight loss regime
 - Attendance to BWL sessions and retention

- Mental health (t0 – t3)
 - Eating disorder psychopathology (EDEQ)
 - General psychopathology (PHQ-9)
 - Quality of life (IWQoL-Lite)
- Physical health (t0 – t3)
 - Hip and waist circumference
 - Blood pressure
 - Bioelectrical impedance (fat mass, total body water)
 - Triceps and subscapularis skinfolds

2.3 Further variables

The following potential covariates are assessed:

- Sociodemographic variables (t0)
- Measures of intelligence (t0)
 - Vienna Test System (Raven’s Advanced Progressive Matrices)
- Working memory (t0)
 - Vienna Test System (N-Back)
- Alertness (t0)
 - Vienna Test System (WAF-Alertness)
- Food addiction (t0)
 - Yale Food Addiction Scale 2.0
- Expectations and motivation (t0)

2.3.1 Baseline characteristics

The following characteristics of the trial population at baseline will be calculated / reported descriptively by randomization arm.

- Sex
- Age
- Nationality (German vs. other)
- Education (high vs. low)
- Body weight (Kg)
- BMI score

- Proportion of obese class, based on BMI score¹
- Anthropometric parameters (e.g. skin folds, waist circumference)
- Expectations and motivation
- Comorbidities
- The remaining secondary endpoints

This list may be modified for the publication.

2.3.2 Trial intervention

Adherence to therapy in the intervention arm will be assessed using descriptive statistics of the number of sessions attended, which may include a graphic depicting of the proportion that attended each of the 8 group sessions.

The number of patients in the per protocol set (see below) will also be provided along with the reasons as to why the remainder of the patients are not included in it.

2.3.3 Predictor variables

Predictor variables are assessed at t0 and include all outcome variables, sociodemographic variables, weight history, expectations and motivation (rated on an 11-point Likert scale from 0 (not at all) to 10 (completely)) and compliance with CRT. In addition, patient evaluation of CRT is assessed at t1 (0 (not at all) to 10 (completely)).

3 General analysis definitions

3.1 Analysis populations

The *confirmatory analysis* will be based on all randomized patients (full analysis set, FAS) according to the arm to which they were randomized.

Secondary endpoints will also be analysed based on the FAS.

The Per-Protocol Set (PPS) is made up of those patients randomised to the CRT arm without major protocol violation who attended ≥ 5 CRT sessions and provided data for the primary endpoint.

Major protocol violations are:

- baseline BMI < 35 kg/m²
- bariatric surgery (performed before t2)
- pregnancy or lactation (before t2)

¹Class I: $30 \text{ kg/m}^2 \leq \text{BMI} < 35 \text{ kg/m}^2$; Class II: $35 \text{ kg/m}^2 \leq \text{BMI} < 40 \text{ kg/m}^2$; Class III: $\text{BMI} \geq 40 \text{ kg/m}^2$

3.2 Subgroups

No subgroup analyses were pre-specified in the study protocol. Exploratory subgroup analyses – if performed – will be clearly labelled as such.

4 Planned analysis

A flowchart according to the CONSORT statement will describe all patients registered to the trial detailing withdrawals, drop-outs and inclusion in the analysis sets defined above. It will also provide details regarding treatment and assessment completion.

Standard methods of descriptive statistics will be used always indicating the number of valid values, frequencies, mean (standard deviation), minimum, maximum and/or quartiles (median [25%; 75%]), depending on the scale and distribution. Summary statistic will be reasonably rounded to avoid pseudo-precision.

4.1 Demographic and other baseline parameters

Demographic and other baseline parameters will be described for the whole ITT population and by randomization arm.

4.2 Primary endpoint

A partially nested mixed-effects model ([Candlish et al. 2018](#)) with the stratification variables (sex, age > 45 years) randomisation arm and baseline weight as fixed effects and the CRT group modelled as a partially nested random effect will be used to determine the efficacy of CRT compared with no treatment regarding the percent weight change at 6-month follow-up (t2) compared with pre-treatment (t0), both derived from objectively measured body weight. The model can be specified with the following R code:

```
lme4::lmer(  
  # dependent variable  
  percent_weight_change_t0_t2 ~  
  # fixed effects  
  sex + age_categorical + arm + weight_baseline +  
  # random effect (partially nested)  
  (0 + arm_random | crt_group)  
)
```

If data on body weight in either arm are missing “six months after BWL therapy” (t2), then multiple imputation will be performed assuming that drop-outs do not have weight loss on average. Multiple imputations will also take into account baseline body weight, body height, sex, age, and BWL program and attendance. Imputed values will be drawn 50 times. The nested term in the random

effect for intervention patients who never attended a CRT session will be treated on the same footing as control patients. In the ITT analysis, these patients remain part of the intervention arm. For technical reasons, a new variable must be introduced to model the random effect. In the new variable (`arm_random`), the values of 1 vs. 0 are assigned to all patients who attended at least one CRT group session vs. attended no CRT group session at all. If patients undergo bariatric surgery or become pregnant, all anthropometric measures (including body weight) will be set to missing.

Sensitivity analyses will use:

1. linear regression models for both absolute and percent weight change with randomization arm, stratification variables, pretreatment weight, and attendance to BWL treatment as covariates;
2. the linear-mixed regression model from the primary analysis in the complete case sample;
3. a linear model analysis comparing percent weight change for patients in the CRT arm with good protocol adherence versus control patients, controlling for pretreatment weight.

4.3 Secondary endpoints

For percent weight change between baseline (t_0) and post-CRT-treatment (t_1) and 12-month follow-up (t_3), the same analysis strategy will be used as for the primary analysis.

Change in body weight over time for the whole ITT population will be analysed using a partially nested mixed-effects model having the structure of a repeated measures analysis with the absolute weight difference to baseline for post-CRT, 6 and 12-month follow-up as a dependent variable. As fixed effects, we include the stratification variables (sex, age > 45 years), randomisation arm, baseline weight, a categorical time variable and BWL therapy programme (AOK-Plus vs. not AOK-Plus) into the model. Random effects will be modelled for subjects (not nested) and CRT group (partially nested). The model can be specified with the following R code:

```
lme4::lmer(  
  # dependent variable  
  delta_body_weight(t1, t2, t3) ~  
  # no intercept  
  -1 +  
  # fixed effects  
  arm +  
  sex +  
  age_categorical +  
  time_categorical +  
  weight_baseline +  
  bwl_programme +  
  # random effect (not nested)  
  (1 | subject) +
```



```
# random effect (partially nested)
(0 + arm_random | crt_group)
)
```

To assess differences between the randomisation arms at each follow-up, a partially nested mixed-effects model with body weight at t0, t1, t2 and t3 as a dependent variable will be analysed. As fixed effects, we include the stratification variables (sex, age > 45 years), randomisation arm, a categorical time variable and BWL therapy programme into the model. Interactions will be modelled for time and randomisation arm. Random effects will be modelled for subjects (not nested) and CRT group (partially nested). The model can be specified with the following R code:

```
lme4::lmer(
  # dependent variable
  body_weight(t0, t1, t2, t3) ~
  # fixed effects
  time_categorical +
  arm +
  sex +
  age_categorical +
  bwl_programme +
  # interaction
  arm:time_categorical +
  # random effect (not nested)
  (1 | subject) +
  # random effect (partially nested)
  (0 + arm_random | crt_group)
)
```

Regarding executive functioning, a partially nested mixed-effects model with the absolute difference between the score at the end of CRT (t1) and the pretreatment score (t0) as the dependent variable will be analysed. As fixed effects we include the stratification variables (sex, age > 45 years), randomisation arm, and the pretreatment score into the model. Partially nested random effects will be modelled for the CRT group. The model can be specified with the following R code:

```
lme4::lmer(
  # dependent variable
  score_t1 - score_t0 ~
  # fixed effects
  arm + sex + age_categorical +
  score_baseline +
  # random effect (partially nested)
```

```
(0 + arm_random | crt_group)
)
```

The statistics of change in each endpoint between baseline and post-CRT follow-up regardless of the randomisation arm will be derived from mixed-effects models with absolute change between baseline score and the score at the end of CRT as the dependent variable. As fixed effects we will include the stratification variables (sex, age > 45 years), and randomisation arm into the model. Random intercepts will be modelled for subjects and partially nested random effects will be modelled for the CRT group. The model can be specified with the following R code:

```
lme4::lmer(
  # dependent variable
  delta_score(t0, t1) ~
  # fixed effects
  arm +
  time_categorical +
  sex +
  age_categorical +
  score_baseline +
  # random effect (not nested)
  (1 | subject) +
  # random effect (partially nested)
  (0 + arm_random | crt_group)
)
```

For questionnaire-based endpoints, a partially nested mixed-effects model having the structure of a repeated measures analysis will be used. In this model, the score at baseline, post-CRT follow-up, 6-month, and 12-month follow-up will be treated as the dependent variable. As fixed effects we include the stratification variables (sex, age > 45 years), randomisation arm, and a categorical time covariate into the model. Interactions will be modelled for randomisation arm and time (categorical). As random effect (not nested), we will have an intercept for subjects. Partially nested random effects will be modelled for the CRT group. The model has the same structure as specified in the second code chunk in Section 4.3.

The statistics of change over time regardless of the randomisation arm will be analysed using a partially nested mixed-effects model having the structure of a repeated measures analysis. The absolute change between baseline, post-CRT follow-up, 6-month follow-up, and the end of BWL therapy will be treated as the dependent variable. As fixed effects we will include the stratification variables (sex, age > 45 years), randomisation arm, the baseline score and a categorical time covariate into the model. As random effect (not nested), we will have an intercept for subjects. Partially nested random effects will be modelled for the CRT group. The model has the same

structure as specified in the first code chunk in Section 4.3.

Multiple imputation will account for missing data taking into account the baseline value of the relevant variable, the relevant variable's value at t1 or t1 and t2 (for endpoints measured at t2 and t3 respectively), sex, age, and adherence to BWL therapy. Imputed values will be drawn 50 times.

5 Appendix

5.1 Methods for determining psychological scores

Psychological scores are calculated using the R `qscorer` package, which is hosted on [GitHub](#). The package may be obtained upon request from the [author](#).

If not otherwise specified, scores are only calculated, if no more than 20% of items have missing values.

5.1.1 Eating Disorder Examination Questionnaire (EDE-Q8)

The EDE-Q8 is evaluated following the guidelines specified in ([Kliem et al. 2016](#)). The mean score is calculated as long as at least four questions (50%) have been answered. The EDE-Q8-score uses the following variables: EDEQ1 to EDEQ8.

R-Syntax

```
# data: data.frame
# items: EDE-Q8 items ordered from 1 to 8
scoring_edeq8 <- function(data, items) {
  library(dplyr)
  if (min(data[, items], na.rm = T) < 0) {
    stop("Minimum possible value for items is 0")
    break
  }
  if (max(data[, items], na.rm = T) > 6) {
    stop("Maximum possible value for items is 6")
    break
  }
  data %>%
    mutate(
      nvalid.edeq8 = rowSums(!is.na(select(., items))),
      score.temp = rowSums(select(., items), na.rm = TRUE) / nvalid.edeq8,
      score.edeq8 = ifelse(nvalid.edeq8 >= 4, round(score.temp, 1), NA)
    ) %>%
    select(-score.temp)
}
```

5.1.2 Dutch Eating Behaviour Questionnaire (DEBQ)

The DEBQ (German version) is evaluated following the guidelines specified in (Nagl et al. 2016). Mean scores are calculated as long as at least 25% of the questions from the sub-score have been answered. The sub-score for *restrained eating* uses variables DEBQ5, DEBQ7, DEBQ10, DEBQ12, DEBQ13, DEBQ15, DEBQ19, DEBQ21, DEBQ24 and DEBQ27. The sub-score for *emotional eating* uses variables DEBQ1, DEBQ4, DEBQ6, DEBQ8, DEBQ9, DEBQ11, DEBQ14, DEBQ17, DEBQ22 and DEBQ30. The sub-score for *external eating* uses variables DEBQ2, DEBQ3, DEBQ16, DEBQ18, DEBQ20, DEBQ23, DEBQ25, DEBQ26, DEBQ28 and DEBQ29.

R-Syntax

```
# data: data.frame
# items: DEBQ items ordered from DEBQ1 to DEBQ30
scoring_debq <- function(data, items) {
  library(dplyr)
  if (min(data[, items], na.rm = T) < 1) {
    stop("Minimum possible value for items is 1")
    break
  }
  if (max(data[, items], na.rm = T) > 5) {
    stop("Maximum possible value for items is 5")
    break
  }
  items.emo <- items[c(1, 4, 6, 8, 9, 11, 14, 17, 22, 30)]
  items.ext <- items[c(2, 3, 16, 18, 20, 23, 25, 26, 28, 29)]
  items.res <- items[c(5, 7, 10, 12, 13, 15, 19, 21, 24, 27)]
  data %>%
  mutate(
    nvalid.debq.emo = rowSums(!is.na(select(., items.emo))),
    nvalid.debq.ext = rowSums(!is.na(select(., items.ext))),
    nvalid.debq.res = rowSums(!is.na(select(., items.res))),
    score.debq.emo = ifelse(nvalid.debq.emo >= 3,
      round(rowSums(select(., items.emo), na.rm = TRUE) /
        nvalid.debq.emo, 1), NA
    ),
    score.debq.ext = ifelse(nvalid.debq.ext >= 3,
      round(rowSums(select(., items.ext), na.rm = TRUE) /
        nvalid.debq.ext, 1), NA
    ),
```

```

    score.debq.res = ifelse(nvalid.debq.res >= 3,
      round(rowSums(select(., items.res), na.rm = TRUE) /
        nvalid.debq.res, 1), NA
    )
  ) %>%
  mutate(score.debq.tot = round(rowMeans(select(.,
    score.debq.emo:score.debq.res), na.rm = FALSE), 1))
}

```

5.1.3 General Self-Efficacy Scale (GSES)

The GSES (German version) is evaluated following the guidelines specified in (Schwarzer and Jerusalem 1999). The sum score is calculated unless no more than three items on the ten-item scale are missing. The GSES-score uses the following variables: GSES1 to GSES10.

R-Syntax

```

# data: data.frame
# items: GSES items ordered from GSES1 to GSES10
scoring_gses <- function(data, items) {
  library(dplyr)
  if (min(data[, items], na.rm = T) < 1) {
    stop("Minimum possible value for items is 1")
    break
  }
  if (max(data[, items], na.rm = T) > 4) {
    stop("Maximum possible value for items is 4")
    break
  }
  data %>%
  mutate(
    nvalid.gses = rowSums(!is.na(select(., items))),
    mean.temp = rowSums(select(., items), na.rm = TRUE) / nvalid.gses
  ) %>%
  mutate_at(
    vars(items),
    funs(ifelse(is.na(.), as.integer(mean.temp), .))
  ) %>%
  mutate(
    score.temp = rowSums(select(., items), na.rm = TRUE),

```

```

    score.gses = ifelse(nvalid.gses >= 7, as.integer(score.temp), NA)
  ) %>%
  select(-mean.temp, -score.temp)
}

```

5.1.4 Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (depression scale from PHQ) is evaluated following the guidelines specified in (Kroenke et al. 2010). Questionnaires with up to two missing values are scored, replacing any missing values with the average score of the completed items (Arrieta et al. 2017). The PHQ-9 total score ranges from 0 to 27. Scores of 5, 10, 15, and 20 represent cutpoints for mild, moderate, moderately severe and severe depression, respectively (Kroenke et al. 2010). The PHQ-9-score uses the following variables: PHQD1A to PHQD1I.

R-Syntax

```

# data: data.frame
# items: PHQ-9 items ordered from PHQD1A to PHQD1I
scoring_phq9 <- function(data, items) {
  library(dplyr)
  if (min(data[, items], na.rm = T) < 0) {
    stop("Minimum possible value for items is 0")
    break
  }
  if (max(data[, items], na.rm = T) > 3) {
    stop("Maximum possible value for items is 3")
    break
  }
  items <- enquos(items)
  data %>%
    mutate(
      nvalid.phq9 = rowSums(!is.na(select(., !!!items))),
      mean.temp = rowSums(select(., !!!items), na.rm = TRUE) / nvalid.phq9
    ) %>%
    mutate_at(
      vars(!!!items),
      funs(ifelse(is.na(.), round(mean.temp), .))
    ) %>%
    mutate(
      score.temp = rowSums(select(., !!!items), na.rm = TRUE),

```

```

score.phq9 = ifelse(nvalid.phq9 >= 7, as.integer(score.temp), NA),
cutoff.phq9 = case_when(
  score.phq9 >= 20 ~ "Severe",
  score.phq9 >= 15 ~ "Moderately Severe",
  score.phq9 >= 10 ~ "Moderate",
  score.phq9 >= 5 ~ "Mild",
  score.phq9 < 5 ~ "Minimal"
),
cutoff.phq9 = factor(cutoff.phq9, levels = c(
  "Minimal",
  "Mild",
  "Moderate",
  "Moderately Severe",
  "Severe"
))
) %>%
select(-ends_with("temp"))
}

```

5.1.5 Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite)

The IWQOL-Lite is evaluated following the guidelines specified in (Kolotkin et al. 2001). The *Physical Function* score uses variables IWQOLB1 to IWQOLB11, the *Self-esteem* score uses variables IWQOLP1 to IWQOLS7, the *Sexual Life* score uses variables IWQOLSB1 to IWQOLSB4, the *Public Distress* score uses variables IWQOLP1 to IWQOLP1, and the *Work* score uses questions IWQOLA1 to IWQOLA4. All sub-scores are calculated if at least 80% of the questions have been answered. The total score is calculated if no sub-score is missing.

R-Syntax

```

# data: data.frame
# items: IWQOL Lite items ordered from 1 to 31
scoring_iwqoll <- function(data, items) {
  if (min(data[, items], na.rm = T) < 1) {
    stop("Minimum possible value for items is 1")
    break
  }
  if (max(data[, items], na.rm = T) > 5) {
    stop("Maximum possible value for items is 5")
    break
  }
}

```



```

}
# items <- enquos(items)
data %>%
  mutate_at(vars(items), funs(6 - .)) %>% # recode all items
  mutate(
    nvalid.iwqol.ts = rowSums(!is.na(select(., items))),
    mean.iwqol = rowSums(select(., items), na.rm = TRUE) / nvalid.iwqol.ts,
    nvalid.iwqol.pf = rowSums(!is.na(select(., items[1:11]))),
    nvalid.iwqol.se = rowSums(!is.na(select(., items[12:18]))),
    nvalid.iwqol.sl = rowSums(!is.na(select(., items[19:22]))),
    nvalid.iwqol.pd = rowSums(!is.na(select(., items[23:27]))),
    nvalid.iwqol.wo = rowSums(!is.na(select(., items[28:31]))),
  ) %>%
  mutate_at(vars(items), funs(ifelse(is.na(.), round(mean.iwqol), .))) %>%
  mutate(
    score.iwqol.pf = rowSums(select(., items[1:11]), na.rm = TRUE),
    score.iwqol.pf = ifelse(nvalid.iwqol.pf >= 6, round(score.iwqol.pf), NA),
    score.iwqol.se = rowSums(select(., items[12:18]), na.rm = TRUE),
    score.iwqol.se = ifelse(nvalid.iwqol.se >= 4, round(score.iwqol.se), NA),
    score.iwqol.sl = rowSums(select(., items[19:22]), na.rm = TRUE),
    score.iwqol.sl = ifelse(nvalid.iwqol.sl >= 2, round(score.iwqol.sl), NA),
    score.iwqol.pd = rowSums(select(., items[23:27]), na.rm = TRUE),
    score.iwqol.pd = ifelse(nvalid.iwqol.pd >= 3, round(score.iwqol.pd), NA),
    score.iwqol.wo = rowSums(select(., items[28:31]), na.rm = TRUE),
    score.iwqol.wo = ifelse(nvalid.iwqol.wo >= 2, round(score.iwqol.wo), NA),
    score.iwqol.ts = rowSums(select(., items), na.rm = TRUE),
    score.iwqol.ts = ifelse(nvalid.iwqol.ts >= 24, round(score.iwqol.ts), NA)
  ) %>%
  select(-starts_with("mean"))
}

```

5.1.6 Yale Food Addiction Scale, Version 2.0 (YFAS V2.0)

The YFAS V2.0 is evaluated following the guidelines specified in (Meule et al. 2017). A symptom count summarizes how many of the 11 substance use disorder (SUD) criteria an individual endorsed with respect to the consumption of highly palatable foods. Based on the symptom count, three different severity levels of SUD as specified in DSM-5 can be calculated (“mild” with ≥ 2 symptoms, “moderate” with ≥ 4 symptoms, “severe” with ≥ 6 symptoms). For the symptom count, the following variables are used: YFAS1 to YFAS35.

R-Syntax

```
# data: data.frame
# items: YFAS 2.0 items ordered from 1 to 35
scoring_yfas <- function(data, items) {
  if (min(data[, items], na.rm = T) < 0) {
    stop("Minimum possible value for items is 0")
    break
  }
  if (max(data[, items], na.rm = T) > 7) {
    stop("Maximum possible value for items is 7")
    break
  }
  data %>%
    mutate_at(
      vars(items[c(9, 10, 19, 27, 33, 35)]),
      funs(ifelse(. >= 2, 1, 0))
    ) %>%
    mutate_at(
      vars(items[c(8, 18, 20, 21, 34)]),
      funs(ifelse(. >= 3, 1, 0))
    ) %>%
    mutate_at(
      vars(items[c(3, 11, 13, 14, 22, 28, 29)]),
      funs(ifelse(. >= 4, 1, 0))
    ) %>%
    mutate_at(
      vars(items[c(5, 12, 16, 17, 23, 24, 26, 30, 31, 32)]),
      funs(ifelse(. >= 5, 1, 0))
    ) %>%
    mutate_at(
      vars(items[c(1, 2, 4, 6, 7, 15, 25)]),
      funs(ifelse(. >= 6, 1, 0))
    ) %>%
    mutate(
      score.yfas.act = ifelse(rowSums(select(
        .,
        items[c(8, 10, 18, 20)]
      )), na.rm = TRUE) >= 1, 1, 0),
```

```
score.yfas.amo = ifelse(rowSums(select(
  ,,
  items[c(1, 2, 3)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.att = ifelse(rowSums(select(
  ,,
  items[c(4, 25, 31, 32)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.con = ifelse(rowSums(select(
  ,,
  items[c(22, 23)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.cra = ifelse(rowSums(select(
  ,,
  items[c(29, 30)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.obl = ifelse(rowSums(select(
  ,,
  items[c(19, 27)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.pro = ifelse(rowSums(select(
  ,,
  items[c(9, 21, 35)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.sit = ifelse(rowSums(select(
  ,,
  items[c(28, 33, 34)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.tim = ifelse(rowSums(select(
  ,,
  items[c(5, 6, 7)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.tol = ifelse(rowSums(select(
  ,,
  items[c(24, 25)]
), na.rm = TRUE) >= 1, 1, 0),
score.yfas.wit = ifelse(rowSums(select(
  ,,
  items[c(11:15)]
```

```

    ), na.rm = TRUE) >= 1, 1, 0)
  ) %>%
  mutate(
    score.yfas.sympnum = rowSums(select(
      .,
      starts_with("score.yfas")
    ), na.rm = TRUE),
    score.yfas.imp = ifelse(rowSums(select(
      .,
      items[c(16, 17)]
    ), na.rm = TRUE) >= 1, 1, 0),
    cutoff.yfas.foodadd = case_when(
      score.yfas.sympnum >= 6 & score.yfas.imp == 1 ~ "Severe",
      score.yfas.sympnum >= 4 & score.yfas.imp == 1 ~ "Moderate",
      score.yfas.sympnum >= 2 & score.yfas.imp == 1 ~ "Mild",
      is.na(score.yfas.sympnum) | is.na(score.yfas.imp) ~ NA_character_,
      TRUE ~ "None"
    ),
    cutoff.yfas.foodadd = factor(cutoff.yfas.foodadd,
      levels = c("Severe", "Moderate", "Mild", "None")
    )
  )
}

```

5.1.7 International Physical Activity Questionnaire, short form (IPAQ)

The IPAQ short form is evaluated following the guidelines specified in (IPAQ-group 2005). Data are summarized according to the physical activities recorded (walking, moderate, and vigorous activities) and estimated time spent sitting per week. Activity scores are calculated weighting the reported minutes per week within each activity category by a MET (Metabolic Equivalent of Task) energy expenditure estimate assigned to each category of activity (Craig et al. 2003). Based on the activity scores, three levels of physical activity can be differentiated. (“low”², “moderate”³, “high”⁴). For the evaluation of *vigorous activities*, the variables IPAQ1AT to IPAQ1BM and for the evaluation of *moderate activities* the variables IPAQ2AT to IPAQ2BM will be used. *Walking time per*

²Individuals not meeting for categories “medium” or “high” are considered low/inactive.

³Any one of the following 3 criteria must be fulfilled: (1) 3 or more days of vigorous activity of at least 20 minutes per day or (2) 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day or (3) 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week

⁴Any one of the following 2 criteria must be fulfilled: (1) Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week or (2) 7 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 3000 MET-minutes/week.

week is measured using the variables IPAQ3AT to IPAQ3BM and *sitting time per week* is measured using the variables IPAQ4H and IPAQ4M.

R-Syntax

```
# data: data.frame
# items: IPAQ items ordered from 1 to 11
# bweight: body weight in kg
scoring_ipaqsf <- function(data, items, bweight) {
  bweight <- enqu(bweight)
  newvars <- c(
    "VigDays", "VigHours", "VigMin", "ModDays",
    "ModHours", "ModMin", "WalkDays", "WalkHours",
    "WalkMin", "SitHours", "SitMin"
  )
  data %>%
  mutate(
    VigDays = as.double(unlist(data[items[1]])),
    VigHours = as.double(unlist(data[items[2]])),
    VigMin = as.double(unlist(data[items[3]])),
    ModDays = as.double(unlist(data[items[4]])),
    ModHours = as.double(unlist(data[items[5]])),
    ModMin = as.double(unlist(data[items[6]])),
    WalkDays = as.double(unlist(data[items[7]])),
    WalkHours = as.double(unlist(data[items[8]])),
    WalkMin = as.double(unlist(data[items[9]])),
    SitHours = as.double(unlist(data[items[10]])),
    SitMin = as.double(unlist(data[items[11]]))
  ) %>%
  # If number of days == 0, set hours and minutes to 0
  # If number of days is missing, set hours and minutes to missing
  mutate_at(vars(VigHours, VigMin), funs(case_when(
    VigDays == 0 ~ 0,
    is.na(VigDays) ~ as.numeric(NA),
    TRUE ~ .
  ))) %>%
  mutate_at(vars(ModHours, ModMin), funs(case_when(
    ModDays == 0 ~ 0,
    is.na(ModDays) ~ as.numeric(NA),
    TRUE ~ .
  )))
```

```

))) %>%
mutate_at(vars(WalkHours, WalkMin), funs(case_when(
  WalkDays == 0 ~ 0,
  is.na(WalkDays) ~ as.numeric(NA),
  TRUE ~ .
))) %>%
mutate(
  # If number of hours is missing, but number of minutes is not missing,
  # set hours = 0
  # If number of minutes is missing, but number of hours is not missing,
  # set minutes = 0
  VigHours = ifelse(!is.na(VigDays) & !is.na(VigMin) &
    is.na(VigHours), 0, VigHours),
  VigMin = ifelse(!is.na(VigDays) & !is.na(VigHours) &
    is.na(VigMin), 0, VigMin),
  ModHours = ifelse(!is.na(ModDays) & !is.na(ModMin) &
    is.na(ModHours), 0, ModHours),
  ModMin = ifelse(!is.na(ModDays) & !is.na(ModHours) &
    is.na(ModMin), 0, ModMin),
  WalkHours = ifelse(!is.na(WalkDays) & !is.na(WalkMin) &
    is.na(WalkHours), 0, WalkHours),
  WalkMin = ifelse(!is.na(WalkDays) & !is.na(WalkHours) &
    is.na(WalkMin), 0, WalkMin),
  SitHours = ifelse(!is.na(SitMin) & is.na(SitHours), 0, SitHours),
  SitMin = ifelse(!is.na(SitHours) & is.na(SitMin), 0, SitMin),
  # Calculate Variables
  vminday = VigHours * 60 + VigMin,
  mminday = ModHours * 60 + ModMin,
  wminday = WalkHours * 60 + WalkMin,
  sminday = SitHours * 60 + SitMin
) %>%
mutate(
  totalhourday = ifelse(is.na(vminday) + is.na(mminday) +
    is.na(wminday) + is.na(sminday) > 2,
  NA, round(rowSums(select(., ends_with("minday")), na.rm = TRUE) / 60, 1)
),
  vminwk = VigDays * vminday,
  mminwk = ModDays * mminday,
  wminwk = WalkDays * wminday,

```

```

sminwk = sminday * 7,
sumpa = ifelse(is.na(vminday) + is.na(mminday) + is.na(wminday) > 2,
  NA, rowSums(select(., matches("[vmw]minday")), na.rm = TRUE)
),
sumday = ifelse(is.na(VigDays) + is.na(ModDays) + is.na(WalkDays) > 2,
  NA, rowSums(select(., ends_with("Days")), na.rm = TRUE)
),
excMin = ifelse(sumpa > 960, TRUE, FALSE),
excDay = ifelse(sumday > 21, TRUE, FALSE),
exc16h = ifelse(totalhourday > 16, TRUE, FALSE),
vminday = ifelse(vminday < 10, 0, vminday),
mminday = ifelse(mminday < 10, 0, mminday),
wminday = ifelse(wminday < 10, 0, wminday),
vminwkMET = 8 * vminwk,
mminwkMET = 4 * mminwk,
wminwkMET = 3.3 * wminwk,
MET = vminwkMET + mminwkMET + wminwkMET,
kilocalories = MET * (!bweight / 60),
pacat = case_when(
  VigDays >= 3 & MET >= 1500 ~ "High",
  sumday >= 7 & MET >= 3000 ~ "High",
  VigDays >= 3 & vminday >= 20 ~ "Moderate",
  ModDays + WalkDays >= 5 & mminday + wminday >= 30 ~ "Moderate",
  sumday >= 5 & MET >= 600 ~ "Moderate",
  is.na(VigDays) | is.na(vminday) | is.na(mminday) |
  is.na(wminday) | is.na(sumday) ~ as.character(NA),
  TRUE ~ "Low"
),
pacat = factor(pacat, levels = c("High", "Moderate", "Low"))
) %>%
select(-newvars) %>%
mutate_at(
  vars(vminwkMET:kilocalories),
  list(~ ifelse(excMin == TRUE | excDay == TRUE, NA, .))
) %>%
rename_at(vars(vminday:pacat), list(~ paste0("ipaq.", .)))
}

```

5.1.8 Iowa Gambling Task (IGT)

Data will be extracted from the `IGT_output.csv` file as exported from the *Inquisit* software (Millisecond 2015). Performance in the IGT will be evaluated using the *Total Net Score* (TNS). The TNS is calculated by subtracting the value of the variable `TotalBestWorst` from zero.

5.1.9 Wisconsin Card Sorting Test (WCST)

Data will be extracted from the `wcst-report.txt` files (one file for each subject and measurement) as exported from the *Inquisit* software. For analysis, the variable “Perseverative Errors” will be used.

5.1.10 Delay Discounting and Probability (DDP)

Data will be extracted from the `DPDT-summary.iqdat` files (one file for each subject and measurement) as exported from the *Inquisit* software. For the calculation of the area under the curve (AUC), the following variables will be used: `values.t1_ip` to `values.t5_ip` (obtained indifference point estimates for the five different probabilistic ‘delays’), and `values.t1_ip_found` to `values.t5_ip_found` (values reflecting whether an indifference point has been successfully determined (‘1’) or not (‘0’)).

R-Syntax

```
library(dplyr)

# 'Maximum' amount of money to use throughout the task.
ip.max <- 10

# Values for the five temporal delays in days.
time.norm <- c(t1 = 0, t2 = 2, t3 = 30, t4 = 180, t5 = 365)

df.DDP <- df.DDP %>%
  mutate(
    values.t1_ip.rec = ip.max,
    values.t2_ip.rec = ifelse(values.t2_ip_found == 1, values.t2_ip,
      (values.t1_ip + values.t2_ip) / 2
    ),
    values.t3_ip.rec = ifelse(values.t3_ip_found == 1, values.t3_ip,
      (values.t2_ip + values.t4_ip) / 2
    ),
    values.t4_ip.rec = ifelse(values.t4_ip_found == 1, values.t4_ip,
```



```

      (values.t3_ip + values.t5_ip) / 2
    ),
    values.t5_ip.rec = ifelse(values.t5_ip_found == 1, values.t5_ip,
      values.t4_ip
    ),
    values.t1_ip.norm = values.t1_ip.rec / ip.max,
    values.t2_ip.norm = values.t2_ip.rec / ip.max,
    values.t3_ip.norm = values.t3_ip.rec / ip.max,
    values.t4_ip.norm = values.t4_ip.rec / ip.max,
    values.t5_ip.norm = values.t5_ip.rec / ip.max,
    time.t1.norm = time.norm["t1"] / max(time.norm),
    time.t2.norm = time.norm["t2"] / max(time.norm),
    time.t3.norm = time.norm["t3"] / max(time.norm),
    time.t4.norm = time.norm["t4"] / max(time.norm),
    time.t5.norm = time.norm["t5"] / max(time.norm)
  ) %>%
mutate(DDT_AUC = ifelse(values.t1_ip_found + values.t2_ip_found +
  values.t3_ip_found + values.t4_ip_found +
  values.t5_ip_found > 0,
  (abs(values.t1_ip.norm + values.t2_ip.norm) / 2 * (time.t2.norm - time.t1.norm)) +
  (abs(values.t2_ip.norm + values.t3_ip.norm) / 2 * (time.t3.norm - time.t2.norm)) +
  (abs(values.t3_ip.norm + values.t4_ip.norm) / 2 * (time.t4.norm - time.t3.norm)) +
  (abs(values.t4_ip.norm + values.t5_ip.norm) / 2 * (time.t5.norm - time.t4.norm)),
  NA
)) %>%
select(-ends_with("rec"), -ends_with("norm"))

```

5.1.11 Vienna Test System (VTS)

Data will be extracted from the following SPSS-files: *APM.sav*, *INHIB.sav*, *NBACK.sav*, *TMT.sav*, *TOL.sav*, and *WAFSA.sav*. The following VTS modules and variables will be evaluated:

- Trail Making Test (*TMT.sav*)
 - BTB (Working time – Part B: Measure of cognitive flexibility)
- Tower Of London (*TOL.sav*)
 - COR (Planning ability: Measure of the ability to plan ahead in a given context on the basis of clear rules)
- Raven's Advanced Progressive Matrices (*APM.sav*)

- SET1 (Total of correct answers: Estimate of the respondent’s general intelligence)
- N-Back (NBACK.sav)
 - TR (Correct and omissions: Measure of the ability to maintain and constantly update visual memory representations)
- Response Inhibition (INHIB.sav)
 - FA (Number of commission errors: Measure of the effectiveness of the inhibition process obtained by measuring the absence of inhibition)

5.2 Abbreviations

AE	Adverse event
BMI	Body mass index
BWL	Behavioural weight loss
CRF	Case Report Form
CRT	Cognitive Remediation Therapy
FAS	Full analysis set
ITT	Intent to treat
MET	Metabolic Equivalent of Task
PPS	Per protocol set
SAE	Serious adverse event
SUD	Substance use disorder

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