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Research paper

Efficacy of an internet-delivered cognitive enhancement intervention for subjective residual cognitive deficits in remitted major depressive disorder: A randomized crossover trial

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A B S T R A C T

Background: Cognitive deficits such as difficulties with attention, memory, and executive functions are frequently reported during remission from depression and relates to adverse functioning in daily life and risk of relapse. There is therefore a need for interventions targeting cognitive deficits after depression. However, few randomized controlled trials have investigated the efficacy of interventions targeting subjective residual cognitive deficits in adults remitted from depression.
Methods: This randomized crossover trial aimed to investigate the efficacy of an internet-delivered cognitive enhancement intervention on subjective residual cognitive deficits. Forty-four formerly depressed adults (89 % female;mean age = 39 years) were included. Twenty-three participants received the intervention, and 21 participants were assigned to a waitlist control group. The waitlist control group received the intervention after seven weeks. Analyses of follow-up assessment after six months were conducted for the combined sample.
Results: Significant differences were found between the intervention and waitlist control group in subjective cognitive functioning ($d = 1.83$) and rumination ($d = 1.65$). There was a difference in symptoms of depression between the groups ($d = 1.22$), whereas symptoms of depression increased in the waitlist control, but not in the intervention group. Fewer participants in the waitlist control group (43 %), compared to the intervention group (78 %) showed reliable improvement in self-reported cognitive deficits after receiving the intervention.
Limitations: Findings should be interpreted with caution due to the small sample, and lack of an active control group.
Conclusions: Internet-delivered cognitive enhancement interventions may improve subjective cognitive deficits. Waiting time to receive cognitive enhancement interventions may worsen symptoms and treatment response.

1. Introduction

Depression is a highly prevalent mood disorder that stands as a leading cause of burden of disease worldwide (WHO, 2017). Depression is characterized by high relapse rates, with approximately 50 % of individuals experiencing relapse of depression after their first episode (Eaton et al., 2008). In addition to the core symptoms of low mood and loss of interest, cognitive deficits are frequently observed in patients with depression (Rock et al., 2014). Among individuals suffering from depression, between 73 % and 67 % report problems with concentration and memory, respectively (Srisurapanont et al., 2015). Specifically, individuals suffering from depression report that their minds drift away, they forget appointments, and have problems maintaining focus during activities such as reading (Fehnel et al., 2016; Srisurapanont et al., 2018). In line with this, depression is related to reduced performance on neuropsychological tests measuring executive functions, attention, and memory (Rock et al., 2014).

The cognitive deficits observed during the acute state of depression often persist as residual symptoms (Christensen et al., 2020; Conradi et al., 2011; McClintock et al., 2011), which involves difficulties with aspects of cognition after the core symptoms of depression are normalized. A study showed that 44 % of formerly depressed adults self-reported residual cognitive deficits (Conradi et al., 2011). Moreover, a meta-analysis found that individuals in remission from depression performed worse on 73 % of administered neuropsychological tests compared to healthy controls (Semkovska et al., 2019). These deficits impact daily functioning in important areas such as work, school, and home (Saragoussi et al., 2018), leading to emotional distress and

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increased risk of depression relapse (Lorimer et al., 2020; Schmid and Hammar, 2021).

Studies indicate that there are none or weak associations between subjectively reported cognitive deficits and performance on neuropsychological tests (Hagen et al., 2023; Ott et al., 2016). Specifically, among depressed individuals, subjective experiences of cognitive deficits are more pronounced than those observed in neuropsychological tests performance (Lahr et al., 2007; Svendsen et al., 2012). This discrepancy may be attributed to negative beliefs about cognitive functioning and resources, leading to lack of motivation and self-efficacy in undertaking cognitive complex tasks (Suhr and Wei, 2013; Tran et al., 2021). Ruminating on these negative beliefs might also occupy cognitive resources away from daily life tasks (Levens et al., 2009). Therefore, there is a need for interventions that target subjective residual cognitive deficits, as well as the negative beliefs and rumination associated with these deficits.

Cognitive enhancement interventions show promise in improving cognitive deficits during remission from depression (Miskowiak et al., 2022). These interventions may include biological and behavioral approaches. Behavioral approaches to cognitive enhancement often include elements such as psychoeducation, drill-and-practice cognitive exercises, and/or strategy training (Douglas et al., 2019). These may also involve active guidance from a therapist (Vita et al., 2021). Behavioral cognitive enhancement interventions may also be combined with other psychological interventions, such as cognitive behavioral therapy, to adress the negative belifes associated with cognitive deficits (Porter et al., 2017).

Results from the few studies investigating behavioral cognitive enhancement interventions are mixed regarding the impact on subjective residual cognitive deficits. An open feasibility trial including remitted individuals testing working memory training (Cogmed) did not show improvement in subjective cognitive functions and rumination (Hammar et al., 2022). A recent open pilot trial conducted by our research group investigated the outcomes of a guided internet-delivered cognitive enhancement intervention specifically developed to target subjective residual cognitive deficits. Planning and development of the intervention was based on qualitative research with formerly depressed adults and experienced therapists (Myklebost et al., 2022b). This intervention included psychoeducation, strategy training, attention training, in addition to techniques from other psychological interventions to address rumination and negative beliefs associated with cognitive deficits. Results from the pilot study showed significant improvements in self-reported cognitive functions and rumination (Myklebost et al., 2022a). A follow-up study showed that the improvements persisted over the two-year period (Myklebost et al., 2023). However, the efficacy of the tailored intervention has not yet been tested in a randomized controlled trial.

A few randomized controlled trials have investigated behavioral cognitive enhancement interventions in remitted adults. One trial showed that formerly depressed adults completing computerized cognitive control training (adaptive PASAT) reported improvements in self-reported cognitive functions and rumination (Hoorelbeke and Koster, 2017). Another trial found drill-and-practice cognitive training (CogniPlus) combined with psychoeducation and strategy guidance, compared to being in a passive control group, improved self-reported psychosocial functioning (Listunova et al., 2020b). Lastly, a randomized controlled trial showed that formerly depressed adults improved their psychosocial functioning after receiving functional training combined with computerized cognitive training (Vicent-Gil et al., 2022). Taken together, the results from interventions addressing cognitive deficits after depression are promising and should be further investigated.

The aim of the current study is to investigate the efficacy of a tailored internet-delivered behavioral cognitive enhancement intervention on residual cognitive deficits through a crossover randomized controlled study. Participants in the waitlist control group crossed over and received the intervention after seven weeks. The following hypotheses were investigated in this study:

1. The intervention group will show larger improvements in self-reported residual cognitive deficits and rumination compared to the waitlist control group.
2. Symptoms of depression will not change in the intervention nor the waitlist control group due to participants being remitted at inclusion.
3. Improvements in self-reported residual cognitive deficits and rumination are expected after crossover, while no change is expected in symptoms of depression.
4. There will be no change in outcomes from post-assessment to six-month follow-up assessments.

2. Methods

2.1. Study design

The study was a randomized crossover trial with follow-up assessment after six months.

2.2. Participants and procedures

The participants were recruited between April 2021 to October 2023 through social media and posters in public areas. Those interested in participating in the study underwent a telephone screening interview led by a clinical psychologist or a psychiatric nurse. The inclusion and exclusion criteria were assessed during the interview. The inclusion criteria were: (a) having previously received psychological or medical treatment for depression in primary or secondary health care services, (b) currently exhibiting minor symptoms of depression (<12 on the MADRS-S; Svanborg and Åsberg, 2001), (c) not fulfilling the diagnostic criteria for depression within the last 12 weeks (MINI Mental Neuropsychiatric Interview; Leiknes et al., 1999), (d) self-reporting cognitive deficits affecting functioning in daily life domains, which was assessed by a clinical psychologist, (e) not changing the dosage of antidepressive medication during the intervention period, (f) age between 18 and 65 years, and (f) having access to the internet. The exclusion criteria were: (a) ongoing substance abuse, (b) neurological conditions or brain damage affecting cognitive functioning (e.g. multiple sclerosis, autism, brain tumor), (c) life-time bipolar disorder, and (d) life-time psychosis.

Informed consent was collected from eligible participants before they received digital baseline measures (T1). After baseline assessments participants were randomly assigned to either the intervention group or a waitlist control group using a data generated randomization list. The intervention group then started the treatment, and received post-assessments after completing the intervention, whereas the waitlist group was re-assessed seven weeks after baseline assessment (T2). The waitlist control group then crossed over to receive the intervention. Participants in the crossover waitlist control group completed post-treatment assessments after completing the intervention (T3). Six-months after completing the intervention, both groups received a follow-up assessment (T4). At this time participants were also offered a brief telephone call from their therapist to summarize their experiences in the follow-up period.

A total of 44 participants were included in the trial. Among the included participants were 23 assigned to the intervention group and 21 to the control group. Participant flow is presented in Fig. 1.

2.3. Intervention

To ensure that the user perspective was taken into consideration, the development of the intervention was guided by the person-based approach (Yardley et al., 2015) which involved qualitative research with individuals in remission from depression and therapists experienced with internet-delivered interventions (Myklebost et al., 2022b).

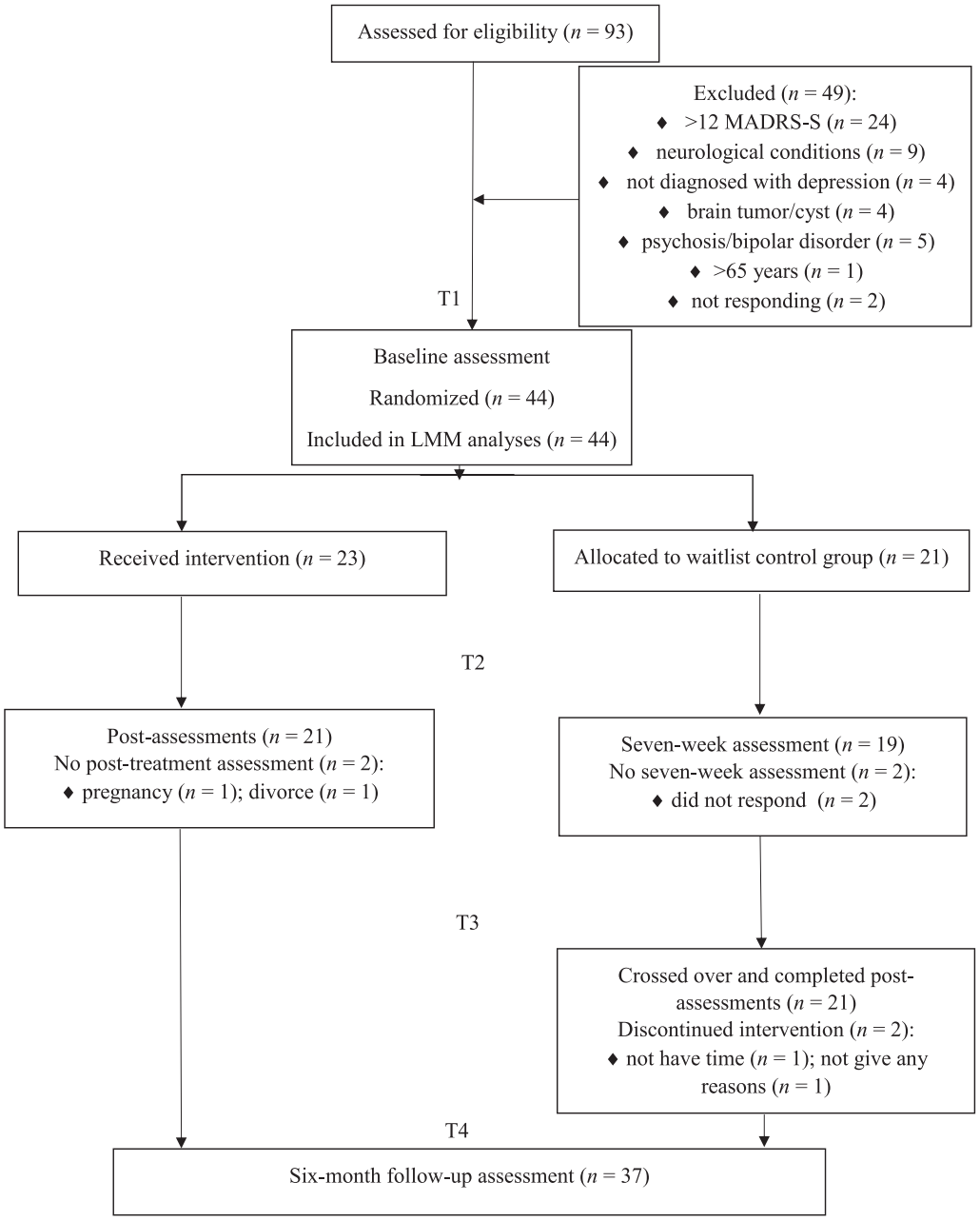

Fig. 1. Participant flow diagram.
Note. LMM analyses: linear mixed model analyses.

The intervention consisted of ten modules that were provided to the participants in a linear approach starting with module 1 and finishing with module 10. The mean of completed modules was 9.38. Participants were encouraged to complete the intervention within five weeks, but the program was available up to nine weeks. This implicated completion of two modules each week. The mean of days in treatment was 43.08 days. The intervention addressed common residual deficits such as difficulties with attention, memory, social cognition, and executive functions, in addition negative beliefs and rumination. The cognitive tasks included in the intervention consisted of both drill-and-practice training based on a restorative approach, and strategy training based on a compensatory approach. Participants self-tailored the intervention by selecting the training or strategies, within each module, that they found relevant to apply in their daily life. A brief weekly telephone guidance was provided by a clinical psychologist or trained nurse to support participants in setting goals, understanding intervention content, and monitoring symptoms of depression. The therapists assessed participants work within the modules and based on this provided new modules in a linear approach. The intervention content, rehabilitation approach, theory, and mechanisms are presented in Table 1.

2.4. Ethics

The study was approved by the Regional Committee for Medical Research Ethics of Western Norway (204287) and was conducted in accordance with the Helsinki Declaration of Ethical Research (World Medical Association, 2013). Pre-registration of the study was done at ClinicalTrials.gov (NCT04864353).

Table 1
Overview of intervention.

Modules	Main content/rehabilitation and theorical approaches	Mechanisms
1. Introduction	Practical information on how to use the internet-delivered intervention. Setting personal goals.	Increasing insight and goal management.
2. Attention training	Adapted attention training technique (Siegle et al., 2007; Wells, 1990). *Based on a restorative approach.* Recognizing worries and negative thoughts about cognitive deficits and using cognitive restructuring techniques to promote helpful thoughts. *Based on cognitive behavioral therapy*.	Improving cognitive control. Modification of maladaptive thoughts.
3.Attention in daily life	Using self-talk during complex tasks, taking breaks, and removing distractions. *Based on a compensatory approach.*	Establishing habits and implicit learning.
4.Rumination	Postponing rumination and worries and writing down ruminative thoughts and worries. *Based on meta-cognitive theory.* Gratitude exercise (Emmons and McCullough, 2003). *Based on positive psychology*.	Reducing rumination and increasing positive emotions.
5.Memory aids	Rephrasing and repeating information, using notebooks and calendars, and preparing before meetings. *Based on a compensatory approach.*	Establishing habits and implicit learning.
6.Memory training	Categorizing information (e.g. chunking, mind maps), creating mental images, method of loci, and matching situations with strategies. *Based on a compensatory approach.*	Establishing habits and implicit learning.
7.Executive functioning	Sorting and organizing surroundings and using an activity day planner. *Based on a compensatory approach.*	Establishing habits and implicit learning.
8.Problem-solving	Utilizing a 7-step problem solving model with reflection tasks. *Based on a compensatory approach.*	Establishing habits and implicit learning.
9.Social cognition	Practicing active listening, asking questions, maintaining eye contact, and reducing distractions. *Based on a compensatory approach.*	Establishing habits and implicit learning.
10.Recap of modules	Summarizing intervention modules and planning strategies to use post-intervention. *Based on a compensatory approach.*	Implementing durable changes in habits and implicit learning to daily life.
Features common across modules	Psychoeducation on cognitive deficits and strategies/training tasks. "Your story": describing experiences with cognitive deficits in daily life and coping. Monitoring sub-goals. Vignettes of others with similar difficulties. My plan: self-tailoring of tasks to implement in daily life. Weekly therapist support. *Based on self-determination theory* (Ryan and Deci, 2000) *and common factor guiding principles* (Yardley et al., 2015).	Increasing: insight, knowledge, hope, motivation, relatedness, competence, autonomy, and generalization of newly acquired skills.

2.5. Measures

2.5.1. Subjective residual cognitive deficits

The Behavior Rating Inventory of Executive Function-Adult Global Executive Composite (BRIEF-A GEC; Roth et al., 2005) was used as primary outcome measure to assess subjective residual cognitive deficits. The measure consists of 75-items where participants rate the frequency at which they experience cognitive deficits in daily life as "never", "sometimes", or "often". Higher scores indicate more perceived cognitive difficulties. Responses can be organized into the following nine sub-scales: Inhibit, Shift, Self-monitor, Emotional control, Working memory, Plan/Organize, Task monitor, and Organization of materials. These sub-scales can be combined to comprise the Global Executive Composite (GEC). The BRIEF-A has shown high levels of internal consistency and been validated (Ciszewski et al., 2014; Roth et al., 2005). Cronbach's alpha at pre-screening was 0.96.

The Perceived Deficits Questionnaire-Depression 5-item (PDQ-5: Sullivan et al., 1990) is a five-item questionnaire used to assess subjective residual cognitive deficits. Shorter measures of cognitive deficits, such as the PDQ-5, are relevant to explore because they may be feasible tools for clinicians to use in routine care and are less burdensome for patients to complete. The PDQ-5 measures difficulties with concentration, memory, and executive functioning. Items are rated on a scale from 0 (never) to 4 (almost always). Higher scores indicate greater severity of cognitive deficits. Cronbach's alpha at pre-screening was 0.67.

2.5.2. Rumination

The Rumination Response Scale (RRS: Treynor et al., 2003) was used to assess self-reported ruminative responses to depressed mood. The RRS is a 22-item questionnaire where items are rated from 1 (almost never) to 4 (almost always). Higher scores reflect greater levels of rumination. The RRS has been found to be a reliable and valid measure of rumination (Johnson et al., 2008; Roelofs et al., 2006). Cronbach's alpha at pre-screening was 0.90.

2.5.3. Symptoms of depression

The Patient Health Questionnaire (Spitzer et al., 1999) was used to measure self-reported symptoms of depression. The PHQ-9 comprises nine items where participants rate the severity of depression symptoms from 0 to 3. Higher scores indicate more severe symptoms of depression. Previous studies have demonstrated the reliability and validity of the PHQ-9. Cronbach's alpha at pre-screening was 0.40.

2.6. Statistical analyses

All analyses were conducted using STATA version 17.0. Summary statistics (Chi^2 and independent samples *t*-tests) were used to evaluate potential between-group differences in background and outcome variables at pre-treatment assessments. The threshold for statistical significance was set to $p < .05$.

Two separate sets of random intercepts, fixed slopes, linear mixed model analyses were conducted.

The first set of models were estimated to evaluate between group differences in outcomes between the intervention group and waitlist control group. Separate random intercept fixed slope models were estimated for each outcome measure. Intervention efficacy was represented as an intervention group (0 = waitlist control, 1 = intervention group) x time (0 = T1, 1 = T2) interaction term, entered alongside a separate fixed effects term representing time. Paired sample t-tests were used to assess change in outcome variables for the control group.

The second set of models were estimated to evaluate changes for the whole crossover sample in outcome variables over time from pre-treatment assessment to post-treatment assessment and from post-treatment assessment to the six-month follow-up assessment. Separate random intercept fixed slope models were estimated for each outcome measure. Two dummy variables were entered into the model as fixed

effects, one representing change from pre-treatment assessment to post-treatment assessment (0 = pre-treatment assessment, 1 = post-treatment assessment and six-month follow-up assessment) and one representing change from post-treatment assessment to six-months follow-up assessment (0 = pre-treatment assessment and post-treatment assessment, 1 = six-month follow-up assessment).

Cohen's d effect sizes were calculated to evaluate the magnitude of group level change. For the between groups set of models, Cohen's d was calculated based on methods suggested by Morris (2008) for pre-treatment and post-treatment control group designs. For the within subjects set of models, Cohen's d was calculated from estimated means for both baseline assessment to post-treatment assessment change and post-treatment to follow-up assessment change.

To examine the number of participants who exhibited reliable change in the BRIEF-A GEC, we calculated the Reliable Change Index (RCI). The upper- and lower-bound cut-off values for reliable change (RC) was calculated using the following formula: RC boundaries = $0 \pm \mathrm{SD}^* \sqrt{2^*(1-\mathrm{r})}$. Participants exhibiting a pre-treatment to post-treatment change above or below the upper and lower RC boundaries were classified as having achieved reliable deterioration or improvement respectively. Participants exhibiting pre-treatment to post-treatment change scores within the RC boundaries were classified as not having achieved any reliable change. Chi-square analyses were conducted to determine if the number of participants showing reliable improvement was significantly associated with the intervention group.

All participants were included in the linear mixed models, in accordance with an intention to treat framework assuming missing data to be missing at random (Rubin, 1976). Linear mixed models were carried out using the Restricted Maximum Likelihood (REML) method for linear mixed models. The Satterthwaite approximation was selected for estimating degrees of freedom.

3. Results

3.1. Sample characteristics, baseline comparisons and post-hoc analysis

A total of 44 participants were included in the study sample and randomized to either the intervention group (n = 23) or the waitlist control group (n = 21). The sample consisted of 89 % females and 11 % men, these gender categories were the only available response alternatives. The mean age was 39 years, and 85 % of the participants had completed higher education. On average, participants had experienced three episodes of depression and 41 % had been depressed for more than two years. Participants demographics are presented in Table 2. There were no significant differences in baseline demographic variables across the two groups. Differences were observed in some clinical variables. The participants in the waitlist control group scored lower on the BRIEF-A (t = −2.3, p = .013) as well as on the RRS (t = −0.2.15, p = .019).

Post-hoc power calculations shows that the study's power was 98.5 %.

Table 2
Overview of demographic variables and history of depression at baseline.

Variables	Total *n*/*M* (*SD*)	IG *n*/*M* (*SD*)	WCTR *n*/*M* (*SD*)
Age	38.09 (11.45)	38.50 (10.52)	37.67 (12.6)
Female	39	22	17
Partner	23	12	11
Higher education	35	20	15
Antidepressant	6	4	2
Depression episodes	3.02 (2.70)	3.13 (2.85)	2.91 (2.59)
Duration depression			
<1 year	10	4	6
<2 years	16	12	4
<5 years	10	4	6
≥5 years	8	3	5

Note. *M*: mean; *SD*: standard deviation; IG: intervention group; WCTR: waitlist control group.

3.2. Between-groups analyses

Table 3 summarizes the results from the between groups linear mixed models analyses. In contrast to the waitlist control group, the intervention group showed significant improvement from pre-treatment assessment (T1) to post-treatment assessment (T2) across the two primary outcome measures (BRIEF-A, PDQ-5) and secondary outcome measures (PHQ-9, RRS). Estimated change (regression coefficient beta) represented symptom reduction for all outcome variables.

3.2.1. Primary outcomes

There were significant differences between the intervention group and waitlist control group, and large between group effect sizes on the primary outcome measures BRIEF-A (d = 1.83) and PDQ-5 (d = 1.00). Results from paired sample t-test showed that the waitlist control group did not change significantly on the BRIEF-A (t = −0.45, p = .349) or PDQ-5 (t = 1.18, p = .873) from T1 to T2. Examining within group effect sizes for change from T1 to T2 these were large for the intervention group across both BRIEF-A (d = 2.09) and for PDQ-5 (d = 1.26). In contrast, effect sizes for the waitlist control group were small across both the BRIEF-A (d = 0.31) and the PDQ-5 (d = 0.20).

3.2.2. Secondary outcomes

There were significant differences between the intervention group and waitlist control group, and large between group effect sizes on the secondary outcome measures PHQ-9 (d = 1.22) and RRS (d = 1.65). Results from paired sample t-tests showed an increase in levels of rumination and symptoms of depression measured by the RRS (t = −3.08, p = .003) and PHQ-9 (t = −1.99, p = .031) for the waitlist control group. Examining within group effect sizes for change from T1 to T2 for the control group, these were both large for the RRS (d = 1.15) and PHQ-9 (d = 1.06). In contrast, within group effect sizes for change across these outcomes for the intervention group were small for the PHQ-9 (d = 0.24) and large for the RRS (d = 1.28). Looking at the direction of change observed for the RRS in the intervention group, this large effect size represents a reduction in rumination.

3.2.3. Reliable change analyses

For the primary outcome BRIEF-A, we calculated RCI to identify the number of participants within each group, who exhibited reliable change. Based on these calculations, change in excess of ±13.64 was defined as representing reliable change.

Between T1 and T2, 18 participants in the intervention group showed reliable improvement in their BREIF-A scores, while three participants remained unchanged, and none deteriorated. In the waitlist control group, one participant exhibited reliable improvement, 16 participants remained unchanged, and two participants deteriorated during the same period.

Results from the chi-square analysis showed that the number of participants improving was associated with being in the intervention group (p = .000).

3.3. Within-subjects analyses

Table 4 summarizes the results from the crossover linear mixed model analyses.

3.3.1. Primary outcomes

There was a reduction in the BRIEF-A and PDQ-5 from pre-treatment assessment (T1 for the intervention group and T2 for the waitlist control group) to post-treatment assessment (T2 for the intervention group and T3 for the waitlist control group). The effect sizes for the change between pre-treatment to post-treatment assessments were large. From post-treatment assessment to follow-up assessment (T4 for both groups)

Table 3
Results from linear mixed model analyses of differences in outcomes between the intervention group and waitlist control group.

		T1		T2		Time		Group*Time		*ES*
		M (*SD*)		*M* (*SD*)		*p*	*b*	*p*	*b*	*d*
BRIEF	IG	138.04	(17.17)	105.10	(16.96)	0.695	−1.48	<0.001	−29.20	1.83
	WCTR	127.19	(13.75)	128.53	(18.08)					
PDQ-5	IG	10.04	(3.35)	5.95	(2.82)	0.358	−0.71	<0.001	−3.50	1.00
	WCTR	10.05	(3.51)	9.44	(2.81)					
PHQ-9	IG	5.26	(2.12)	4.75	(3.43)	0.005	2.35	0.006	−2.69	1.22
	WCTR	4.91	(2.12)	7.44	(4.19)					
RRS	IG	43.17	(9.01)	32.60	(10.27)	0.006	4.50	<0.001	−13.51	1.65
	WCTR	37.95	(6.83)	43.72	(10.40)					

Note. T1: Baseline (Total $N = 44$, IG n = 23, WCTR n = 21); T2: post-intervention assessment for the intervention group or seven-week assessment for the waitlist control group (Total N with no missing values = 40, IG $n = 21$, WCTR $n = 19$); BRIEF: Behavior Rating Inventory of Executive Function Adult Global Executive Composite; PDQ-5: Perceived Deficits Questionnaire-Depression 5-item; PHQ-9: Patient Health Questionnaire; RRS: Rumination Response Scale; *M*: mean; *SD*: standard deviation; *b*: regression coefficient; *ES*: Cohen's d effect size. IG: intervention group; WCTR: waitlist control group.

Table 4
Overview of the results from the linear mixed models analyses of within-subject change in outcomes.

	Pre T1/T2	Post T2/T3	FU T4	Pre to post			Post to FU		
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*p*	*b*	*d*	*p*	*b*	*d*
Outcomes									
BRIEF	133.74 (18.02)	106.52 (17.35)	111.18 (21.24)	<0.001	−26.42	1.49	0.041	6.19	0.32
PDQ-5	9.78 (3.10)	5.35 (2.81)	5.46 (2.66)	<0.001	−4.39	1.44	0.832	0.11	0.04
PHQ-9	6.22 (3.34)	4.90 (3.16)	6.71 (4.12)	0.083	−1.05	0.33	0.003	1.94	0.51
RRS	43.41 (9.52)	33.03 (8.90)	33.18 (9.37)	<0.001	−9.14	0.99	0.456	0.94	0.09

Note. N with no missing values: Pre = 44, Post = 40, FU = 37; BRIEF: Behavior Rating Inventory of Executive Function-Adult Global Executive Composite; PDQ-5: Perceived Deficits Questionnaire-Depression 5-item; PHQ-9: Patient Health Questionnaire; RRS: Rumination Response Scale; *b*: regression coefficient (beta); *d*: Cohen's d. effect size statistics are calculated from differences between time points; *M*: mean; *SD*: standard deviation; IG: intervention group; WCTR: waitlist control group; Pre: IG T1/WCTR T2; Post: IG T2/WCTR T3; FU: follow-up after six months (T4 both groups).

there was no change in the PDQ-5, but there was a significant increase in the BRIEF-A. Despite this significant increase on the BRIEF-A, within group effect sizes from pre-treatment assessment to follow-up assessment were large for both the BRIEF-A ($d = 1.15$), and the PDQ-5 ($d = 1.40$).

3.3.2. Secondary outcomes

There was a significant reduction in the RRS from pre-treatment assessment (T1 for the intervention group and T2 for the waitlist control group) to post-assessment (T2 for the intervention group and T3 for the waitlist control group). The effect sizes for the change between pre-treatment to post-treatment assessments for the RRS were large. There was no significant change in the PHQ-9. From post-assessment to follow-up assessment (T4 for both groups) there was no significant change in the RRS, but there was a significant increase in the PHQ-9. Looking at the change from pre-treatment assessment to follow-up assessment, within group effect sizes were small for the PHQ-9 ($d = 0.24$), and large for the RRS ($d = 0.90$).

3.3.3. Reliable change analyses

Reliable change analyses were conducted for the whole sample to assess individual change from pre-treatment to post-treatment assessment and pre-treatment to follow-up assessment.

From pre-assessment to post-assessment,18 participants in the intervention group and nine participants in the waitlist control group show reliable improvement. In the intervention group were three participants unchanged, while eight participants in the waitlist control group did not change in the BRIEF-A. Between pre-assessment to follow-up assessment did 14 participants in the intervention group and 9 participants in the waitlist control group show reliable improvement. In the intervention group, five participants did not show change, two participants deteriorated, and two participants did not respond to the follow-up assessment. In the waitlist control group did six participants not change in the BRIEF-A, none of the participants deteriorated, while nine participants did not respond to the follow-up assessment.

Results from chi-square analyses indicated that the number of participants showing improvement from pre-treatment assessment to post-treatment assessment ($p = .016$) and pre-treatment assessment to follow-up assessment ($p = .032$) were associated with being in the intervention group.

4. Discussion

This study aimed to investigate the efficacy of an internet-delivered cognitive enhancement intervention in improving subjective residual cognitive deficits. The intervention was specifically developed to target subjective residual cognitive deficits in adults remitted from depression. Our first hypothesis, that the intervention group would show large improvements in subjective residual cognitive deficits and rumination compared to the waitlist control group, was supported. The second hypothesis, which stated that symptoms of depression would remain unchanged in both the intervention and waitlist control group were not supported, as the waitlist control group reported an increase in depression symptoms during the waiting period. Our third hypothesis, predicting improvements in subjective residual cognitive deficits and rumination after the crossover, while expecting no change in symptoms of depression was consistent with the results from the within-subject analyses. However, the fourth hypothesis, which suggested that there would be no change in outcomes from post-assessment to six-month follow-up assessments, was only partly supported, as there was a minor but significant increase in residual cognitive deficits (BRIEF-A) and symptoms of depression during this period.

As expected, there was a large difference in change for subjective residual cognitive deficits observed between participants receiving the intervention and those in the waitlist control group. The results indicate that the intervention is associated with experiencing less residual cognitive deficits, aligning with a previous randomized controlled trial investigating the efficacy of cognitive enhancement interventions in the

remitted phases of depression (Hoorelbeke and Koster, 2017). The results are also in accordance with the results from our previous pilot study (Myklebost et al., 2022a). Moreover, results from the reliable change analyses showed that 18 participants (78 %) who received the intervention showed a reliable improvement, in contrast to only one participant in the waitlist control group. Notably, the percentage of reliable improvers in the intervention group were larger than that reported in other cognitive enhancement trials for depressed and formerly depressed adults (Hagen et al., 2020; Listunova et al., 2020a). This also applies to our previous pilot study where 51 % of the participants had a reliable improvement (Myklebost et al., 2022a). However, fewer participants in the waitlist control group exhibited improvement (43 %) after crossing over to receive the intervention. One explanation for this finding is the difference in symptoms of depression and rumination from pre-treatment assessment to post-treatment assessments between the intervention group and waitlist control group. Symptoms of depression such as difficulties with initiating activities, diminished interests and rumination might have affected efforts to work with the intervention, thereby, reducing these participants response to the intervention. Overall, delaying provision of cognitive enhancement intervention for this patient group may have adverse consequences, including an increase in symptoms of depression and reduced response to cognitive enhancement interventions.

The durability of outcomes in this study was mixed. There was no change from post-treatment to follow-up assessments in one measure of subjective residual cognitive deficits (PDQ-5) and rumination (RRS), while there was an increase in the BRIEF-A measuring subjective residual cognitive deficits. There was still a large reduction in the BRIEF-A between pre-treatment and follow-up assessment. However, in our previous pilot study, we found that the scores on the BRIEF-A continued to decrease from post-treatment to six-month follow-up assessments. This discrepancy in results between these two studies might partly be a consequence of the waitlist control group in the current study not gaining as much effect as the intervention group. Another explanation is that most of the participants in the pilot study received a short follow-up telephone call from their therapist before responding to the six-month follow-up. Participants in the present study were offered telephone support after completing digital self-report measures, with only 5 participants accepting this. Taken together, this may suggest that therapist support in the follow-up period increases long-term effects.

Regarding symptoms of depression there was an increase from post-treatment to follow-up assessments. However, the level of depression symptoms at follow-up were similar as those at the pre-treatment assessment. This indicates little or no change in depression symptoms at group level from pre-treatment to follow-up assessment. Since participants needed to have a low symptom load to be included in this study, it was anticipated that there would be no substantial changes in symptoms of depression. This finding is consistent with a meta-analysis reporting that only studies including participants with higher symptom loads showed a reduction in symptoms of depression after three-months (Legemaat et al., 2022). In this study we lack data on how many participants had a relapse of depression in this period. However, long-term outcomes of our pilot study found that 40 % of the participants had a relapse after two years (Myklebost et al., 2023). In the present study participants on average had a history with three episodes of depression. The research literature shows that relapse rates are 50 % after a first episode of depression that increases with 16 % for each new episode (Eaton et al., 2008; Solomon et al., 2000). This indicates that the current sample is at risk of relapse. Stability of depression symptoms is therefore of importance. Further research reporting on long-term effects is still warranted.

4.1. Clinical implications

Findings from the present randomized crossover trial suggests that internet-delivered cognitive enhancement interventions may be promising in reducing subjective residual cognitive deficits. Furthermore, results indicate that prolonged waiting time for cognitive enhancement interventions might increase depression symptoms and therefore reduce treatment response. Notably, the current intervention was internet-delivered. Potentially meeting the challenge of access to cognitive enhancement intervention such as shortage of health care professionals and economic resources.

4.2. Limitations

The small sample size of this study limits the generalizability, and consequently the clinical implications of the findings. Nevertheless, the post-hoc power calculation indicate that the study was sufficiently powered for a waitlist control trial. Another limitation is that a waitlist control group cannot rule out placebo effects, and an active control group might therefore have been relevant to include in this trial. A limitation concerning the measures used in this study is that we employed only subjective measures and not objective neuropsychological tests. We therefore have limited insights into the efficacy of the intervention on objective cognitive deficits. However, subjective cognitive deficits are often more severe than those observed in performance on neuropsychological tests (Lahr et al., 2007) and are associated with reduced daily life functioning (Cha et al., 2017; Saragoussi et al., 2018). Self-reported cognitive deficits are therefore an important treatment target.

5. Conclusion

The present study indicates that the internet-delivered cognitive enhancement intervention might improve residual cognitive deficits and rumination in formerly depressed adults. Waiting time for the intervention may reduce treatment response, thus patients with residual cognitive deficits may be treated with cognitive enhancement therapy early in the recovery phase. However, the results must be interpreted with caution due to the small sample size and not using an active control group.

CRediT authorship contribution statement

Sunniva Brurok Myklebost: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Aleksander Heltne:** Writing – review & editing, Writing – original draft, Software, Formal analysis. **Åsa Hammar:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Tine Nordgreen:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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