Can Cognitive Remediation in Groups Prevent Relapses?

Results of a 1-Year Follow-up Randomized Controlled Trial

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Abstract: International guidelines define relapse prevention for schizophrenia patients as a key therapeutic aim. However, approximately 80% to 90% of schizophrenia patients experience further symptom exacerbation after the first episode. The purpose of this study was to investigate whether group integrated neurocognitive therapy (INT), a cognitive remediation approach, reduces relapse rates in schizophrenia outpatients. INT was compared with treatment as usual (TAU) in a randomized controlled trial. Fifty-eight stabilized outpatients participated in the study with 32 allocated to the INT group and 26 to the TAU group. A test battery was used at baseline, posttreatment at 15 weeks, and a 1-year follow-up. Relapse rates were significantly lower in the INT condition compared with TAU during therapy as well as at follow-up. The relapse rate after therapy was associated with significant reductions in negative and general symptoms, improvements in functional outcome, and overall cognition. Out of these variables, negative symptoms were identified to show the strongest association with relapses after therapy. The primary outcome of this study suggests that INT can prevent relapses in schizophrenia outpatients.

Key Words: Schizophrenia, RCT, psychological therapy, cognitive remediation, group therapy, relapse prevention

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Schizophrenia is a chronic and debilitating illness that is associated with reduced functioning and overall quality of life (Khalesi et al., 2019; Strauss et al., 2010). The majority of patients experience multiple relapses throughout the course of the illness, whereas only 10% to 20% of patients never have a recurrent episode after their first psychosis episode (Emsley et al., 2013). The resurgence of symptoms after stabilization is often referred to as a relapse. Such relapses can be associated with progressive functional deterioration, a decline in treatment response, worsening clinical outcomes, increasing caregiver burden, and an increased economic burden for families, society, and healthcare systems (Alphs et al., 2016; Pennington and McCrone, 2017; Rosenberg, 2009).

Many factors can contribute to symptom relapse. Antipsychotic medication has been shown to reduce relapses compared with placebo (Leucht et al., 2012); however, many patients with schizophrenia have trouble adhering to medication, which is ultimately a risk factor for relapse and a strong factor for overall recovery (Kane et al., 2018; Kishimoto et al., 2013). Although there are many dimensions to "recovery" (Roder et al., 2019; Whitley and Drake, 2010; Windell et al., 2012), symptom relapse remains a germane component of recovery. The discontinuation or reduction of antipsychotic medication seems to be the most common risk factor for relapse. Studies have revealed that approximately 50% of patients are not compliant with their medications, where the risk of relapse increases from 20% to 30% to 60% to 80% when patients do not take their medication consistently (Kane et al., 2018; Rosenberg, 2009). In fact, medication incompliance in first-episode patients leads to symptom resurgence between 41% and 79% within 12 months after a single episode and the likelihood of relapse increases to 96% after 24 months of medication incompliance (Emsley et al., 2013; Zipursky et al., 2014). As such, relapse prevention is at the forefront of goals to treatment response and recovery (Tibbo et al., 2014).

Given the personal, emotional, and economical costs associated with symptom relapse, it is important to delineate which additional interventions, besides medication, provide evidence for relapse prevention. There is a controversy about the efficacy of psychosocial interventions for relapse prevention in schizophrenia. The use of psychosocial interventions has shown effective reductions of relapse rates for some psychological treatments (*e.g.*, Jones et al., 2012; Pharoah et al., 2010; Xia et al., 2011). Specifically, studies using manualized psychoeducation programs and family therapy have demonstrated the strongest impact on relapse prevention up to 1-year follow-up (Pharoah et al., 2010; Xia et al., 2011). Relatively few studies have been conducted examining the efficacy of other psychological interventions, such as cognitive behavioral therapy for psychosis and social skills training (SST), on relapse prevention (*e.g.*, Jones et al., 2012; Kurtz and Mueser, 2008; Naeem et al., 2016; Revell et al., 2015; Turner et al., 2018).

Some studies have examined the impact of cognitive remediation (CR) therapy approaches for relapse prevention (*e.g.*, Kurtz et al., 2016; Trapp et al., 2013; Wykes et al., 2011). The CR effects on positive symptoms were generally described as small (McGurk et al., 2007) and as small to moderate regarding negative symptoms (Cella et al., 2017). These low effects may be in line with previous literature suggesting that positive symptoms may be independent of cognition and functioning (Green and Nuechterlein, 1999; Roder and Mueller, 2015). That said, there is evidence supporting an indirect association of cognition and relapse. Cognition is related to treatment adherence and therapeutic alliance, which is ultimately related to relapse rates (Alphs et al., 2016; Cella and Wykes, 2019; Higashi et al., 2013). The studies mentioned previously mainly used bottom-up neurocognitive training that utilize computer programs to improve basic neurocognitive domains (*e.g.*, attention, memory), which can have limited generalization effects. These interventions tend to have minimal emphasis on the therapeutic relationship, group interactions, and other variables of cognition (such as facets of social cognition including perception and attribution). There are, however, some CR variations and techniques that may help improve relapse rates. The intervention we have used in this study incorporated both a bottom-up and top-down approach that also builds on the therapeutic relationship, group interactions, and other facets of cognition. This type of intervention has previously shown a significant reduction of severe negative symptoms (integrated neurocognitive therapy [INT]; Mueller et al., 2017) and may have more generalizable effects in treatment response than basic bottom-up CR approaches. In this approach, CR for neurocognition is combined with CR for social cognition, a stress training task, and an emotion regulation task similar to the tasks that can be found in successful psychoeducation approaches for relapse prevention. Consequently, CR approaches focusing on therapeutic alliance and social cognition rather than only the use of computer programs, combining neurocognitive and social cognitive rehabilitation with tasks to regulate emotional stress experience, may potentiate their impact on relapse prevention.

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Although relapse prevention is among the top goals for treatment, it is often defined in different ways across studies (Csernansky et al., 2002; Leucht, 2014; Olivares et al., 2013). The definition of a relapse as an increase in symptom severity suggests that symptom remission is a primary goal of treatment. The Remission in Schizophrenia Working Group (RSWG; Andreasen et al., 2005) created standardized guidelines to evaluate remission in schizophrenia across studies. The RSWG defines remission as "a state in which patients have experienced an improvement in core signs and symptoms to the extent that any remaining symptoms are of such low intensity that they no longer interfere significantly with behavior and are below the threshold typically utilized in justifying an initial diagnosis of schizophrenia" (Andreasen et al., 2005). This definition relies on commonly used assessment instruments such as diagnostic interview scales for a period of at least 6 months. For example, the RSWG defines symptom remission, when measured using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), as mild symptom severity (≤3; range, 1–7) in 8 relevant items out of the 30 PANSS items (for a detailed description, see *Method* later). As such, a relapse can be defined as an increase of symptom severity ≥3 (≥mild symptom severity) at least in one of the defined items by RSWG.

The purpose of this study was to investigate whether a group CR therapy, utilizing both bottom-up and top-down approaches, has an impact on relapse prevention in stabilized schizophrenia outpatients. We used INT (Roder and Mueller, 2015). We hypothesized that INT combined with antipsychotic medication reduces relapses compared with treatment as usual (TAU).

METHODS

Participants

A total of 58 patients with a diagnosis of schizophrenia or schizoaffective disorder according to *ICD-10* were recruited for this study. The inclusion criteria for this study were the following: patients referred from outpatient clinics had to have cognitive impairments identified, a cognitive battery was also completed at baseline before group allocation; IQ scores of greater than or equal to 80 and were assessed by the Reduced Wechsler Intelligence Test (Dahl, 1986); symptoms were in remission for at least 2 months before study inclusion, as assessed by their referring physician; finally, the age inclusion criteria was between 18 and 50 years old. In addition, baseline PANSS (Kay et al., 1987) assessments were conducted to confirm remission criteria for a 2-week period defined by the RSWG (Andreasen et al., 2005). The RSWG defined the criterion for symptom remission as mild symptom severity (≤3; range, 1–7) in 8 of the 30 PANSS items a) positive symptoms: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3); b) negative symptoms: blunted affect (N1), social withdrawal (N4), or lack of spontaneity (N6); and c) general symptoms: mannerisms/posturing (G5), unusual thought content (G9). Exclusion criteria for the outpatients in symptom remission were neurological disorders, substance abuse according to *ICD-10* within 6 months before baseline assessments, and changes in medication doses within 2 months before baseline assessments.

All participants provided written informed consent before participation under protocols approved by the ethics committee at the University of Bern. After this procedure, a flowchart summarized the patient's progress (Fig. 1). Participants were allocated to INT or TAU based on a statistical randomization procedure by an independent statistician. First, computer-generated random numbers were used to generate two groups. Afterwards, these two groups were randomly assigned to INT or TAU. Thirty-two patients were randomly assigned to the experimental group (INT) and 26 patients to the control group (TAU). Four patients in the INT condition and two patients in the TAU condition dropped out during the 1-year assessment period. Two of the patients from the INT group returned to competitive work that was maintained successfully during the study period; the remaining two in the INT and two from the TAU group either moved or could not be contacted for further assessments. For these patients, no further information was available.

Procedure

The INT groups consisted of biweekly sessions (90 minutes each) for 15 weeks with a total of 30 sessions. Five separate INT groups composed of five to eight participants each were led by one main therapist and one cotherapist. The main therapists, clinical psychologists, were trained in cognitive and behavior therapy, and all had experience

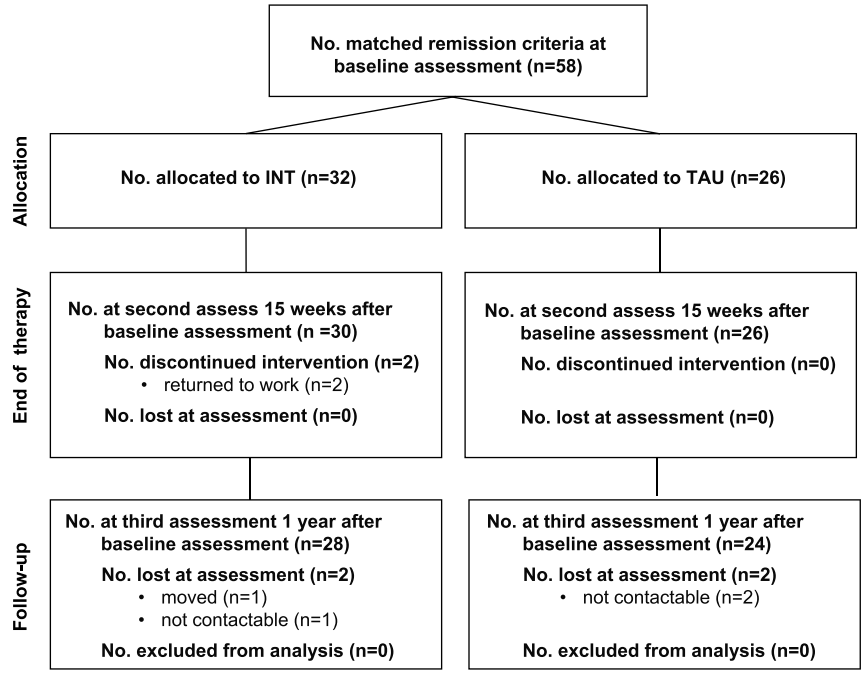

FIGURE 1. Flow diagram of the RCT for the INT and TAU group.

with CR interventions and group therapy. Treatment fidelity was controlled by using a detailed protocol for the therapy sessions. A comprehensive battery was administered for both INT and TAU groups at baseline (before randomization), posttreatment (ie, after 15 weeks), and after a follow-up period of 9 months (1 year after baseline assessment). Trained research assistants with an MSc degree carried out all assessments; they were independent from the treatment and blind to group allocation.

Intervention

INT is a manualized CRT group approach (Roder and Mueller, 2015). The treatment consists of all initially defined 11 neurocognitive and social cognitive domains by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS; Green et al., 2005; Nuechterlein et al., 2004) of the National Institute of Mental Health. These domains are divided into four therapy modules with increasing complexity and emotional strain throughout the course of therapy. Each module starts with interventions on neurocognitive MATRICS domains followed by interventions on social cognition. Each module focusing on a specific cognitive domain includes all four components: first, define the respective cognitive domain and applies the definition to the patient's real-life functioning; second, a compensation or learning part to develop the coping strategies; third, a restitution or training part to practice the coping strategies using both group exercises and computer-based exercises; and fourth, in vivo exercises are administered. The final sessions of INT then focus on emotion regulation and stress reduction tools. The control condition TAU was defined as standard care including a broad array of interventions (*e.g.*, medication, individual therapy, case-management). Furthermore, all study participants were not allowed to take part in evidence-based group therapies targeting cognitive outcomes, though were permitted to enroll in other kinds of group interventions such as music therapy, art therapy, dance therapy, psychoeducation, supportive and vocational counseling, and leisure time-groups throughout the course of the study. It should be noted that the TAU group likely received significantly less time with healthcare professionals due to the constraint of not enrolling in an active treatment targeting cognitive symptoms, whereas the INT group received the biweekly therapeutic sessions for 15 weeks.

Assessments

Symptoms

The PANSS (Kay et al., 1987) was the key assessment instrument for this study. The whole PANSS interview was administered for a 2-week period to rate negative, positive, and general symptom severity. The 2-week period differed slightly from the standard instruction recommending 1-week only. The reason for the longer observation period was to improve the change sensitivity of the assessment. All blinded raters received specific training and revealed high interrater reliability (ICC = 0.91).

Functional Outcome

The Global Assessment of Functioning (GAF) scale of the *DSM-4* was used to measure functional outcome. GAF was administered by the same independent and blinded raters as PANSS. Again, the interrater reliability was high (ICC = 0.92).

Cognition

A broad array of assessments regarding cognitive functioning was conducted: 1) speed of processing assessed using the Trail Making Test, Part A (TMT; Reitan, 1958); 2) attention measured with the d2 task (Brickenkamp et al., 2010), which is a paper-and-pencil cancellation test that has proven to be a reliable and valid measure of selective attention; 3) verbal learning and memory were assessed using the Auditory Verbal Learning Test (AVLT), a delayed recognition memory task (Lezak, 2004); 4) reasoning and problem solving was measured using the Wisconsin Card Sorting Test (WCST), number of perseverative errors (Loong, 1989); 5) working memory measured with the Letter-Number Span (LNS; Gold et al., 1997); 6) emotion perception assessed with the Picture of Facial Affect (PFA) test (Frommann et al., 2003); and 7) the Emotion Recognition Questionnaire (EMOREC; Bähler, 2012). Both measures require the patients to view photographs of faces and to identify specific basic emotions (PFA) or to rate the intensity of the perceived emotion on a 5-point Likert scale (EMOREC); and 8) the Schema Component Sequencing Task–Revised (SCST-R; Vauth et al., 2004) as a computerized measure of social schema.

Statistical Analyses

All analyses were conducted using SPSS 24.0 (SPSS Inc., Chicago, IL). Raw data were checked for normality and outliers. Group comparisons between INT and TAU as well as between completers and noncompleters of therapy at baseline were performed using chi-square analyses and *t*-tests. With regard to therapy outcomes, the intent-to-treat analysis was based on a repeated measures General Linear Model (GLM) for two (2 × 2) and three assessment points (2 × 3). Pearson correlation coefficients were used to detect associations between negative symptoms and other areas of functioning. However, a power analysis at

TABLE 1. Patient Characteristics (*N* = 58)

	INT (*n* = 32)		TAU (*n* = 26)			
	M	(SD)	M	(SD)	t/χ^2	*p*
Age at baseline, y	32.1	(9.1)	31.5	(7.7)	0.3	0.76
Age at first episode, y	24.3	(7.2)	22.7	(6.8)	0.9	0.38
Duration of illness, y	7.4	(5.9)	8.8	(5.6)	0.9	0.35
No. hospitalizations	3.9	(3.3)	3.7	(4.1)	0.3	0.79
IQ (WAIS-R)	107.7	(9.6)	106.3	(12.0)	0.5	0.65
Education, y	12.5	(2.6)	12.7	(3.1)	0.3	0.79
Symptom sum score (PANSS)	53.3	(10.6)	55.2	(10.2)	0.7	0.49
GAF	53.4	(8.0)	55.4	(8.5)	0.9	0.36
Medication (chlorpromazine equivalent dose)	307.2	(259.9)	371.6	(308.0)	0.8	0.45
Sex (% male)	56.3		61.5		0.2	0.68

WAIS-R, Reduced Wechsler Intelligence Test (WIP, Dahl, 1986); PANSS (Kay et al., 1987); GAF (*DSM-4*); *t*, *t*-tests for normally distributed variables; χ^2, χ^2 tests for categorical variables.

an alpha level significance of 5% suggested that the study sample size fits only to detect large effects in chi-square, *t*-tests, Spearman coefficients, binary logistic regression, and medium effects in GLM with repeated measures (Cohen, 1988). Following recent recommendations, we also focused on effect sizes (Nakagawa, 2004). Cohen's *d* was calculated at posttherapy and follow-up using the difference of the respective group means divided by their pooled standard deviation (Cohen, 1988; Rustenbach, 2003). Cohen's *d* can be categorized into small (0.2), medium (0.5), and large (0.8) effects.

RESULTS

INT and TAU did not differ significantly in demographic variables, antipsychotic medication, or in any outcome variable at baseline ($t_{56} < 1.7$, $p > 0.09$) (Table 1). All patients were taking antipsychotic medication. Patients assigned to the INT group attended an average of 81.8% (SD = 9.8%) of therapy sessions.

Relapse Rate

Of the 32 INT patients, 13.3% relapsed in INT group during therapy, according RSWG criteria addressing PANSS (Andreasen et al., 2005). This was significatly less compared with 13 of the 26 control patients under TAU conditions (Fig. 2). Transformed into effect size, this relationship comprises Cohen's $d = 0.80$, which represents a high effect. During the 9-month follow-up, the INT group displayed nearly half of the relapse rate (24.1%) as the TAU group (53.8%); $d = 0.63$. Including dropped-out patients as from whom no further data were available at follow-up and defining them as relapsed, the superiority of INT regarding relapses is still significantly lower ($\chi^2 = 4.2$; $p < 0.04$; $d = 0.54$) compared with controls.

Symptoms, Antipsychotic Medication, and Functioning Outcomes

Symptom response was operationalized using the RSWG criteria (Andreasen et al., 2005), which are based on eight PANSS items. The change of symptom severity over the three assessment points in these items has been analyzed using a GLM for repeated measures. From these variables, the INT group had significantly lower symptoms of passive social withdrawal than TAU at both posttreatment and follow-up (Table 2). The INT group also had significantly lower symptoms of "delusions" and "unusual thought content" as measured by the PANSS positive and general subscales at posttreatment but not follow-up. Finally, INT showed significant improvements in negative and general symptoms as well as in the total PANSS score; however, there were no significant differences in positive symptoms between INT and TAU groups.

The mean dose of antipsychotic medication was relatively stable over the assessment period of 1 year. GLM modeling including all three assessment points showed no interaction effect ($F = 0.34$; p = nonsignificant); however, there was a trend for time ($F = 2.4$; $p = 0.09$).

The INT group had significant improvements in functioning as assessed by the GAF. Regarding cognition, the only significant changes found were in speed of processing and social schema. There were no significant differences between groups in attention, memory, and verbal working memory. The INT group had superior effects during therapy in problem solving, but at follow-up, patients under the TAU condition improved strongly in this domain. Lastly, the INT group was better able to recognize the intensity of the perceived emotion (EMOREG) both at posttreatment and follow-up, but there were no differences in accuracy of identifying the emotions (PFA) (see Table 2).

Many of these very stable patients with schizophrenia or schizoaffective disorder showed relatively high cognitive functioning in most of the assessed cognitive domains at baseline, which reduced the range of improvement. We analyzed the cognitive profile of each participant at baseline and extrapolated the neurocognitive measures that fell below the 10th percentile of the standardized test score for each participant so that each participant's profile had at least one severe deficit represented in their profile. This was represented in the average neurocognitive deficit (AND) score for each participant. Because no standard values were available for most of the used social cognitive measures, a social cognitive composite (SCC) score representing the mean of the standardized raw data of the three measures in that cognitive area was also created. Finally, we created a global measure of outcome called the proximal outcome mean (POM) score, which includes both AND score and SCC scores for each participant. All three cognitive scores were significant during therapy and at follow-up favoring INT compared with TAU (Table 2).

Factors Associated With Relapse

We calculated a binary logistic regression analysis to control for factors associated with the treatment, patient characteristics, level of cognitive and social functioning, or severity of symptoms and relapse. For that purpose, we first pooled the two comparison groups INT and TAU and correlated the patient characteristics, treatment condition, PANSS symptom scores, three cognitive scores (AND, SCC, POM), and the GAF score after treatment with patients' respective relapse status using Spearman's rho. We included the outcome variables assessed after treatment for two reasons: 1) the randomization procedure allows

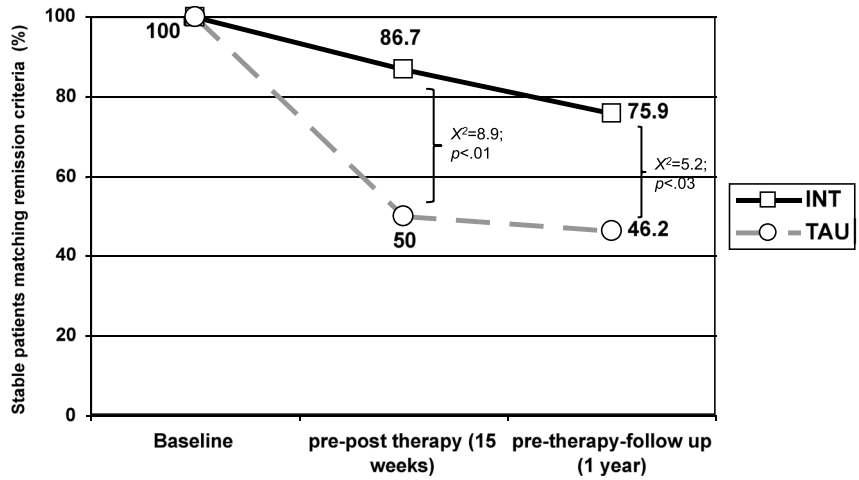

FIGURE 2. Rates of stable outpatients matching remission criteria in INT and TAU group during therapy and follow-up.

TABLE 2. Outcome Variables (GLM With Repeated Measurement)

	INT						TAU						GLM			GLM		
	T1		T2		T3		T1		T2		T3		T1–T2		Effect Size	T1–T2–T3		Effect Size
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	*F*	*p*	*d*	*F*	*p*	*d*
PANSS delusions	1.8	(0.8)	1.6	(0.9)	1.7	(1.0)	1.9	(0.9)	2.3	(1.1)	2.0	(1.1)	**6.4**	**0.02**	**0.78**	2.0	0.14	0.37
PANSS conceptual disorganization	1.3	(0.6)	1.2	(0.4)	1.3	(0.7)	1.7	(0.7)	1.7	(0.9)	1.5	(0.8)	0.6	0.44	0.36	0.5	0.59	0.40
PANSS hallucinations	1.7	(0.7)	1.2	(0.6)	1.4	(1.0)	1.7	(0.8)	1.6	(1.1)	1.8	(1.1)	0.9	0.36	0.34	0.5	0.63	0.43
PANSS blunted affect	1.9	(0.8)	1.6	(0.7)	1.5	(0.8)	1.9	(0.9)	1.9	(1.2)	1.8	(1.0)	1.6	0.21	0.29	1.0	0.37	0.28
PANSS passive social withdrawal	2.0	(0.8)	1.7	(0.9)	1.8	(0.8)	2.2	(0.7)	2.8	(1.1)	2.3	(0.9)	**11.6**	**0.00**	**1.39**	**6.3**	**0.00**	**0.55**
PANSS lack of spontaneity	1.5	(0.7)	1.3	(0.7)	1.3	(0.9)	1.5	(0.7)	1.7	(0.7)	1.6	(0.9)	3.5	0.06	0.68	1.1	0.35	0.35
PANSS mannerisms and posturing	1.4	(0.6)	1.2	(0.6)	1.3	(0.6)	1.2	(0.6)	1.3	(0.6)	1.3	(0.6)	1.6	0.22	0.49	0.8	0.45	−0.01
PANSS unusual thought content	1.6	(0.9)	1.4	(0.6)	1.3	(0.7)	1.8	(0.7)	2.2	(0.8)	1.8	(0.9)	**6.7**	**0.01**	**0.74**	2.3	0.10	0.63
PANSS positive symptoms	12.1	(2.9)	10.5	(2.9)	10.4	(3.7)	12.8	(3.4)	13.0	(3.8)	12.3	(4.0)	3.6	0.06	0.63	1.1	0.35	0.61
PANSS negative symptoms	12.6	(3.7)	10.8	(3.1)	11.0	(4.1)	13.1	(4.2)	14.4	(5.3)	12.7	(4.8)	**7.4**	**0.01**	**0.63**	**3.9**	**0.02**	**0.45**
PANSS general symptoms	29.0	(6.9)	24.1	(5.2)	23.6	(5.8)	28.1	(4.9)	31.4	(7.2)	27.2	(5.6)	**13.4**	**0.00**	**1.39**	**7.2**	**0.00**	**0.60**
PANSS total score (sum)	51.7	(10.5)	45.3	(8.9)	45.3	(12.8)	54.5	(10.3)	59.2	(14.4)	52.1	(12.2)	**9.3**	**0.00**	**1.17**	**4.1**	**0.02**	**0.70**
GAF	55.1	(8.1)	59.7	(7.4)	59.7	(6.9)	55.6	(8.4)	52.0	(8.5)	55.0	(9.3)	**9.1**	**0.00**	**0.73**	**6.9**	**0.00**	**0.57**
D2	99.2	(12.3)	104.8	(13.9)	105.0	(14.0)	99.1	(12.9)	100.0	(15.4)	104.8	(11.9)	2.3	0.13	0.24	1.9	0.16	0.07
TMT	36.4	(12.9)	31.7	(10.9)	29.4	(10.6)	31.1	(8.2)	32.0	(12.5)	31.2	(11.8)	**5.1**	**0.03**	**0.52**	**3.8**	**0.03**	**0.15**
AVLT	46.0	(9.7)	50.2	(8.8)	51.5	(9.6)	50.6	(9.5)	51.4	(9.5)	52.4	(10.3)	0.1	0.80	0.02	1.8	0.17	0.06
WCST	22.1	(15.0)	16.0	(12.6)	18.9	(14.0)	24.9	(22.2)	29.7	(26.4)	17.9	(16.1)	**8.4**	**0.00**	**0.66**	**4.4**	**0.02**	**−0.26**
LNS	13.5	(4.1)	13.7	(3.1)	14.1	(3.6)	12.8	(3.7)	12.3	(2.9)	13.3	(3.6)	1.5	0.22	0.14	0.6	0.53	0.19
PFA	85.0	(8.2)	87.6	(7.1)	86.4	(8.2)	84.1	(9.8)	79.7	(14.3)	82.6	(13.3)	1.7	0.20	0.38	2.7	0.07	0.28
EMOREC	6.6	(0.9)	6.9	(0.7)	7.1	(0.6)	6.8	(0.6)	6.3	(1.0)	6.6	(1.0)	10.2	0.00	1.26	**6.7**	**0.00**	**0.61**
SCST-R	63.5	(7.0)	68.0	(6.1)	67.8	(5.7)	61.1	(12.7)	57.4	(18.2)	62.3	(16.3)	3.1	0.08	0.38	**3.0**	**0.05**	**0.55**
Neurocognition (AND)	−0.36	(0.4)	0.59	(0.7)	0.54	(0.9)	−0.43	(0.7)	0.11	(0.8)	0.55	(1.0)	**5.3**	**0.03**	**0.46**	**3.7**	**0.03**	**0.37**
Social cognition (SCC)	−0.01	(0.6)	0.20	(0.5)	0.30	(0.6)	0.00	(0.6)	−0.42	(1.1)	−0.18	(1.0)	**10.6**	**0.00**	**1.05**	**6.0**	**0.00**	**0.78**
Cognition (POM)	−0.09	(0.4)	0.32	(0.4)	0.34	(0.6)	−0.07	(0.6)	−0.16	(0.8)	0.13	(0.7)	**17.5**	**0.00**	**1.02**	**7.6**	**0.00**	**0.40**

GLM (for repeated measurement); *F*- and *p*-values for group × time interaction effects; T1, pretherapy; T2, posttherapy; T3, follow-up assessment; PANSS (Kay et al., 1987); GAF (*DSM-4*); d2, Aufmerksamkeits-Belastungs test, number of correctly marked items (Brickenkamp et al., 2010); TMT, time to completion (Reitan, 1958); AVLT, summary score of correctly remembered words after each trial (Lezak, 2004); LNS (Gold et al., 1997); WCST, total number of perseverative faults (Loong, 1989); PFA test, % correct answers (Frommann et al., 2003); EMOREC, total number of correct judgments (Bähler, 2012); SCST-R (Vauth et al., 2004); AND score, mean of z-transformed variables of neurocognition, only lowest 10% of baseline assessments; SCC score, mean of z-transformed variables of social cognition; POM score, mean of AND and SCC variables; effect size *d* at follow-up (T3) has been calculated using the following formula: $d = (M_{INT} - M_{TAU})/SD_{pooled}$ (Cohen, 1988); all effect sizes and test scores are presented in a way that higher scores indicate improvement or better performance in the respective measure, with the exception of PANSS, TMT, and WCST scores.

for homogeneous comparison groups at baseline. This allows us to attribute group differences after treatment to the intervention; 2) we were interested in examining the effects of the treatment impact, which is strongest after therapy. None of the patient characteristic variables correlated significantly with the relapse status at posttreatment ($r < 0.15$; p = nonsignificant). Relapse status after treatment, however, correlated with the treatment condition, GAF score, PANSS negative and positive symptoms ($r > 0.39$), and a significant correlation with the POM score representing the proximal cognitive outcome of the experimental group ($r = 0.30$). All of the variables that correlated with relapse status were included in the logistic regression model as covariates. Medication was also included in the model because of the time effect trend over the three assessments noted previously. The overall model was highly significant ($\chi^2 = 35.4$; $p < 0.01$). The model declared $R^2 = 69\%$ of the variance and identified 87% of the relapse and maintained remission status respectively. Thereby, negative symptoms ($\chi^2 = 6.1$; $p = 0.02$) and treatment condition ($\chi^2 = 3.5$; $p = 0.05$) had by far the largest impact on relapse. The POM score ($\chi^2 = 2.1$; p = nonsignificant) had a marginal impact; antipsychotic medication and positive symptoms had no impact ($\chi^2 < 1.5$; p = nonsignificant).

DISCUSSION

The main objective of this randomized controlled trial (RCT) study was to evaluate the efficacy of INT for relapse prevention in stabilized outpatients with schizophrenia. For this purpose, we operationalized relapse according to the RSWG (Andreasen et al., 2005) criteria using the PANSS assessment. As expected, the INT intervention significantly reduced relapses compared with the TAU condition where only 13.3% of participants relapsed in the INT group during therapy compared with 50% of participants in the TAU group. The relapse rate of the INT group increased to 24.1% during follow-up of 12 months compared with 53.8% under TAU. Furthermore, when including the participants who dropped out as relapses into the analysis, the favorable effects supporting INT were maintained. This result was determined by the very low 1-year study dropout rate of only 10.3%, which also suggests high acceptance and feasibility of INT implementation in schizophrenia outpatients. These positive results regarding relapses are similar to meta-analyses using psychoeducation or family interventions for relapse prevention (Lincoln et al., 2007; Pharoah et al., 2010; Xia et al., 2011). It should be noted, however, that the relatively high relapse rate observed in the TAU group is surprising and is not related to differences in patient variables due to no differences found at baseline between groups. That said, a study conducted by Tao et al. (2015) using CR also reported a relapse rate of 41% for the TAU condition, indicating that relapse rates can be relatively high in some patient samples.

Upon examination of the patient's symptom scores, it appears that the initial symptom scores assessed by PANSS were very low at study intake. Due to the low symptoms at baseline, there was limited range for improvement. The goal of INT was to maintain the low symptom level in the stabilized patient population. We observed some effects that had favored the INT condition. These resaults are contradictory to a previous study that examined the effects of INT on symptom remission: patients in the INT condition showed a significant reduction in positive symptoms after therapy compared with TAU (Mueller et al., 2015). Indeed, previous studies have also shown large effect sizes for reductions in positive symptoms using integrated psychological therpy, which is an intervention that combines both CR and SST (Roder et al., 2010; Mueller et al., 2013): other meta-analyses focusing on CR more generally provide support for relatively small effects in the reduction of positive symptoms (Revell et al., 2015; Wykes et al., 2011). Regarding negative symptoms, CR seems to have some effects (Cella et al., 2017) as does INT in outpatients suffering from severe negative symptoms (Mueller et al., 2017).

CR treatment using INT strongly improved the reported functioning of participants, as assessed by the GAF during therapy as well as at follow-up. This increased functioning is a common and robust outcome of studies using INT (Mueller et al., 2015, 2017). Due to the fact that INT does not include exercises focusing on social functioning, this improvement represents a generalization effect. These results are in line with meta-analyses examining the effects of CR on functioning (McGurk et al., 2007; Wykes et al., 2011), where such generalization effects were only reported in studies using CR approaches that combine different therapeutic techniques rather than focus on neurocognition alone.

Contrary to our expectations, we did not initially find many improvements in the neurocognition and social cognition domains. This paucity of findings could have been due to many of our patients having minimal symptoms at baseline and did not have many cognitive deficits. This could explain why INT worked only on some of the cognitive domains. Once we calculated the AND score, which represents the mean of all assessed neurocognitive impairments that ranged within the lowest 10% for each participant (individual profile of each patient with their impaired cognitive domains), we found significantly higher perfomance of INT patients compared with TAU posttreatment and at follow-up. The same effect could be found after averaging all assessed social cognitive scores to an SCC score. The combination of the two cognitive scores AND and SCC to a POM score was significant after therapy and at follow-up too. That said, because the POM combines cognitive domains that may belong to two different and distinct concepts of cognition related in different ways to functional outcome (Hoe et al., 2012), the results should be interpreted with caution. On the other hand, the POM score represents a simple and global measure of proximal outcome within INT intervention even in this population of very stable outpatients. These positive effects of AND, SCC, and POM are in line with the results of meta-analysis on CR (McGurk et al., 2007; Wykes et al., 2011).

Decreases in relapse rates in INT patients compared with controls were also associated with reductions in negative and general symptoms, as well as improvements in functioning (GAF) and the cognitive POM score as depicted in the correlation analyses. The regression analysis showed that the INT treatment and level of negative symptoms and, to a lower extent/level, also the POM score after treatment had the highest impact on relapse during the treatment period. These results suggest that the daily dose of medication and positive symptoms did not have a strong impact on relapses. It should be noted that the statistical power was low and therefore reduced its validity. This may explain why our findings are inconsistent with other studies that found discontinuation of medication or antipsychotic agents to be a strong indicator of relapses in individuals with schizophrenia (Alphs et al., 2016; Bowtell et al., 2018b; Kishimoto et al., 2013). Such studies found that the duration of illness and symptom increases were also identified as relapse predictors. A recent quantitative review on predictors of continuing remission or relapse after discontinuation of antipsychotic medication (Bowtell et al., 2018a) indicated that negative symptoms were identified as predictor of relapses in the early course of schizophrenia illness. This is in line with previously published findings showing that INT reduces negative symptoms to a clinically relevant level of remission (Mueller et al., 2017).

The procedures specific to INT should be taken into consideration when examining the reduced relapse rates. First, INT represents an integrated CR approach that combines interventions on neurocognition and social cognition. Today, there is sufficient data available supporting evidence for CR for proximal outcomes. In addition, there is some evidence that integrated CR approaches are more successful to support functional outcomes compared with neurocognitive remediation alone (McGurk et al., 2007; Wykes et al., 2011; Revell et al., 2015). Moreover, previous studies found that INT supported symptom remission of severe negative symptoms (Mueller et al., 2017). Second, By taking individual cognitive experiences in the daily life into consideration, the

INT group therapy may support distal outcome of functioning and symptoms (such as generalization and transfer effects; Mueller et al., 2015; Roder et al., 2010). Throughout the intervention, patients learn to recognize the impact of cognition on coping strategies. Third, therefore, the inclusion of tools for emotion regulation and stress reduction in INT comparable to common behavioral psychoeducation programs may provide participants with coping strategies that reduce relapses (Pharoah et al., 2010). Taken together, participants may have learned to choose helpful coping strategies taught in the treatment to compensate for their cognitive deficits and to reduce emotional strain in real-life situations. Besides the INT specific effects, some unspecific therapy effects may have also had an impact on the relapse rates. First, INT interventions are conducted in a group setting, which ultimately generates supporting interactions among patients and therapists. A precondition for successful group processes in CR procedures also seems to rely on the therapeutic alliance built between the patients and therapist (Cella and Wykes, 2019). Moreover, good therapeutic alliance is linked with higher medication compliance (Higashi et al., 2013) and better adherence (Velligan et al., 2009), which could ultimately impact the relapse rates. The therapeutic relationship is one of the key challenges in INT training due to the different levels of group processes and therapeutic structuring (Roder and Mueller, 2015). Second, there is some evidence that the use of strategies to maintain treatment gains may be associated with better therapeutic alliance (Cella and Wykes, 2019; McGurk et al., 2007; Roder et al., 2011; Wykes et al., 2011). INT is based on strategy learning as well as on drill and practice tasks. Third, the low dropout rate during INT intervention (6.7%) and the high attendance rate (81.8%), which was homogeneous across participants (SD = 9.8%), suggest a high acceptance, motivation, and feasibility of INT in stabilized schizophrenia outpatients.

In summary, our results support the notion that INT reduces relapses. This may be due to improvements seen in cognition, functional outcome, and symptoms resulting from training specific to neurocognitive, social cognitive, emotion regulation, and stress reduction domains throughout the treatment. Unspecific therapy factors such as group setting and therapeutic alliance may have also had an additional impact. That said, these mechanisms need to be further investigated to provide evidence. The results of this study also point to the possibility that there may be individual differences in treatment outcome based on the cognitive profile of the patient; however, more evidence is needed to address this question. Moreover, this study also demonstrated that negative symptoms have an impact on relapse. This result corroborated the importance of taking negative symptoms into consideration within psychosocial treatment such as CR.

There are some limitations to this study regarding patient selection and methodological rigor. First, our sample of only well-stabilized outpatients according to RSWG criteria may undermine the validity of some results that may not be generalizable to other patient populations in psychiatric care. Regarding the generalization of the results, it should also be considered that the relapse rate of the controls was relatively high, especially during the treatment phase. The strict use of RSWG criteria for relapse definition seems to be one way of measuring relapses. Others such as rehospitalization or increases in the level of psychiatric care may lead to different results. To date, no consensus has been found regarding relapse definition (Csernansky et al., 2002; Leucht, 2014; Olivares et al., 2013). Second, relapses according to RSWG criteria were based on the PANSS assessments after therapy and at follow-up. However, the PANSS assessment takes a 2-week time frame into account. As such, it might be possible that some patients suffered from increased symptoms during the limited time between assessments, which was not captured by our study. An additional assessment capturing longer periods would have closed this gap. Third, the GAF scale was administered as a measure of functional outcome. Although it is widely used and seems appropriate in samples of stable patients, it is confounded with symptom severity and may not be very sensitive for psychosocial changes (Startup et al., 2002; Robertson et al., 2013). It would have been useful to include more measures of this domain. Fourth, we did not include measures assessing therapeutic ingredients such as therapeutic alliance defined by Cella and Wykes (2019). Fifth, patients in the TAU condition did not receive the same amount of treatment as INT patients, which might have accounted for some of the differences in the outcome (*i.e.*, relapses and functioning). Because we did not include an active control group, the impact of the time and attention provided by the INT facilitators could not be controlled for. Sixth, because of the relatively small sample size, we were only able to describe the potential mechanisms of change related to relapses rather than using statistical analyses such as structural equitation modeling to determine this mechanism. Seventh, we do not know any study investigating on the impact of group therapy in schizophrenia patients on the mechanism of change or relapses.

Overall, this study is one of the first providing evidence that CR approaches similar to INT in combination with antipsychotic medication may prevent relapses in schizophrenia outpatients during a 1-year observation period. Future studies are still needed to assess longer follow-up periods to determine the long-term effects of CR interventions. Future studies could use larger sample sizes, active comparison conditions, and more adequate test batteries. They could also include a more heterogeneous sample that could be prospectively observed over a longer period.

DISCLOSURE

The authors declare no conflict of interest.

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