Prevention and prediction of relapse in schizophrenic patients: RCT results on integrative cognitive remediation during 8-year follow-up

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Introduction

In today's psychiatric care systems for schizophrenia, relapse prevention is an important goal for several reasons: Relapses are a major burden for schizophrenic patients, their relatives and caregivers, which potentially reduce functioning and thus compromise individual recovery goals. Relapses result mostly in hospitalization and increased treatment costs. Preventing and predicting relapses is therefore a serious challenge for psychiatric treatment.
Relapse rates are high: the risk of relapse in first-episode patients is estimated at 62-96% after 2 years (Emsley 2013); later on, with good medication compliance at 24% after 1 year (Ceraso et al. 2020; Schneider-Thoma et al. 2022), rising to 60-80% with non-compliance and irregular medication intake (Kane et al. 2013).
Today, several evidence-based psychotherapy approaches are available for the treatment of schizophrenia patients, each focusing on different treatment goals. However, there are only a few psychotherapy studies that have examined relapses over a long period of time. The classic follow-up studies on psychoeducational and family therapy approaches are a desirable exception (Pharoah et al. 2010; Xia et al. 2011, but are usually limited to 1-2 years. For other evidence-based approaches such as cognitive remediation, on the other hand, there are hardly any corresponding long-term studies that also include the prediction of relapse. In order to bridge this gap, we designed the following study on the impact of cognitive remediation on long-term relapse prevention. In addition, predictors of relapse should be identified already during and after therapy intervention.

Methodology

Design

For this purpose, the **cognitive remediation group approach** Integrated Neurocognitive Therapy, INT, (Roder & Mueller 2015; Mueller et al. 2015, 2017, 2020) was compared with control patients who did not participate in therapy groups (Treatment as Usual, TAU). INT was developed in our lab and follows a restitution and compensation learning approach. It consists of 4 modules addressing all NIMH-MATRICS domains of neuro- and social cognition. At the end of the last module, tasks on emotion regulation and stress reduction are included (Fig. 1). INT was conducted twice a week over a therapy duration of 15 weeks.

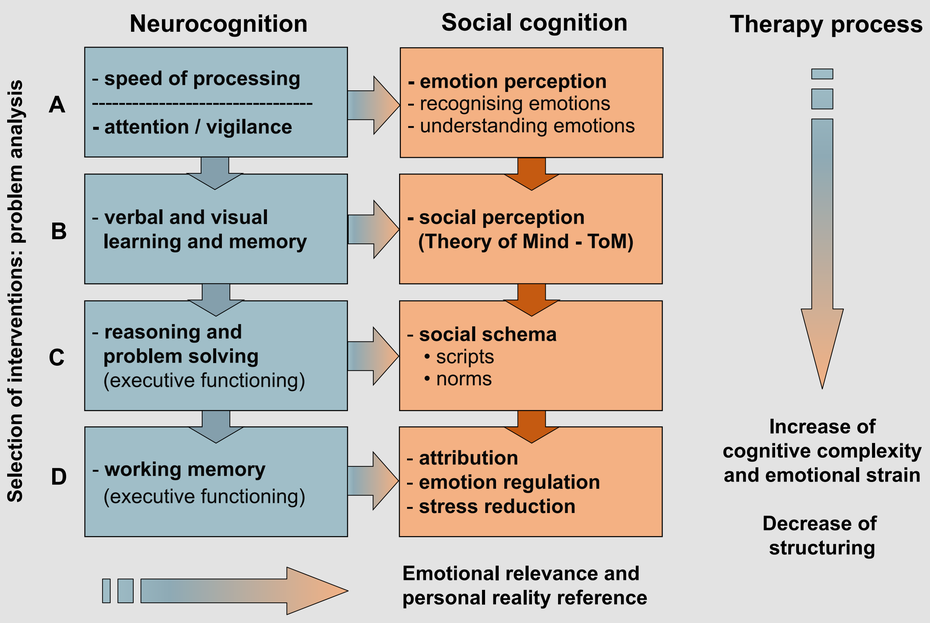

Fig. 1 Integrated Neurocognitive Therapy (INT).

Assessments

Relapses were defined as an increase in psychotic symptoms with simultaneous hospitalization. Observation periods of relapses were 1, 5 and 8 years after baseline assessment.
In addition, a broad test batterie was administered before and after therapy of 15 weeks and at 1-year follow-up. Among others, the following assessments were included: **Symptoms**: Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987); **Functioning**: Global assessment of functioning scale (GAF; DSM); **Neurocognition: Executive functions**: Wisconsin Card Sorting Test (WCST; Loong 1989); **Emotion regulation:** Pictures of Facial Affect Test (PFA; Frommann et al. 2003); W: **Social schemata**: Schema Component Sequencing Task (SCST; Vauth et al. 2004).

Sample and patient characteristics

A total of 71 outpatients with schizophrenia (ICD 10) were randomly assigned to INT or TAU. Due to moving, death or incomplete documentation, only the data of 43 outpatients are available: INT (N=25) and TAU (n=18). None of the patient characteristics summarized in table 1 showed a significant difference between INT and TAU at baseline (Table 1).

Tab. 1 Patient characteristics (N=43).

	INT (*n*=25)		TAU (*n*=18)			
	M	*(SD)*	*M*	*(SD)*	t/χ^2	*p*
Age at baseline (years)	36.5	(8.7)	36.7	(10.5)	0.1	.95
Age at first episode (years)	24.0	(6.3)	23.9	(5.0)	0.0	.97
Duration of illness (years)	7.4	(5.9)	8.8	(5.6)	0.2	.82
Number of Hospitalization	4.7	(4.1)	5.5	(5.4)	0.5	.59
IQ (WAIS-R)	106.0	(10.5)	100.2	(10.8)	1.6	.11
Education (years)	11.4	(2.5)	10.2	(1.6)	1.9	.06
Medication (daily dose in chlorpromazine-equivalents)	345.1	(293.5)	273.3	(235.2)	0.8	.41
Gender (% male)	64.0		66.7		0.0	.86

Abbrevations: INT, Integriated Neurocognitive Therapy; TAU, Treatment As Usual; WAIS-R, Reduced Wechsler Intelligence Test (WIP, Dahl, 1986); *t*, t-tests for normally distributed variables; χ^2, χ^2-tests for categorial variables

Results

1. Relapse rate and number of rehospitalization days
In general, INT shows a lower relapse rate in all 3 assessed time intervals, but the superiority over TAU becomes significant only in the 5- and 8-year follow-up. Due to high variance between patients, only a trend can be depicted in the 1-year follow-up (Fig. 2). The same result was found regarding number of rehospitalization days. However, the superiority of INT over TAU is much more pronounced here: patients on TAU conditions require 3-5 times more hospital days than INT patients in the 8- or 5-year follow-up (Fig. 3).

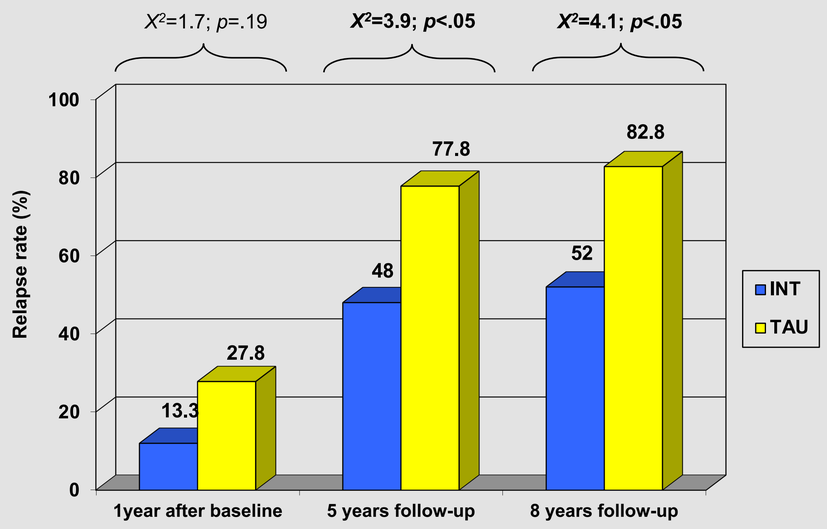

Fig. 2 Relapse rates in INT and TAU during therapy and follow-up

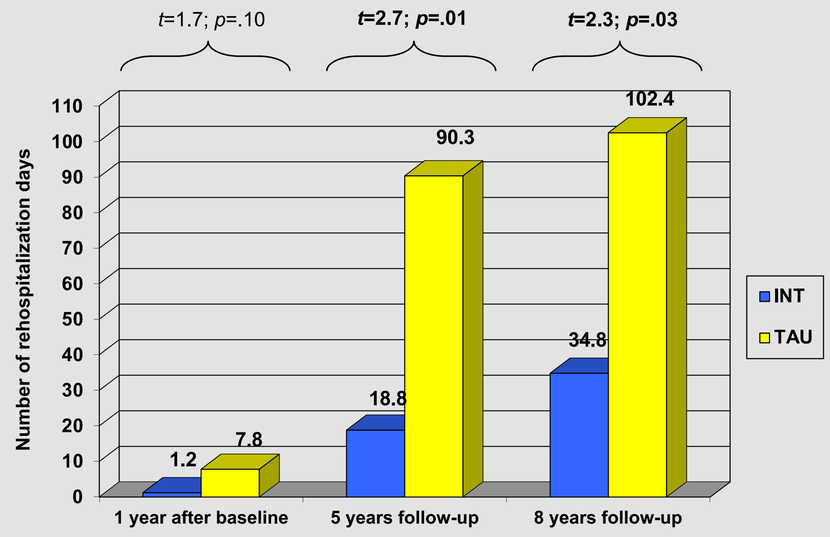

Fig. 3 Number of rehospitalization days in INT and TAU during therapy and follow-up

2. Predictors of relapses
The significant results of the Pearson correlations of the 3 time intervals with all variables of the patient characteristics and the outcome variables (cognition, social functioning, symptoms) after therapy are summarized in Table 2. In terms of cognitive parameters, only the social-cognitive functions of social schema and emotion regulation and, in the neurocognitive area, executive functions were identified as predictors of relapse. Positive and negative symptoms were not found to be predictors in this sample, but general symptoms (PANSS) were. Medication, all other patient characteristics and social functioning (GAF) also do not appear to be predictors either. As expected, the relapse rate correlates highly with the number of rehospitalization days.

Tab. 2 Pearson correlations of relapse rates to outcome and patient characteristics.

Relapse rate	Correlated variables	r	*p*
1 year follow-up	Days of hospitalization	.56	0.00
	Emotion regulation	.55	0.00
	Social schema	.48	0.00
5 years follow-up	Relapse rate 1 year follow-up	.67	0.00
	Days of hospitalization	.37	0.02
	Exekutive functions	.41	0.02
8 years follow-up	Relapse rate 1 year follow-up	.51	0.00
	Relapse rate 5 years follow-up	.88	0.00
	Days of hospitalization	.86	0.00
	Emotion regulation	.38	0.04
	Exekutive functions	.54	0.00
	General symptoms	.39	0.04

Executive functions: WCST: Wisconsin Card Sorting Test (Loong 1989); **Emotion regulation:** PFA: Pictures of Facial Affect Test (Frommann et al. 2003);
Social schema: Schema Component Sequencing Task (Vauth et al. 2004); **General symptoms:** PANSS: Positive and Negative Syndrome Scale (Kay et al. 1987)

Conclusion

Integrated cognitive remediation using the example of INT significantly reduces relapse rates in follow-up phases of 5 and 8 years. INT reduces rehospitalization days in these periods and thus possibly also reduces treatment costs. The course of relapse over 8 years can already be partially predicted in the first follow-up year. Performance in various neuro- and social cognitive functions and some symptoms could be determined as further predictors of relapse. However, protective factors still remain unclear. Larger prospective studies are therefore desirable.