Cognitive Improvement of Schizophrenia Patients: Enhancing Cognition while Enjoying Computer-Aided Cognitive Training

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Abstract

Cognitive deficits are a core symptom in schizophrenia, but until now controlled efficacy studies of cognitive training methods have shown inconclusive results. This study examined the effects of computer-aided cognitive training using motivational software that evokes positive emotions in patients suffering from schizophrenia. Forty patients were included: twenty of them received cognitive training; twenty received occupational therapy. Both before and after treatment, all patients were assessed with a battery of neuropsychological tests measuring executive functions, attention and verbal memory. Enhancing effects on executive functioning level and verbal memory could be found. At the same time, effects on positive and negative symptom levels could be observed. Changes in symptom levels and cognitive improvement were uncorrelated. Our findings imply that cognitive achievement of schizophrenia patients can be improved using pleasant and "game-like" cognitive training tasks. This may be due to a motivating effect and, to a greater extent, because these tasks cause enhanced processing.

Key Words: Schizophrenia, Cognition, Cognitive Remediation

Introduction

Both Kraepelin (1) and Bleuler (2) have already considered dysfunction of attention as a key symptom of schizophrenic illness. During the last two decades, however, cognitive dysfunction in schizophrenia has received broader scientific interest from psychiatrists and psychologists and a number of studies have reported deficits in memory (3), attention (4), executive function (5), as well as visual-motor planning (6). Some of these variables have been discussed as trait markers in the context of the diathesis-stress model (7); see also the overviews (8, 9). Moreover, their occurrence in childhood seems to be a predictor for the eventual onset of schizophrenia, which has been elicited in several high-risk studies (10-14).

At the same time, it has been discovered that cognitive dysfunction limits social and vocational functioning (see reviews, 15-17) and tends to persist even after antipsychotic treatment. Because of these findings it was claimed that schizophrenic patients should receive cognitive training to positively influence the further course of their illness.

Meanwhile, a substantive number of studies have demonstrated that patients suffering from schizophrenia are able to improve their performance in attention, memory, visual-motor and executive tasks. Computer-aided training has

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several advantages: firstly, complex tasks can be repetitively adapted according to the individual state of skills of the trainees; secondly, the use of computers in cognitive training has proved to be more motivational than other training methods.

Controlled efficacy studies of cognitive training in schizophrenia patients using psychometric output measures different from training tasks have remained inconclusive hitherto (see [18] for a critical review and [17] for a less critical review). While some authors (19-23) are reporting significant effects mainly on working memory and executive function, minor or no effects are reported in other studies.

Several authors have proposed a variety of variables to explain these conflicting findings (16, 17, 24-26). Apart from the extent of cognitive training received by the patients (e.g., duration and frequency), evidence points to the fact that patients benefit even more than healthy controls from reinforcing feedback and the teaching of strategies in the sense of "cognitive remediation." Furthermore, motivating tasks offered to patients suffering from motivational deficits and the avoidance of negative feedback are expected to be helpful to overcome avolition. Error-free learning, with the help of gradually increasing levels of difficulty, is widely regarded as another supportive measure.

Such variables may be of additional interest as most of the patients are known to suffer from emotional deficits, as well. On the morphological side, volume changes in the amygdala have been repeatedly found (27). This limbic structure is known to be involved predominantly in negative emotions. Simultaneously, decreased activation of prefrontal cortex (PFC) areas has been observed during cognitive tasks (28-32). The latter has been reported as another structure of the brain that is involved in the generation of positive emotions (33). In fMRI studies, both circuits demonstrate altered levels of function during the experience of positive and negative emotions (34).

In this context, it may be worth noting that even *recognition* of emotions from facial expressions is found to be disturbed in schizophrenia patients (35-40).

The present study examines the effects of computer-aided cognitive training using motivational software that evokes positive emotions. We expect that this method of training is particular effective because (positive) emotions and cognition are addressed simultaneously.

Methods

Participants

Forty outpatients of the psychiatric hospital in Regensburg, Germany were recruited. All of them fulfilled the *International Classification of Diseases-10 (ICD-10)*, as well as the *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)* criteria for schizophrenia and were diagnosed based on the Structured Clinical Interview for the DSM-IV (SCID) (41). After a complete description of the study, written informed consent was obtained from all subjects. Symptom levels were rated for all patients with the German versions of the Positive and Negative Syndrome Scale (PANSS) (42) and the Beck Depression Inventory (BDI) (43), and all patients were asked to perform self-rating on the Paranoid-Depression Scale (PD-S) (44) and on the State-Trait Anxiety Inventory (STAI) (45).

Cognitive functioning was tested with the Wisconsin Card Sorting Test (WCST) (46), the German version of the California Verbal Learning Test (CVLT) (47) and the subtests "tonic alertness" (selective attention) and "phasic alertness" (reaction speed) of the "Testbatterie zur Aufmerksamkeitsprüfung" (TAP), a test battery for the investigation of attention, which is a German computer test for several subtypes of attention (48).

Finally, twenty patients were included in the experimental group (EG); twenty patients matched by gender, age and educational level formed the control group (CG). Clinical and demographic characteristics of all participants are described in Table 1.

The groups do not differ in any of the demographic measures shown in Table 1, nor with regard to symptom level and cognitive achievement, except the measure for sustained attention (TAP tonic alertness) where the CG scores were better than the EG (t=1.89, p<.10).

Table 1 Demographic and Clinical Characteristics

Characteristics	Experimental Group (n=20)		Control Group (n=20)	
	N	%	N	%
Gender				
Male	5	25	5	25
Female	15	75	15	75
Medication				
Atypical antipsychotic	15	75	15	75
Typical antipsychotic	2	10	2	10
Both	3	25	3	15
	Mean	**SD**	**Mean**	**SD**
Age	30.85	8.70	33.20	10.97
Years of education	9.90	1.17	9.90	1.17
Duration of illness (yrs)	4.53	2.63	5.61	2.84
Number of hospitalizations	1.62	0.73	2.05	0.82
Dose of atypical antipsychotic medication in olanzapine equivalents	16.40	12.6	15.51	9.25
Dose of typical antipsychotic medication in chlopromazine equivalents	435.4	442.1	340.3	379.7

SD=standard deviation

Treatment

The experimental group received two cognitive training sessions per week for ten weeks (for a total of twenty sessions) using the cognitive training software X-Cog® (49), see the detailed description below. The cognitive and psychopathological measures described above were obtained before experimental/control treatment, and the final investigation of these parameters was carried out after ten weeks for both groups. The CG received no training, but similar to the EG, they met their medicating physician three times during the time of the study and, instead of cognitive training, they received occupational therapy (painting and handicraft) twice weekly for ten weeks.

X-Cog® is computer software that was explicitly designed to cover the cognitive domains mentioned above and to motivate patients as much as possible while "playing" with the exercises. In the current version, X-Cog® consists of sixteen visuomotor, memory, executive and attention tasks. The player has to control characters that face several adventures, such as rescuing a princess who has been captured inside of a maze, protecting salads from hungry snails, etc. All tasks are programmed using Microsoft's® Direct-X®-technology to provide fluent animations and stereo sound. Each task can be administered in five different levels of difficulty ranging from "beginner" to "super-professional." All patients within the CG started with the "beginner" level. Every time a specified level for each task is successfully completed, this is indicated by the software, and the participants then move up to the next level of difficulty. Figure 1 presents screen shots and short descriptions of some selected X-Cog® tasks. During the study, trainers supervised the completion of the tasks to ensure that all participants of the CG worked on all of the eight tasks selected for the study.

Data Analysis

In order to avoid extensive repetitive testing for every single cognitive measure, a multivariate MANOVA (dependent variables: cognitive measures; between-subject factor: treatment group; within subject-factor: time of testing [pre- vs. post-test]) was performed.

A significant interaction effect (time x group) was expected because this would indicate a training effect for the EG compared to the CG.

To examine whether there was a similar effect of cognitive training on psychopathological outcome, the same general design was applied to psychopathological variables as dependent measures.

Figure 1 **Screen Shots and Descriptions of Some Selected Tasks in X-Cog®**

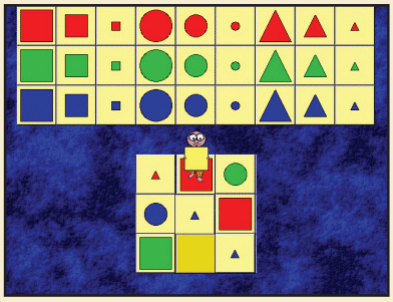


Fig. 1a: Magic carpet: 8 tiles are positioned in a 3x3 square matrix. The missing tile has to be completed following the implicit logical rules for color, shape and size.

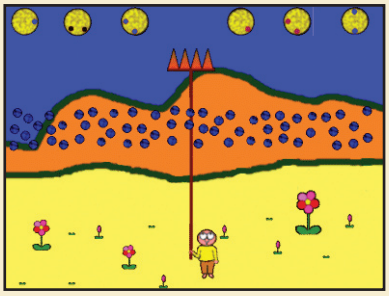


Fig. 1b: Rainmaker: to water a flower field a comet-fork has to stab into passing comets. However, only distinct comets contain water.

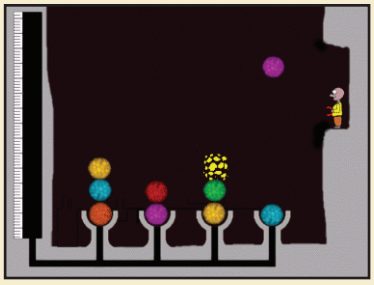


Fig. 1c: Fruit press: to create pink fruit juice, falling comets have to be sorted into dishes. Special comets cannot be sorted and have to be destroyed while falling.

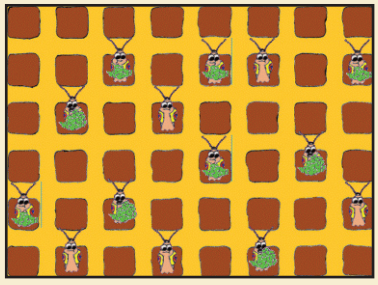


Fig. 1d: Salad clash: hungry snails dig themselves into salad beds. The players have to remember where the snails are hidden.

After general testing, univariate mixed ANOVAs for each dependent variable were carried out as post hoc tests to determine whether there were differential effects for single cognitive or psychopathological variables.

After completion of the training, patients of the experimental group were asked whether they had enjoyed cognitive training ("very much," "rather much," "undecided," "rather not," "not at all"), if they had found it helpful ("very helpful," "rather helpful," "undecided," "rather not helpful," "not helpful at all"), and if they would recommend it to other patients ("would recommend it," "would not recommend it").

Finally, correlation coefficients (Pearson coefficients or, where the "treatment group" variable was affected, point biserial coefficients) between the amount of change in cognitive measures, the amount of change on psychopathological measures and the treatment group (EG vs. CG) were computed to find out on what causal path cognitive training is influencing cognition and symptom level.

Results

All patients assigned to the experimental group remained in the cohort until the end of the training, hence no dropouts were found in this group. When asked for their opinion about the training, 80% (sixteen of the patients) found it "very helpful," 15% (three patients) "rather helpful" and only one participant (5%) remained "undecided." None of them rated training with X-Cog® as "rather not helpful" or "not helpful at all." All patients seemed to enjoy training: 90% (eighteen patients) enjoyed it "very much," 10% (two patients) "rather much," and all of them would recommend it to other patients.

A multivariate MANOVA for the cognitive variables demonstrated significant main effects for "treatment group" (members of the experimental group scored better in cognitive tests, $F[11,28]=4.33$, $p=0.003$), for "time" (all patients were better at the second testing, $F[11,28]=8.57$, $p<0.001$) and for a significant interaction effect (EG improved in cognitive tests to a greater extent than CG, $F[11,28]=3.03$, $p=0.018$). The results of the univariate mixed ANOVAs conducted separately for each dependent variable are shown in Table 2.

As can be seen, significant interaction effects could be found for verbal memory, working memory and problem solving. Sustained attention closely fails to be significant at the $\alpha<0.05$ level.

Inspection of the mean values in Table 2 or in Figure 2 demonstrates that the interaction effect for working memory (CVLT amount of learning) and WCST errors was caused by better scores for the EG at the second time of testing compared to baseline, while performance remained unchanged in CG. In verbal memory (CVLT free recall), however, achievement is worse in CG at post-test compared to baseline, while in EG performance remains unchanged from baseline to post-test.

With regard to symptom scores, multivariate MANOVA demonstrated no significant main effect for "treatment group" (psychopathology across both measurements did not differ between EG and CG, $F[7,32]=.61$, $p=.747$). However, a significant main effect for "time" (all patients were better at the second testing, $F[7,32]=.61$, $p=.747$), as well as a significant interaction effect (EG improved to a greater extent in psychopathology than CG, $F[11,28]=3.03$, $p=0.018$) was found. The results of univariate mixed ANOVAs conducted separately for each dependent variable are also shown in Table 2.

Significant interaction effects were found for positive and negative symptom levels measured by means of PANSS, as well as for PD-S "paranoid thinking." Results are demonstrated in Figure 3. In all three measures, improvement of psychopathology was observed in EG, whereas symptom levels remained unchanged in CG.

No interaction effects could be found with depression (self- and extraneous rating), with general anxiety (STAI trait) or with anxiety during testing (STAI state).

The presented findings of effects on the cognitive functioning level and on psychotic symptoms give rise to the question of causality: is cognitive training directly or indirectly responsible for the improvement of cognition and psychopathology?

At least three models of effect are possible (see Figure 4). One option (Model A) may be that cognitive training may have an immediate effect on the level of cognitive performance, as well as on psychopathology. Another option (Model B) would be that the effect on psychopathology is mediated by the improvement of the level of cognitive functioning. Finally, the third option (Model C) is that the training effect on cognitive achievement is mediated by an improvement of the symptom level.

Table 3 demonstrates the correlations between treatment (training vs. no training) and amount of improvement (result post-test minus result baseline) for all variables where significant interaction effects could be found.

Results seem to support the postulation made in Figure 4, Model A. Significant relations can be found only between training and improvement of cognitive tests and psychopathological measures, while there are no correlations between change in symptom level and change of cognitive functioning level.

Discussion/Conclusions

This study highlights the positive effects of enjoyable, computer-aided cognitive training. We found independent general effects of computer-aided cognitive training on cognitive achievement and psychopathology. When effects on

Table 2 Mean Values and Results of Repeated Measures Analyses of Variance: Cognitive and Symptom Measures

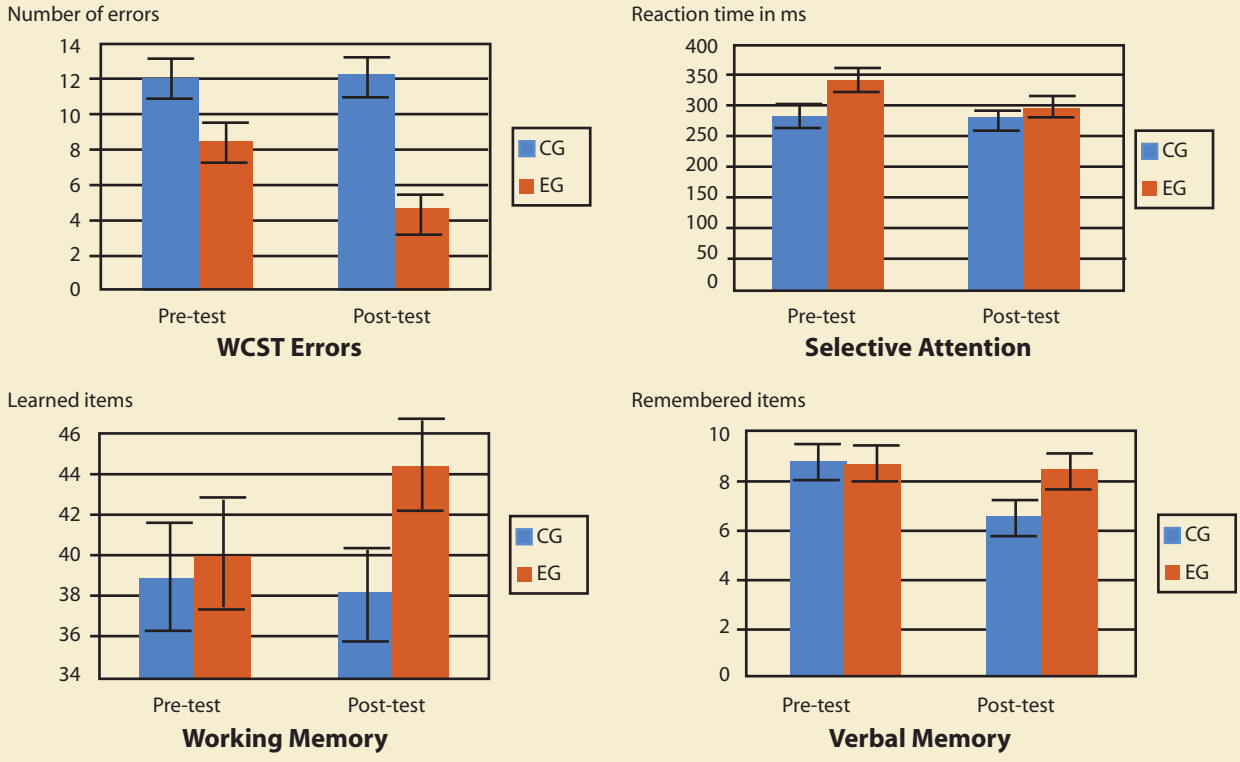
	EG (n=20)		CG (n=20)		Main Effect "Treatment"		Main Effect "Time"		Interaction "Time x Treatment"	
	Pre-test	Post-test	Pre-test	Post-test						
Measure	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	$F_{(11/28)}$	p	$F_{(11/28)}$	p	$F_{(11/28)}$	p
WCST errors	8.55 (4.66)	4.60 (3.28)	12.05 (6.13)	12.25 (6.48)	16.457	<.0001	3.855	.057	4.721	.036
WCST perseveration errors	4.20 (3.58)	2.05 (2.35)	4.55 (3.85)	4.95 (5.34)	2.660	.111	1.400	.244	2.972	.093
Sustained attention	343.25 (123.64)	296.08 (76.33)	284.65 (62.57)	278.85 (76.69)	2.149	.151	6.745	.013	4.114	.050
Reaction task	306.35 (111.85)	279.80 (78.31)	294.43 (70.63)	279.88 (84.23)	.054	.818	3.725	.061	.318	.576
CVLT amount of learning	40.00 (11.37)	44.4 (11.80)	39.00 (12.02)	38.02 (7.42)	1.224	.276	2.904	.097	6.058	.018
CVLT free recall long delay	8.75 (3.68)	8.50 (4.01)	8.80 (3.55)	6.60 (2.66)	.771	.385	12.201	.001	7.729	.008
PANSS positive symptoms	17.00 (6.05)	13.20 (4.41)	17.35 (4.53)	16.80 (4.44)	2.086	.157	8.767	.005	4.894	.033
PANSS negative symptoms	21.90 (7.43)	17.70 (5.30)	19.15 (5.98)	20.20 (6.42)	.004	.948	6.411	.016	17.808	.000
BDI depression	11.35 (8.98)	9.05 (8.43)	13.05 (11.30)	14.15 (13.87)	1.133	.294	.226	.637	1.817	.186
PD-S paranoid thinking	6.00 (5.88)	3.15 (3.39)	5.05 (4.67)	5.75 (6.50)	.300	.587	2.384	.131	6.500	.015
PD-S depression	9.50 (8.23)	8.75 (6.13)	10.00 (7.98)	11.90 (7.77)	.659	.422	.486	.490	2.582	.116
STAI trait anxiety	42.30 (12.11)	41.90 (12.16)	43.30 (12.16)	42.00 (13.05)	.025	.876	.237	.629	.066	.798
STAI state anxiety	43.50 (12.94)	40.90 (12.45)	43.50 (10.29)	42.80 (13.82)	.066	.799	1.541	.222	.511	.479

EG=experimental group; CG=control group; SD=standard deviation; WCST=Wisconsin Card Sorting Test; CVLT=California Verbal Learning Task; PANSS=Positive and Negative Syndrome Scale; BDI=Beck Depression Inventory; PD-S=Paranoid-Depression Scale; STAI=State-Trait Anxiety Inventory

cognition were analyzed in detail, positive effects on executive functions and working memory could be observed. It is worthwhile noting that verbal (working) memory and executive functions have been demonstrated to be of significant influence on rehabilitation and "community functioning" (24). The significant difference between CG and EG on verbal memory results from a decline of verbal memory achievement in CG, while performance remains stable in EG. Whether this can be considered as a treatment effect remains questionable: while some studies report cognitive decline (50-54) during the course of illness, the time span examined in these studies is much wider than the two-month interval between pre- and post-testing in the present study.

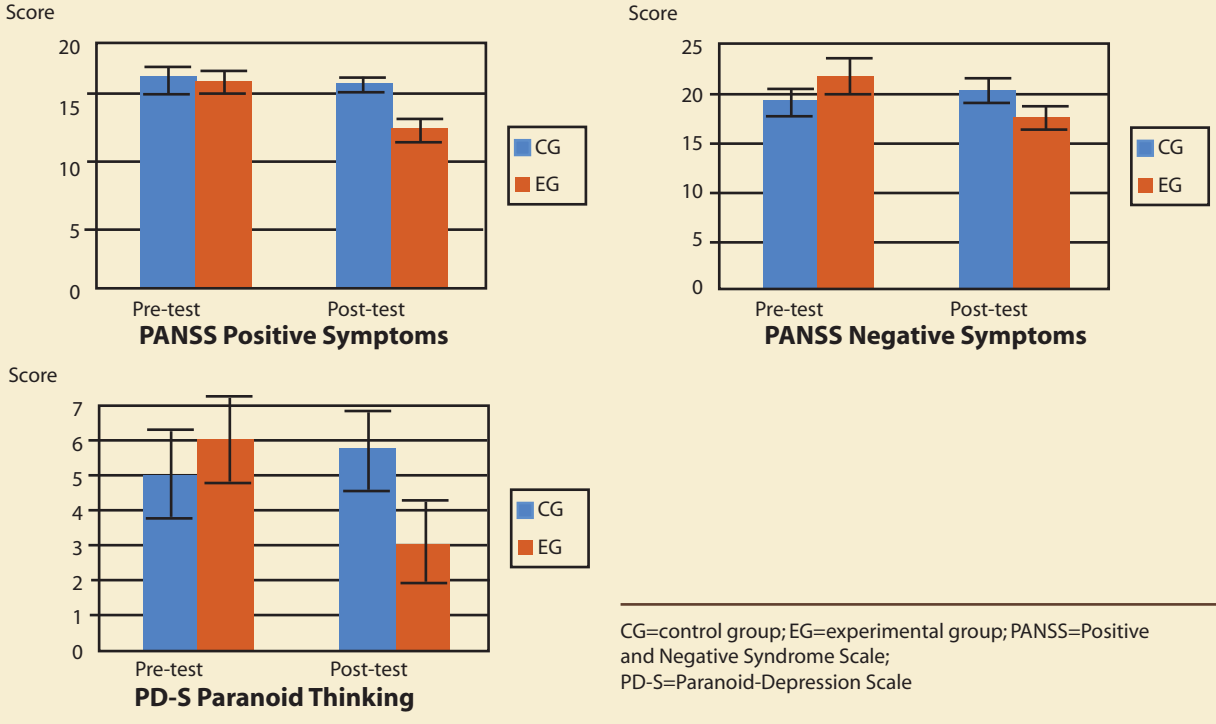
However, the effects of training on attention are reaching no more than a (two-sided) 10% significance level. This may be due to the measurement parameters used in this study, and also to the fact that attention may be rather resistant to cognitive training. Moreover, it must be taken into account that the two groups had already exhibited differences in sustained attention before treatment. An ANCOVA using the sustained attention measures at post-test as dependent variables and the pre-test values as covariates did not result in a significant main effect for "experimental group" ($F[1,39]=1.045$, not significant). (Note: we did not report

Figure 2 **Mean Values and Standard Errors of Psychometric Tests at Pre- and Post-Test for Cognitive Measures with Significant Interaction Effects in Table 2 (n=40)**



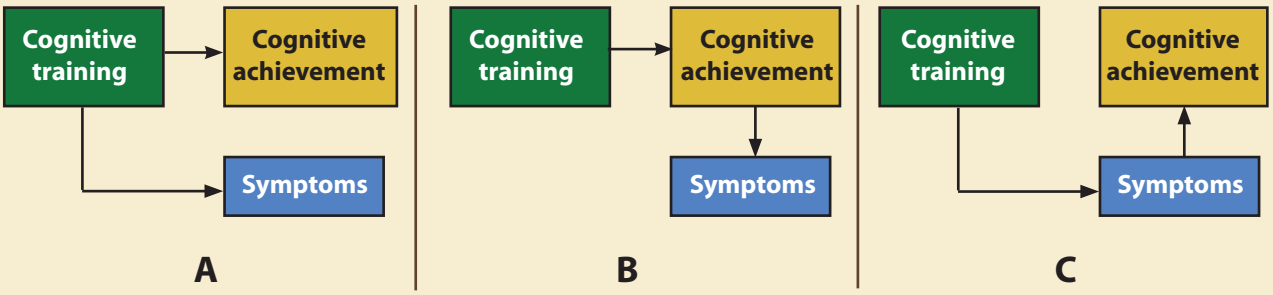
CG=control group; EG=experimental group; WCST=Wisconsin Card Sorting Test

Figure 3 **Mean Values and Standard Errors of Psychometric Tests at Pre- and Post-Test for Symptom Measures with Significant Interaction Effects in Table 2 (n=40)**



CG=control group; EG=experimental group; PANSS=Positive and Negative Syndrome Scale; PD-S=Paranoid-Depression Scale

Figure 4 Cognitive Achievement, Symptom Level and Cognitive Training: Three Models of Effect



the results for this method to test training efficacy because it is less conservative than a repeated measures analysis of variance. For our data, significant effects were found for all other cognitive and psychopathological measures where a significant interaction effect could be found ($F[1,39]$ between 15,999 and 4,850, $p<.05$ for all F-values).

When the general effect on psychopathological scales was further analyzed, effects on positive symptoms (extraneous rating and self-report), as well as on negative symptoms, could be found. Cognitive training led to fewer psychopathological symptoms compared to the control group.

The effects on psychopathology and cognition seem to be independent, for there is no significant relation between psychopathology and cognitive achievement, while there are significant links between cognitive training and achievement, as well as between cognitive training and psychopathology. Strictly speaking, conclusions about causality cannot be drawn on grounds of correlation coefficients. But, unfortunately, the number of subjects in our study is too small to test causal hypotheses via linear modeling procedures such as path analyses.

Working Memory Deficit as a Core Deficit

The effects on working memory are not surprising since working memory is particularly involved in all tasks of the training software. Recent findings indicate that working memory seems to be the only cognitive domain where superior training effects can be found when unspecified computer skills training is used as control condition (55). It has been reported that while working memory tasks do not correlate with other achievement variables in healthy people, they do in cohorts of patients suffering from schizophrenia (56). It may, therefore, be assumed that working memory may be limiting the performance of other cognitive functions in schizophrenic patients. In our study, the variable for working memory correlates significantly with all other cognitive variables (r between -.315 to -.377, p between .048 and .016 two-sided). Therefore, we assume that enhancing working memory performance could be the key to improvement of more complex domains such as executive functions. This could lead to improvement of the overall illness.

Preferred Care for the Treatment Group?

While the influence of cognitive training is not limited to cognitive variables but also affects symptom level, circumstances of the experimental treatment (e.g., personal relations to trainers, etc.) may be responsible for the better outcome of the CG. To avoid such effects in advance, our trainers were instructed to give only technical information about the tasks and not to participate in any further conversation. Also, such a confounding variable should cause effects in *all* symptom measures. However, we only found changes for positive and negative symptoms, while there was no effect on depression or anxiety. The results for anxiety also do not support a stress-training effect: the subjects of the experimental group do not seem overly accustomed to achievement situations and, therefore, are less nervous at the post-test.

Pleasant Stimuli and Memory

Despite the fact that cognitive training surely cannot be conceived as a therapy against depression and anxiety, the software used surely evokes positive emotions because of the rather enjoyable and "game-like" tasks implemented. As mentioned in the results section, ***all*** subjects reported that they experienced fun during training.

For memory tasks, the benefits of positive-connoted stimuli have clearly been proven (57): stimuli that give rise to positive emotions are more likely to be remembered than negatively connoted stimuli, which in turn are easier to remember than neutral stimuli. This may have its cause in the level of elaboration that stimuli undergo during presentation and encoding: emotional stimuli are more likely not only to be rehearsed, but also to be visualized and embedded into personal recollections.

For patients suffering from schizophrenia it has been

Table 3 Correlations between Cognitive Training, Improvement in Cognitive Measures (Post-test, Pre-test) and Symptom Measures (n=40)

	WCST Errors	CVLT Amount of Learning	CVLT Free Recall	PANSS – Positive	PANSS – Negative	PD-S Paranoid Thinking
EG vs. CG	.332 (.036)	.371 (.018)	.411 (.008)	.338 (.033)	.565 (.000)	.382 (.015)
WCST errors		-.377 (.016)	-.314 (.049)	.021 (.899)	.244 (.129)	.128 (.431)
CVLT amount of learning			.894 (.000)	.142 (.383)	.112 (.490)	-.125 (.443)
CVLT free recall				.299 (.061)	.105 (.520)	.210 (.193)

WCST=Wisconsin Card Sorting Test; CVLT=California Verbal Learning Task; PANSS=Positive and Negative Syndrome Scale; PD-S=Paranoid-Depression Scale; EG=experimental group; CG=control group

found that, among stimuli that could consciously be remembered during recall, positive connoted stimuli could be remembered best, followed by negative and neutral. However, among stimuli where persons experienced a feeling of "familiarity" during recall, while the presentation itself could not be remembered, this relation could not be found. In contrast, healthy control persons profit from emotionality for both types of stimuli (58).

Perhaps the "game-like" character may provoke enhanced strategies to a stronger extent during encoding. Possibly this causes higher levels of elaboration, which, in turn, enhances working memory performance for EG during post-testing.

The assumption that not deficits during recall but deficient encoding is the cause for working memory problems in schizophrenia patients is supported by recent findings using fMRI during a word-recognition task (59): although patients performed more poorly than healthy control persons, the authors were unable to find differences in activation of right anterior prefrontal cortex during recall. This suggests that episodic retrieval mechanisms seem to be intact. However, schizophrenia patients had a higher temporal-limbic activation during encoding. When asked about their learning strategies, patients reported that they relied less frequently on associative semantic processing.

Recently it could be found that during the presentation of pleasant and unpleasant visual images, using rCBF limbic and paralimbic regions for negative stimuli as well as prefrontal cortex areas for pleasant stimuli, stimuli were deficiently activated in schizophrenia patients (34). While they rated negative stimuli as unpleasant as did healthy control persons, pleasant stimuli were experienced as less pleasant. The rating of negative stimuli was correlated with positive and negative symptom levels (patients with high levels of positive symptoms were rating the negative stimuli as extremely unpleasant, while patients with high levels of negative symptoms rated them comparably positive), while the authors report no such link for pleasant stimuli. This again may be an argument to utilize positive emotions during cognitive training, because their experience may be rather independent from schizophrenic psychopathology, and to avoid negative emotions as much as possible.

Limitations and Implications for Future Research

In spite of some encouraging results, our study suffers from several limitations. First of all, our sample size of forty patients is rather small compared to those of other controlled studies (60, 61), which leads to a weaker statistical power and makes it harder to generalize our results. However, at least our effect sizes are comparably high (.56 to .85 compared to, for example, .15 to .25 in [61]).

Perhaps a broader measurement of symptom levels and neuropsychological measures would have been desirable. Instead of that, we focused only on one measure per cognitive domain and on rather few symptom scales. This procedure avoids repetitive statistical testing of our dependent variables, but on the other hand, this problem could have been circumvented by using factor values as dependent variables or by performing multivariate MANOVAs if larger psychometric batteries would have been considered.

In the main, the results presented in this paper only give preliminary clues. The questions, whether and how long the described effects remain stable, cannot be answered as yet. In the future it also would be interesting to identify variables, like medication or duration of illness, which influence the effects of neurocognitive training in the sense of moderating variables.

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