

## **Title**

Effectiveness of Integrated Psychological Therapy on clinical, neuropsychological, emotional and functional outcome in schizophrenia: a RCT study.

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## **Abstract**

**Background:** Cognitive impairment is considered a central feature of schizophrenia (SZ) and several rehabilitation treatments have been developed to try to improve cognitive deficits. The aim of the present study was to analyze the effectiveness of Integrated Psychological Therapy (IPT) compared with a standard treatment (TAU) in two groups of patients with SZ, using a comprehensive testing battery of clinical, cognitive, social cognition and functional outcome domains.

**Methods:** Forty-one patients with SZ were assigned to IPT or TAU groups in a randomized controlled trial (RCT). Psychopathological, neuropsychological, emotional and functional outcome variables were assessed at baseline and after 52 weeks of treatment.

**Results:** The IPT group showed significant improvements than the TAU group regarding clinical and functional outcome variables. Besides, the IPT group improved significantly in the cognitive domains and emotional functioning. Finally, linear regression has highlighted that the improvement of cognitive variables depends on having done the IPT treatment.

**Conclusions:** According to our data, the initial hypothesis is validated. In fact, IPT seems to be effective in improving clinical, neuropsychological, emotional and functional outcome in chronic SZ inpatients. Further studies would be desirable to deepen the effectiveness of IPT in the field of the psychiatric rehabilitation pointing to the possibility of recovery from mental illness.

**Keywords:** Schizophrenia, Rehabilitation, IPT, Cognitive function, Functional outcome, Social cognition.

## Title

Effectiveness of Integrated Psychological Therapy on clinical, neuropsychological, emotional and functional outcome in schizophrenia: a RCT study.

### **1. Introduction**

Schizophrenia (SZ) is a chronic, cognitive and heterogeneous clinical syndrome that seems to originate from interruption of brain development caused by environmental or genetic factors, or both (Owen et al., 2016).

The evidence of the important role played by cognitive disorders (Schulz and Murray, 2016; Zai et al., 2017) in the clinical definition of the patient with SZ has encouraged the emergence of different therapeutic programs aimed at the rehabilitation of these functions.

Recently, pharmacological interventions have been used to achieved cognitive improvement but these have yielded little encouraging results in terms of functional outcome (Harvey and Sand, 2017; Zhou et al., 2016). Other treatment strategies such as cognitive behavioral interventions (i.e. Cognitive Behavior Therapy, Cognitive Remediation Therapy) have demonstrated the efficacy of the single approach (Nowak et al., 2016; Revell et al., 2015), as well as the importance of quality of patient experience during rehabilitation treatment (Bassi et al., 2012).

Integrated therapies combine some of these specific approaches. Among these interventions, many studies suggest that the Integrated Psychological Therapy (IPT) (Brenner et al., 1994) have positive effects on the cognitive outcome in SZ (Borriello et al., 2015; Roder et al., 2011; Antonio Vita et al., 2011).

IPT is made up of five sub-programs and its exercises have an increasing level of difficulty. The first three sub-programs are aimed at basic cognitive functions (i.e. cognitive differentiation, social perception, verbal communication); the fourth and fifth, consisting of role-playing and problem solving exercises, address social and behavioral disabilities (i.e. social skills, interpersonal problem solving).

The aim of the present study was to analyze the effectiveness of IPT compared with a standard treatment (TAU) in two groups of schizophrenic patients, using a comprehensive testing battery of clinical, cognitive, social cognition and functional outcome domains. We hypothesized that patients treated with IPT might exhibit a higher improvement in symptom reduction, psychosocial functioning, cognitive and social cognition functions than TAU group.

## **2. Materials and methods**

### **2.1. Patients and procedures**

Patients were recruited at the rehabilitation clinic “San Vincenzo” in Catanzaro (Italy).

All participants were deemed eligible if they were: 1) aged between 18 and 65 years and able to read and understand the informed consent form, 2) diagnosed with Schizophrenia according to the DSM-5 (American Psychiatric Association, 2013), 3) the duration of the disease was more than five years, 4) no relapse 6 months before the study entry, 5) in remission at the time of neuropsychological assessment according to a Clinical Global Impression-Schizophrenia Scale (CGI-SCH) (Haro et al., 2003) score  $\leq 3$ , 6) participants had not previously performed IPT treatment, 7) free of any serious neurological or medical condition, 8) IQ  $>70$ , and 9) free of diagnoses of substance abuse for 6 months and dependence for 12 months.

All participants who met the following criteria were excluded: 1) recent or uncertain diagnosis, 2) comorbid psychiatric diagnosis, 3) medical history that was implausible or undocumented, 4) drug abuse in the previous 6 months and dependence for 12 months, and 5) history of a medical or neurological disease that could affect cognitive function.

Overall, 12 individuals were not eligible for the study for several reasons: 7 patients were not interested in participating and were illiterate and 5 participants dropped out before the conclusion of the treatment (3 IPT group, 2 TAU group). The final sample was made up of 41 participants and were consecutively recruited for this randomized controlled study.

At the baseline (T<sub>0</sub>) the assessment of the participants was performed through the administration of the neuropsychiatric, neuropsychological and emotional battery to evaluate clinical condition, cognitive flexibility and emotional functioning in a naturalistic setting of care.

Then, the patients were randomly divided by an independent person in the experimental group (Group 1, n=21), who received IPT in addition to TAU, and a control group (Group 2, n=20) with TAU only. The second assessment, with the same test battery administered by the same experimenter, was carried out after 52 weeks of intervention (T<sub>1</sub>).

The IPT group, composed of 8–10 patients, attended treatment sessions twice a week, 45 min each session, for 52 weeks. They were conducted by one trained psychologist and a psychiatric rehabilitator who administered the 5 subprograms following the Italian version of IPT manual (Brenner et al., 1997).

Participants were provided with a complete description of the study aims and methods and they gave informed consent to participate in the study according to the Ethical Committee before any procedure took place. The study, approved by the Ethical Committee of the rehabilitation clinic “San Vincenzo” in Catanzaro (Italy), was conducted from April 2016 to March 2017.

## 2.2. Measures

### 2.2.1. Clinical assessment

- Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess for the presence and severity of positive, negative and general symptoms, conceptually allocated to three sub-scales: seven-item scales for positive and negative symptoms and a 16-item scale covering general psychopathology.

### 2.2.2. Functional assessment

- The Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000) is an easy-to-use instrument utilized to rate subjectively the social, occupational, and psychological functioning of an individual on a hypothetical continuum of mental health-

illness, but it does not include impairment in functioning due to physical (or environmental) limitations.

- World Health Organization Quality of Life (WHOQOL) (The WHOQOL Group, 1995) assesses individual's perception of quality of life according to many subjective aspects such as physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of his environment.

### 2.2.3. Neuropsychological assessment

All participants completed the following battery of neuropsychological tests in order to measure their executive functions (Liu et al., 2011) (Wang et al., 2013) (Ben-David et al., 2014):

- The Stroop Color Word Interference Test (Golden, 1978) was administered to evaluate visual and focused attention and the capacity to inhibit cognitive interference. It is divided into three subtests: read a list of color names, say the name of the colors that have some spots of color, say the name of the color in which some color names are printed (for example: if there is the word "green" written in yellow, it must be said "yellow").
- The Trial Making Task (TMT) (Reitan, 1958) is divided into two parts, A and B, and it provides information on visual search, set-shifting and speed of processing. The test requires participants first to draw lines sequentially connecting 25 encircled numbers distributed then a 25-item alphanumeric sequence. The score on each part represents the amount of time required to complete the task as fast as possible.
- The Hayling Sentence Completion Test (HSCT) (Burgess and Shallice. T., 1997) consists of 20 sentences in which the final word is missing but is suggested by the context. Participant is asked to complete each sentence in either a logical (Task A, initiation task) or illogical manner (Task B, inhibition task) with the first word that comes to mind. Other rates provided by Task B are the type of answers: Type C Answer for sentence completion, Type S for semantic-related answers and Type U for semantic-unrelated answers. The amount of the Answers S and C provided the error score, while the last index is the Average time of Type U answers.

- The Wisconsin Card Sorting Test (WCST) (BERG, 1948) evaluates the executive functions and evaluates the perseverance and the inability to abstraction. It consists of 4 stimuli cards and 128 response cards with geometric figures with three features (color, form, or number) in various combination. The task requires subjects to find the correct classification principle by trial and error and examiner's feedback.

#### 2.2.4. Social Cognition assessment

Two tasks were administered to assess the emotional functioning of participants.

- The Reading the Mind in the Eyes (RME) (Baron-Cohen et al., 2001) evaluates an advanced affective Theory of Mind (ToM) task based on the patient's level of empathy that is expressed by the ability to understand the affective states of other people by observing only their eyes. The 36-item full version of the RME involves presentation of 36 photographs of the eye region of human faces (19 male eye pairs and 17 female): participant must choose which of the four options envisaged best describes the mental complex shown for each picture.
- The Ekman 60-Faces (EK-60F) consists of a total of 60 b/w pictures selected from Ekman and Friesen series of Picture of Facial Affect (Ekman and Friesen, 1976), which depict the faces of 10 people (six women and four men), each displaying six basic emotions (i.e. surprise, anger, happiness, sadness, disgust and fear). Subjects is required to answer verbally choosing the option that best described the facial expression shown by the actor.

All the neuropsychiatric, functional, neuropsychological and emotional measures were administered in the same session in this order: PANSS, GAF, WHOQOL, Stroop test, TMT, HSCT, WCST, RME and EK-60F.

#### 2.3. Statistical analysis

Statistical Package for Social Sciences Version 21 (SPSS, Chicago, Illinois, USA) was used for data analysis. Descriptive statistics included frequencies and percentage, means and standard deviations, as appropriate. Differences between groups were explored through chi-squared and T-tests, as

appropriate. Additionally, Cohen's effect sizes (ES) were calculated for all significant findings, and values of 0.2, 0.6, 1.2, and >1.2 can be generally categorized into slight, small, moderate, and large ES, respectively (Cohen, 1988). Finally, linear regression analysis was performed in order to identify the possible clinical and socio-demographic variables related to the change of cognitive and emotional functioning among participants. The change on neuropsychological and social cognitive testing was considered as dependent variable, while clinical and demographic variables as independent predictors. The level of statistical significance was set at  $p \leq 0.05$ .

### **3. Results**

As Table 1 shows, no differences were found regarding age, gender, level of education, duration of illness and mean drug dosage (chlorpromazine equivalents) between groups.

Table 2 illustrates the results of the group's comparison on testing battery at baseline ( $T_0$ ). No significant difference emerged in all investigated variables between groups.

Table 3 displays the findings of the changes on the clinical, emotional, neuropsychological and functional assessment between groups. No significant differences were found on PANSS Positive, Stroop Test, RME and 4 variables of HSCT (i.e. Part A, Total errors, Type S and U Answers) between groups while IPT group showed significant improvement on PANSS Negative and Total, GAF, WHOQOL, TMT, WCST, Ek-60F, and 4 variables of HSCT (i.e. Part B, Part B-Part A, Type C answers and average time Type U answers) with ES that ranging from small to large (0.68-1.66) than TAU group.

Finally, Table 4 shows the results of the linear regression where it is highlighted that the improvement of cognitive variables depends on having done the IPT treatment.

### **4. Discussion**

The aim of this study was to evaluate the effectiveness of IPT compared with TAU group of patients with SZ, using a broad testing assessment of clinical, cognitive, social cognition and functional



outcome domains. IPT treatment has amply demonstrated its effectiveness in cognitive, clinical and functional improvement in SZ according previous studies (Roder, 2006; Roder et al., 2011). To our knowledge, this is the first study where semantic inhibition and facial emotions recognition are assessed within the IPT.

Regarding clinical and functional assessment, the results revealed significant differences in favour of IPT group in the negative and total PANSS and in the GAF and WHOQOL scales. These findings could be explained by the positive effect of the five IPT rehabilitation subprograms on overall symptoms (Mueller et al., 2013), quality of life in the psychological domain (Rakitzi et al., 2016), socio-working and general functioning (Zimmer et al., 2007).

Concerning neuropsychological assessment, we found significant differences in all TMT and WCST indexes, and in four HSCT variables and our outcomes are consistent with other authors (Vita et al., 2011a; Vita et al., 2011b). According to our data, IPT improves many executive functions (e.g. set-shifting, speed of processing) of patients with SZ evaluated through TMT and WCST, while there are no differences on cognitive interference inhibition, assessed by the Stroop test.

The most striking result of our research was the improvement on HSCT, concerning cognitive flexibility performance, achieved after IPT treatment compared to TAU group. To the best of our knowledge, the present research represents the first clinical trial that assessed the effectiveness of IPT on cognitive flexibility and semantic inhibition using HSCT. Executive functioning impairment in SZ is well known and it has already been assessed using response initiation and response suppression latency and error rate of HSCT (Chan et al., 2012; Joshua et al., 2009), therefore our data at T<sub>0</sub> are in line with the international literature. However, the novelty introduced in our work is linked to the great positive impact that IPT seems to have on different HSCT indices, in particular on average time Type U answers, with an ES of 1.66 compared to the TAU group.

Social-cognitive impairment, characterized by difficulties in recognizing emotions relating to others, inferring people's thoughts and responding emotionally to others, has been widely known in SZ and has been carefully studied by many authors (Green et al., 2015) and with different tools (Kalin

et al., 2015; Rose et al., 2015). The baseline results obtained in our sample are similar to those described in other papers. In fact, several authors used EK-60F (Vázquez-Campo et al., 2016) or RME (Bora et al., 2006) or both (Balogh et al., 2014) to study social and emotional perception deficits in patients with SZ, demonstrating the presence of social cognition impairment in this type of patients. Interestingly, another novelty of the present research is represented by the impact of the IPT on EK-60F and RME outcomes. The EK-60F showed significant differences between IPT and TAU patients in the total score after treatment, whereas regarding RME, the results do not reveal any significant differences between the two groups in the ToM ability. In other words, both groups were able to attribute and recognize emotional states similarly also after 52 weeks of interventions according to RME, but IPT group had greater capability in attributing emotional states in third person and recognizing others' emotions assessed with EK-60F. These results could be explained by the application, in our study, of the fourth and fifth subprograms of IPT because many studies deleted social subprograms of IPT from the treatment (Roder et al., 2011).

Although this study has many strengths (i.e. all the five subprograms of IPT, assessment of emotional functioning, IPT effect on HSCT), some limitations must be addressed. Firstly, the small sample size even if most IPT studies have a similar sample to ours (Roder et al., 2011). Secondly, our results derive from an efficacy study after treatment, while a follow-up assessment is missing to verify if the differences are maintained over time. Finally, related to the assessments, the MATRICS Consensus Cognitive Battery (MCCB) that would be the most appropriate to evaluate cognitive functions, has not been used because we have also investigated other domains.

To conclude, according to our data, the initial hypothesis is confirmed. In fact, the five subprograms of IPT seem to be effective in improving clinical, neuropsychological, emotional and functional outcome in chronic SZ inpatients. It would be desirable having future studies to further deepen the IPT implications and fields of application as psychiatric rehabilitation technique for chronic patients with SZ, pointing to the possibility of recovery from mental illness (Rossi et al., 2018; Vita et al., 2016; Zipursky and Agid, 2015).

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### **Contributors Authors**

PDF and CSG designed the study. RdF, MA and AB collected the data. MA performed the statistical analyses. MA and RdF wrote the first draft of the manuscript. FGL and EC administered and scored neuropsychological tests. PDF, CV and CSG made the first critical review and participated to write the final manuscript. All authors commented on and approved the final manuscript.

### **Conflict of interest**

All authors declare that they have no competing interests.

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Table 1. Characteristics of the sample.

		IPT group		TAU group		test	p
Age <sup>a</sup>		50.05	(10.0)	52.14	(9.7)	0.679	.501
Gender <sup>b</sup>	Male	12	(60)	17	(81)	2.172	.141
	Female	8	(40)	4	(19)		
Level of education <sup>b</sup>	Elementary school	3	(15)	5	(23.8)	4.123	.390
	Middle school I	7	(35)	10	(47.6)		
	High school II	8	(40)	3	(14.3)		
	University degree	2	(10)	3	(14.3)		
Duration of illness <sup>a</sup> (years)		22.9	(3.5)	23.4	(2.3)	0.543	.590
Medication <sup>a</sup>	Chlorpromazine equivalents	632.4	(437.9)	674.2	(489.4)	0.288	.775

Table 2. Results of neuropsychological and clinical assessment before treatment (T<sub>0</sub>).

		IPT group		TAU group		t	Sig.
		Mean	SD	Mean	SD		
PANSS	Pos	18.1	2.5	19.5	3.1	1.587	.121
	Neg	28.3	5.6	26.2	4.9	1.280	.208
	Tot	90.7	11.4	92.5	9.7	.545	.589
GAF		39.4	11.8	42.1	14.3	.658	.515
WHOQOL	Tot	14.1	2.5	13.2	3.7	.908	.370
TMT	Part A	93.18	42.5	117.92	55.5	-1.597	.118
	Part B	269.96	147.0	337.51	152.9	-1.440	.158
	Part B - Part A	183.14	117.8	219.64	124.8	-.962	.342
	Errors in Part B	1.70	1.4	2.05	2.1	-.631	.532
WCST	Global Score	49.70	36.2	65.29	34.2	-1.416	.165
	Perseverative errors	4.55	5.4	7.38	7.7	-1.360	.182
	Non perseverative errors	43.50	32.2	59.57	31.1	-1.624	.112
	Failures to maintain set	1.60	2.4	.81	1.1	1.375	.177
HSCT	Part A	1.10	0.5	1.16	0.3	-.514	.610
	Part B	4.29	2.7	4.73	0.9	-.711	.481
	Part B - Part A	3.17	2.6	3.55	0.9	-.613	.544
	Total errors	5.25	1.5	6.33	2.4	-1.737	.090
	Type C answers	.65	1.1	2.05	3.1	-1.894	.066
	Type S answers	4.40	1.4	4.29	2.4	.187	.853
	Type U answers	4.95	1.5	3.87	2.4	1.737	.090
	Average time Type U answers	5.25	3.9	3.91	1.9	1.407	.167
Stroop interference score		-2.92	6.6	0.52	8.6	-1.441	.158
EK-60F		34.75	13.2	29.38	10.9	-1.416	.165
RME		14.75	4.9	12.33	3.4	-1.828	0.75



**Table 3. Comparison of changes in neuropsychological assessment between groups after treatment.**

		IPT group		TAU group		t	Sig.	d
		Mean	SD	Mean	SD			
Δ PANSS	Pos	-1.4	1.7	-1.9	0.4	1.311	.198	
	Neg	5.5	1.1	2.1	0.3	13.351	<.001	4.21
	Tot	12.3	3.8	7.7	5.4	3.167	.003	0.71
Δ GAF		-17.5	1.5	-10.3	3.1	9.389	<.001	2.96
Δ WHOQOL	Tot	-1.5	1.5	-0.4	1.0	2.748	.008	0.86
Δ TMT	Part A	20.15	32.6	-9.18	25.0	3.235	.002	1.00
	Part B	79.94	105.0	-6.55	51.5	3.374	.002	1.05
	Part B - Part A	66.14	90.6	-2.37	35.2	3.222	.003	0.99
	Errors in Part B	.95	1.5	-.29	0.7	3.385	.002	1.06
Δ WCST	Global Score	33.35	30.6	-9.81	21.4	5.258	<.001	1.63
	Perseverative errors	4.05	5.0	.19	0.9	3.491	.001	1.08
	Non perseverative errors	27.65	27.1	-11.81	22.7	5.060	<.001	1.58
	Failures to maintain set	1.15	1.7	-.67	1.5	3.645	.001	1.32
Δ HSCT	Part A	-.20	1.5	-.20	0.3	.002	.998	
	Part B	1.03	1.5	-.93	0.8	4.561	<.001	1.40
	Part B - Part A	.70	1.4	-.85	1.3	3.740	.001	1.15
	Total errors	.85	2.1	.09	2.2	1.123	.268	
	Type C answers	-.30	1.6	-1.5	1.9	2.167	.036	0.68
	Type S answers	.65	2.3	1.62	2.1	-1.415	.165	
	Type U answers	-.35	2.5	-.09	2.2	-.349	.729	
	Average time Type U answers	1.60	1.9	-1.48	1.8	5.328	<.001	1.66
Δ Stroop		-1.94	6.3	1.34	5.4	-1.788	.082	
Δ EK-60F		-9.60	11.7	-3.48	4.6	2.210	.033	0.69
Δ RME		-4.60	7.9	-2.86	3.4	.925	.360	

**Table 4. Results of linear regression analysis.**

Dependent variable		Independent variable	B	t	p	R <sup>2</sup>	F	p
TMT	Part A	Treatment	31.823	3.765	.001	.306	9.802	<.001
	Part B	Treatment	86.497	3.374	.002	.206	11.383	.002
	Errors in Part B	Treatment	1.23	3.385	.002	.207	11.459	.002
	Part B - Part A	Treatment	68.518	3.222	.003	.190	10.381	.003
WCST	Global Score	Treatment	43.160	5.258	<.001	.400	27.651	<.001
	Perseverative errors	Treatment	3.860	3.491	.001	0.219	12.190	.001
	Non perseverative errors	Treatment	39.460	5.060	<.001	0.381	25.604	<.001
	Failures to maintain set	Treatment	1.817	3.645	.001	0.235	13.289	.001
HSCT	Part B	Treatment	1.966	4.561	<.001	0.331	20.805	<.001
	Part B - Part A	Treatment	1.554	3.740	.001	.245	13.984	.001
	Type C answers	Treatment	1.224	2.167	.036	0.085	4.695	.036

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Average time Type U answers	Treatment	3.082	5.328	<.001	.406	28.382	<.001
EK-60F	Treatment	6.124	2.210	.033	.111	4.883	.033

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